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ORIGINAL ARTICLE

Halogenated anesthetics vs intravenous hypnotics for short and long term sedation in the intensive care unit: A meta-analysis

V. Likhvantsev[a,*], G. Landoni[b,c], N. Ermokhina[a], M. Yadgarov[a], L. Berikashvili[a], K. Kadantseva[a,d], O. Grebenchikov[a], L. Okhinko[e], A. Kuzovlev[a]

[a] *V. Negovsky Reanimatology Research Institute, Moscow, Russia*
[b] *Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[c] *Vita-Salute San Raffaele University, Milan, Italy*
[d] *A. Loginov Moscow Clinical Scientific Center, Moscow, Russia*
[e] *V. Demikhov Municipal Hospital №. 68, Moscow, Russia*

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Critically ill;
Anesthesia

Abstract
Objective: To comprehensively assess peer-reviewed studies using volatile (VA) or intravenous (i/v) anesthetics for sedation in intensive care units (ICUs), with the hypothesis that the type of sedation may have an impact on survival and other clinically relevant outcomes.
Design: Systematic review and meta-analysis of randomized and non-randomized trials.
Setting: ICUs.
Participants: Critically ill and postoperative patients.
Interventions: None.
Measurements and main results: Studies comparing VA versus i/v anesthetics used in the ICU settings were independently systematically searched. Finally, 15 studies (1520 patients of predominantly surgical profile needed VA sedation for less than 96 h) were included. VA had no impact on all-cause mortality (very low quality of evidence, Odds Ratio = 0.82 [0.60–1.12], $p = 0.20$). However, VA were associated with a reduction in duration of mechanical ventilation ($p = 0.03$) and increase in ventilator-free days ($p < 0.001$). VA also reduced postoperative levels of cardiac troponin (24 h), time to extubation ($p < 0.001$) and awakening ($p = 0.04$).
Conclusions: In this meta-analysis, volatile sedation vs propofol caused the increase in ventilator-free days, the reduction in the duration of mechanical ventilation, time to extubation and the troponin release in medical or surgical ICU patients, while in surgical ICU patients the time to awakening was shortened.

* Corresponding author.
E-mail address: lik0704@gmail.com (V. Likhvantsev).

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Ventilación mecánica;
Nivel de troponina;
Enfermedad crítica;
Anestesia

Anestésicos halogenados vs. hipnóticos intravenosos para sedación a corto y largo plazo en la unidad de cuidados intensivos: un metaanálisis

Resumen
Objetivos: Evaluar exhaustivamente los estudios revisados por pares que utilizan anestésicos volátiles (AV) o intravenosos (iv) para sedación en unidades de cuidados intensivos (UCI), con la hipótesis de que el tipo de sedación puede tener un impacto en la supervivencia y otros resultados clínicamente relevantes.
Diseño: Revisión sistemática y metaanálisis de ensayos aleatorizados y no aleatorizados.
Ámbito: UCI.
Pacientes: Se incluyeron críticamente enfermos y postoperatorios.
Intervenciones: Ninguna.
Mediciones y resultados principales: Los estudios que comparaban los AV vs. los anestésicos iv utilizados en la UCI se buscaron de forma independiente y sistemática. Finalmente, se incluyeron 15 estudios (1.520 pacientes de perfil predominantemente quirúrgico necesitaron sedación de AV durante menos de 96 h). El AV no tuvo impacto en la mortalidad por cualquier causa (calidad de los datos probatorios muy baja, *Odds Ratio* = 0,82 [0,60-1,12], $p = 0,20$). Sin embargo, el AV se asoció con una reducción de la duración de la ventilación mecánica ($p = 0,03$) y aumento de los días sin ventilación mecánica ($p < 0,001$). La AV también redujo los niveles postoperatorios de troponina cardíaca (24 horas), el tiempo hasta la extubación ($p < 0,001$) y el despertar ($p = 0,04$).
Conclusiones: En este metaanálisis, la sedación volátil vs. propofol causó el aumento de los días sin ventilación, la reducción de la duración de la ventilación mecánica, el tiempo hasta la extubación y la liberación de troponina en pacientes de la UCI médica o quirúrgica, mientras que en pacientes de la UCI quirúrgica el tiempo hasta el despertar se acortó.

Introduction

Sedation, 'the act of calming patients by the administration of sedative medications',[1] is frequently used in intensive care units (ICUs) to prevent arouse and delirium associated harm, relieve anxiety, and reduce the stress of being mechanically ventilated.[2] Since agitation and anxiety occurs in about 30%–80% of patients being treated in ICU settings,[1] sedation is a highly sought strategy for ICU patients.

Volatile anesthetics (VA) sedation uses isoflurane or sevoflurane to achieve the desired level of sedation.[3] It is a more recent and a less frequently used strategy than the traditional intravenous strategy in the ICU setting.[4] However, with the adoption of user friendly devices for VA delivery – AnaConDa (Sedana Medical, Danderyd Sweden) and MIRUS (Pall Medical, Dreieich, Germany) – VA have become increasingly popular among ICU practitioners.[5,6] There are potential lungs protective properties[7,8] and anti-inflammatory activity[9,10] coupled with the intended endothelium-saving effect,[11,12] that contribute to an increased use of VA in the ICU. Malignant hyperthermia and possible environmental pollution are the most common drawbacks of using VA.[13,14]

Early studies confirmed safety and feasibility of VA in the ICU settings[15,16] and a meta-analysis of randomized trials found a significant reduction in time to extubation[17] with findings confirmed in more recent systematic reviews.[18]

The aim of this systematic review and meta-analysis was to comprehensively assess published randomized and non-randomized peer-reviewed studies which compared VA and i/v anesthetics for ICU sedation, with the hypothesis that the type of sedation may have an impact on mortality and other clinically relevant outcomes.

Methods

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] Meta-analysis is registered in PROSPERO (ID: CRD42021277313).

Search strategy

A systematic search of studies published over the past 10 years (2011–2021) was carried out in PubMed, Medline, Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Google Scholar and the Russian Science Citation Index (RSCI) by four independent researchers (NE, LB, MY and KK). The search was carried out in the form of queries with details available in the supplemental material (Supplemental appendix 1). Additionally, the authors used the backward snowballing method (analysis of references of included articles and retrieved reviews) for further studies. We did not restrict search by language. Medical Subject Headings (MeSH) terms were applied.

Study selection

The links obtained from the database were first independently examined at the title/annotation level by two researchers (NE and LB). Randomized controlled trials, prospective and retrospective cohort studies comparing inhaled (volatile) versus i/v sedation in the intensive care unit were considered. After removing duplicates, the appropriate publications were selected. The final decision on inclusion in this study was made based on the analysis of full-text articles. Divergences were resolved by consensus.

For this study, the following inclusion criteria were used: adult patients (≥18 years) who underwent inhalation or i/v sedation in the intensive care unit (no restrictions on dose or time of administration). The exclusion criteria were mixed groups (both inhaled and i/v sedation were used), small sample size (less than 25 patients in two groups), duplicate publications, animal studies, clinical guidelines, articles without a comparison group.

Outcome measures and data extraction

Basic information about the study (design, sample size, intervention plan, inclusion criteria), information about the study objects (age, gender, underlying disease and surgery), types of anesthetics and doses, target sedation level, anesthetic-conserving device, ICU treatment outcomes (mortality, duration of mechanical ventilation, troponin level at 1 postoperative day, ventilator-free days, time to extubation, awakening time, length of stay (LOS) in ICU, hospital LOS, catecholamine requirements) was collected. We have not considered the type of anesthetic used in the surgery room. The data were independently extracted by two researchers (NE and MY) and subsequently compared with each other for verification. The primary outcome of this study was all-cause mortality (30-day mortality). Secondary endpoints were: length of stay in ICU and length of hospitalization (days), duration of mechanical ventilation (days) and ventilator-free days, catecholamine requirements, cardiac troponin levels on the first postoperative day, time to extubation (min), and awakening time (min).

Internal validity and risk of bias assessment

The internal validity and risk of bias of the included studies were assessed by two peer reviewers (MY and LB) and peer-reviewed by a third (VL) according to the latest version of the ''ROB 2'' (the Cochrane tool for assessing risk of bias in randomized trials) and ''ROBINS-I'' (Risk Of Bias In Non-randomized Studies of Interventions) tools.[20,21] Discrepancies in assessment were resolved by consensus. Publication bias was assessed using the Egger's test (MedCalc Statistical Software, version 19.5.6),[22,23] and also by visual examination of the ''funnel plot'' charts. We also used a GRADE systematic approach to rate the certainty of evidence.[24] Two review authors (MY and LB) worked independently to assess the quality of evidence, disagreements were resolved by consensus.

Data analysis and synthesis

To calculate and visualize the results of the meta-analysis in forest plots, the Cochrane tool ''RevMan, version 5.3'' was used. The heterogeneity of studies was assessed using the Cochran's Q test, and the degree of statistical agreement was measured using the coefficient of heterogeneity I^2. The quantitative results of individual studies were brought to the form ''mean ± standard deviation'' and the standardized difference of mean values (SMD) and its 95% confidence interval were calculated. Since many quantitative parameters in this meta-analysis a priori have a deeply skewed distribution, we used the log transformation for summary data of ventilator-free days, time to extubation, time to awakening and ICU/hospital length of stay.[25] We used Cochrane handbook recommendations to re-express SMDs using rules of thumb for effect sizes (<0.40 = small effect, 0.40–0.70 = moderate effect, >0.70 = large effect).[20] Binary research results were used to calculate the odds ratio with the corresponding 95% confidence interval (CI) using the inverse variance method (Mantel–Haenszel method). For a pooled estimate of the magnitude of the standardized mean difference, two models were used: a fixed-effects model (in the case of low statistical inconsistency, $I^2 < 50\%$) and a random-effects model ($I^2 \geq 50\%$ and/or $p < 0.05$). Statistical significance was set at 0.05 for hypothesis testing.

Sensitivity analysis

Sensitivity analyses were performed by considering additional subgroups – analyzing only studies with a low or moderate risk of bias (Hi-QOL studies), only RCT/non-randomized studies and by sequentially removing each study and reanalyzing the remaining data set (producing a new analysis for each study removed). Additionally, a subgroup of studies which used a prolonged sedation (>12 h) regimen was evaluated.

Results

Study characteristics

During the initial search, 427 articles were found, of which 31 were eligible. Upon careful reading of the full-text articles, 16 studies were excluded (Supplemental Table 1). Ultimately, 15 full-text articles published between January 2011 and July 2021were included in the meta-analysis. A flowchart illustrating the study selection process is presented in Fig. 1.

The characteristics of the included studies are summarized in Table 1.

The meta-analysis included 1520 patients: VA (628 patients); i/v sedation (892 patients). Among the 15 included studies, 9 were RCTs. The following settings were represented: seven studies in sedation in postoperative cardiac surgery patients,[27–29,31,34,37,39] two articles in postoperative surgical patients,[26,32] one study in patients who were assigned to more than 24 h of mechanical ventilation sedation,[36] five studies in the intensive care unit critically ill patients (non-traumatic cardiac arrest and

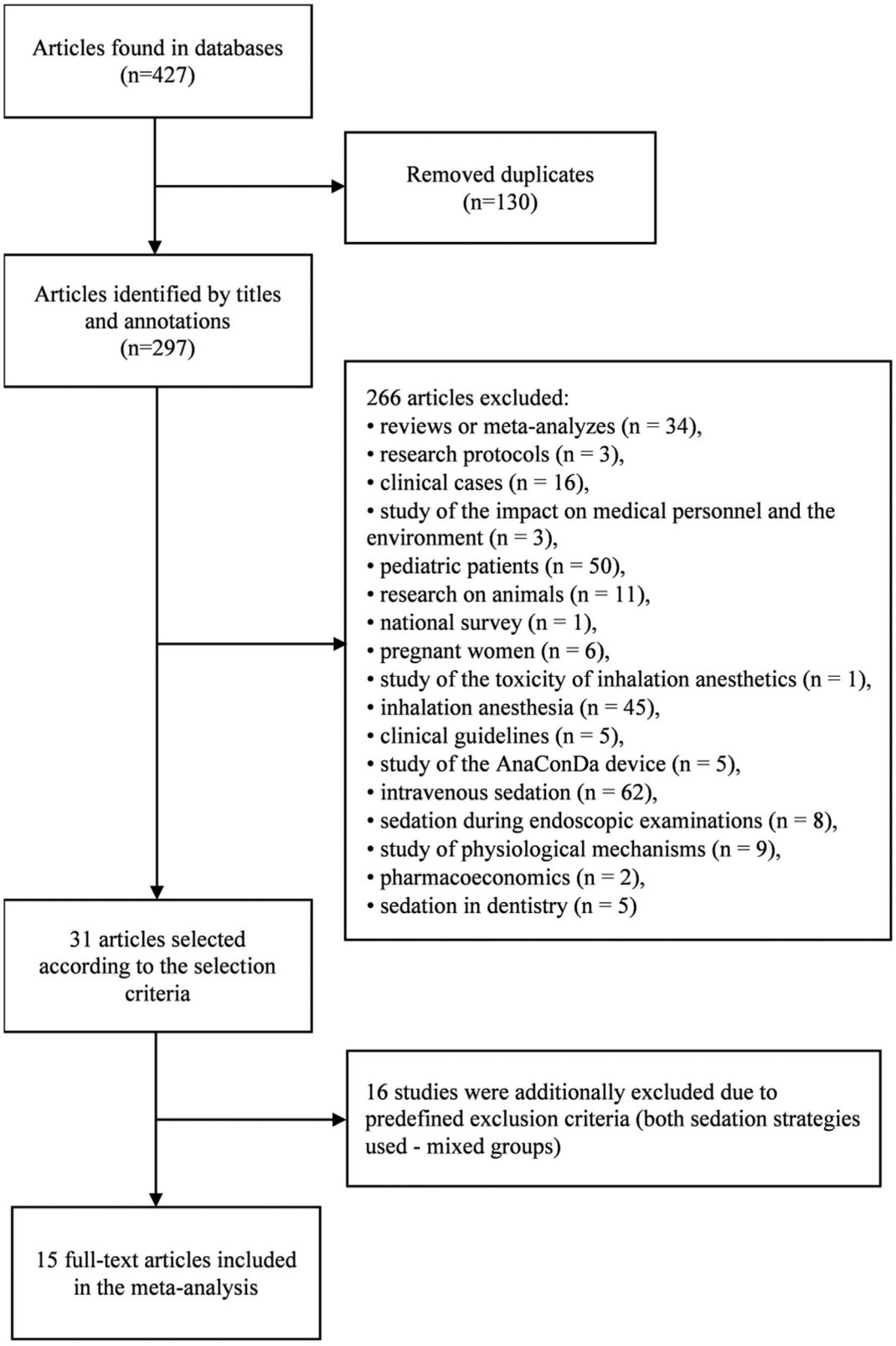

Figure 1 Flowchart used to select the final 15 manuscripts.

successful CPR,[33,40] sepsis-associated delirium[38] and moderate to severe ARDS[30,35]).

Fourteen included studies used the AnaConDa device in the ICU for inhaled sedation, and only one study used MIRUS.[28] Among the 15 included studies, 10 compared sevoflurane with propofol, 4 compared isoflurane with propofol and midazolam, and one study had multiple comparisons.

Table 1 Characteristics and description of the 15 trials included in the meta-analysis.

Study	Design	*N*, VA	*N*, i/v	Volatile agent (dose)	Location volatile started	Anesthetic-conserving device	Comparator (dose)	Journal	Population
Bellgardt M et al. (2016)[26]	Retrospective cohort	72	128	Isofluran MAC 0.3–0.8	Operating room	AnaConDa	Propofol 2–4 mg/kg/h; midazolam 0.05–0.2 mg/kg/h	Eur J Anaesthesiol	Postoperative surgical patients
Guerrero Orriach JL et al. (2013)[27]	RCT	20	40	Sevoflurane MAC 0.5–0.7	Operating room	AnaConDa	Propofol TCI 1–1.5 mg/ml	J Crit Care	Postoperative cardiac surgery patients
Guinot PG et al. (2020)[28]	RCT	42	39	Sevoflurane	Operating room	MIRUS	Propofol	Medicine	Postoperative cardiac surgery patients
Hellström J et al. (2012)[29]	RCT	50	50	Sevoflurane ET 0.5–1.0%	ICU	AnaConDa	Propofol started at 2 mg/kg/h	Scand Cardiovasc J	Postoperative cardiac surgery patients
Jabaudon M et al. (2017)[30]	RCT	25	25	Sevoflurane started at 6 ml/h	ICU	AnaConDa	Midazolam started at 0.1 mg/kg/h	Am J Respir Crit Care Med	Adult patients with ARDS
Jerath A et al. (2015)[30]	RCT	67	74	Sevoflurane or isofluran MAC 0.1–0.3	Operating room	AnaConDa	Propofol 0.6–1.5 mg/kg/h	Crit. Care Med	Postoperative cardiac surgery patients
Jung S et al. (2020)[32]	Retrospective observa-tional	25	24	Sevoflurane ET 0.5%	ICU	AnaConDa	Propofol 3.66 ± 1.30 μg/kg/h	Acute Crit Care	Postoperative surgical patients
Krannich A et al. (2017)[33]	Retrospective observa-tional propensity-matched	110	110	Isofluran ET 0.5–1.5%	ICU	AnaConDa	Midazolam 0.03–0.2 mg/kg/h	Crit Care Med	Adult patients with non-traumatic cardiac arrest
Marcos-Vidal JM et al. (2014)[34]	Prospective cohort	67	62	Sevoflurane ET 0.5–1.0%	ICU	AnaConDa	Propofol 1–4 mg/kg/h	Heart Lung Vessel	Postoperative cardiac surgery patients

Table 1 (*Continued*)

Study	Design	*N*, VA	*N*, i/v	Volatile agent (dose)	Location volatile started	Anesthetic-conserving device	Comparator (dose)	Journal	Population
Meiser A et al. (2017)[35]	Retrospective case match	19	19	Isofluran 3–10 ml/h	ICU	AnaConDa	Propofol. midazolam	Respir Care	Adult patients with ARDS
Mesnil M et al. (2011)[36]	RCT	19	28	Sevoflurane ET 0.5%	ICU	AnaConDa	Propofol started at 2 mg/kg/h	Intensive Care Med	Adult patients, more than 24 h of sedation for mechanical ventilation
Plotnikov GP et al. (2014)[37]	RCT	20	58	Sevoflurane 5.0 ± 2.3 ml/h	ICU	AnaConDa	Propofol 4.35 ± 1.75 mg/kg/h. dexmedetomidin 0.35 ± 0.2 mg/kg/h	Byulleten' NTSSSKH im. A.N. Bakuleva RAMN	Postoperative cardiac surgery patients
Resepov NA et al. (2017)[38]	RCT	20	20	Sevoflurane started at 2 ml/h (max 5 ml/h)	ICU	AnaConDa	Propofol started at 0.5 mg/kg/h	Messenger of Anesthesiology and Resuscitation	Adult patients with sepsis-associated delirium
Soro M et al. (2012)[39]	RCT	36	37	Sevoflurane ET 0.5–1.0%	Operating room	AnaConDa	Propofol 1–4 mg/kg/h	Eur J Anaesthesiol	Postoperative cardiac surgery patients
Staudacher DL et al. (2018)[40]	Retrospective observational propensity-matched	36	178	Isofluran ET 0.5–1.0%	ICU	AnaConDa	Propofol	J Crit Care	Adult patients after cardiopulmonary resuscitation

Abbreviations: VA: volatile anesthetics, i/v: intravenous anesthetics, ICU: intensive care unit, MAC: minimum alveolar concentration, RCT: randomized controlled trial, ET: end-tidal, TCI: target-controlled infusion.

Four studies[30,32,36,38] used long-term sedation (12 h or more). Five of 9 RCTs and two of six non-randomized studies had medium or high quality (Supplemental Figures 1 and 2).

Quantitative data synthesis

Fourteen studies (8 RCTs) including 1453 patients reported mortality data which were not different between groups 112/609 (18.4%) in the VA group versus 202/844 (23.9%) in the i/v group (Odds Ratio (OR) = 0.82 [0.60–1.12]; *p*-value for effect is 0.20; *p*-value for heterogeneity = 0.15; I^2 = 34%, Fig. 2; Table 2).

Analysis of subgroups of RCTs, non-randomized, Hi-QOL studies (studies with low–moderate risk of bias) and studies with long-term sedation did not reveal an association of sedation with mortality. Funnel plot for mortality is presented in Supplement (Supplemental Figure 3).

A pooled analysis of data from five studies (606 patients, four studies with short-term sedation, two RCTs) showed that patients on VA had an increase in ventilator-free days (moderate effect size: SMD = 0.46 [0.28–0.64]; *p*-value for the effect <0.001; *p*-value for heterogeneity = 0.79; I^2 = 0%, Fig. 3; Table 2). The results were confirmed in all subanalyses: RCTs ($p = 0.003$), non-randomized ($p < 0.001$) and Hi-QOL studies (2 trials, $p = 0.004$).

A pooled analysis of 987 patients (9 studies, 5 RCTs) showed that sedation with VA was associated with a reduction in duration of mechanical ventilation (SMD = −0.46 [−0.88 to −0.04] – moderate effect size; *p*-value for effect = 0.03; *p*-value for heterogeneity <0.001; I^2 = 88%, Supplemental Figure 4, Table 2). The results were confirmed in Hi-QOL studies (5 trials, $p < 0.001$), but not when considering only RCTs ($p = 0.09$) or non-randomized studies ($p = 0.29$) (Table 2). When considering only studies using prolonged sedation there was also no significant effect ($p = 0.51$).

Four studies with short-term sedation using sevoflurane (3 RCTs, 350 patients) reported cardiac troponin levels (1 day after surgery) with postoperative cardiac surgery patients on VA having a statistically significantly lower troponin levels (moderate effect size: SMD = −0.52 [from −0.84 to −0.20]; *p*-value for effect 0.001; *p*-value for heterogeneity = 0.10; I^2 = 52%, Supplemental Figure 5; Table 2). The result was robust when considering RCTs ($p = 0.04$) but not Hi-QOL studies (2 trials, $p = 0.21$).

Data from 4 studies (all RCTs, 3 with short-term sedation) in 368 patients showed that sedation with VA was associated with a decrease in time to extubation in both medical and surgical patients (large effect size: SMD = −1.59 [−2.26 to −0.91]; *p*-value for effect <0.001; *p*-value for heterogeneity <0.001; I^2 = 87%, Supplemental Figure 6; Table 2). Results on awakening time (large effect size: SMD = −1.30 [−2.54 to −0.06]; *p*-value for effect 0.04; *p*-value for heterogeneity <0.001; I^2 = 95%) were confirmed when non-randomized studies were excluded ($p = 0.04$, Supplemental Figure 7 and Table 2). The difference in the awakening time was established only for surgical patients, not for medical ones. However, only one study was of high quality. Moreover, the time to extubation and the awakening time were less in VA group than in i\v group, regardless of the duration of sedation ($p < 0.05$). Despite the depth of sedation across the majority of the studies were approximately similar (from RASS = −1 to RASS = −3), these results were difficult to compare them to the ones in the other studies where the depth of sedation were measured according to other scales.

No differences were observed in length of ICU stay ($p = 0.93$), length of hospital stay ($p = 0.69$), and need for catecholamines ($p = 0.5$, Table 2 and Supplemental Figures 8–10).

Certainty of evidence for all studied outcomes was qualified using GRADE approach for RCTs. Overall, very low quality of evidence shows that volatile sedation has no impact on hospital mortality. Certainty of evidence for other outcomes ranged from very low to high. The reasons for the decrease in the quality of evidence are summarized and presented in Table 3.

Discussion

Overall analysis showed that the use of VA for sedation in patients in the ICU does not affect hospital mortality (OR = 0.82 [0.60–1.12]; $p = 0.20$). This finding is consistent with previous meta-analyses.[17,41] The level of evidence obtained in current study for mortality outcome was downgraded to very low due to clinical inconsistency, presence of publication bias and serious imprecision (wide confidence interval for overall effect). It should be noted that the presence of publication bias was found, and statistical heterogeneity was not high (I^2 = 34%).

In this study, inhalation sedation in the ICU was associated with an increase in ventilator-free days, but the final level of evidence was very low. To the best of the authors' knowledge, this was the first meta-analysis which has shown impact of VA on patients' ventilator-free days.

This meta-analysis performed mostly from studies including surgical patients suggests that volatile sedation is associated with a reduction in duration of mechanical ventilation. In a meta-analysis by Jerath et al. (2017)[41] (523 patients, 8 studies) the duration of mechanical ventilation was lower in VA group ($p = 0.03$).

According to our data, there is moderate quality evidence that VA reduce time to extubation in ICU patients and very low quality evidence that VA reduce time to awakening (when including only RCTs). In the meta-analysis of Landoni et al. (2016) the use of halogenated agents was associated with a significant reduction in time to extubation ($p < 0.00001$).[17] Meta-analysis of Kim et al. (13 studies, 1027 patients) showed that volatile sedation delivered through a special AnaConDa device in the ICU shortens the awakening ($p = 0.004$) and extubation time ($p < 0.001$) compared to i/v anesthetics sedation.[4] A similar result was obtained in a meta-analysis by Jerath et al. (2017),[41] which also showed a decrease in extubation time when using inhaled sedation compared with i/v sedation ($p < 0.00001$).

Halogenated anesthetics are known to have cardioprotective effects,[26,42] which, according to our study, was expressed in a decrease in the content of specific markers – cardiac troponins on the first postoperative day in postoperative cardiac surgery patients. This fact has also been confirmed by a number of other studies.[43,44] Results from a meta-analysis by Kim et al. (2017) also indicate a decrease in troponin levels in patients with VA, and the effect size was largest between 12 and 24 hours after ICU

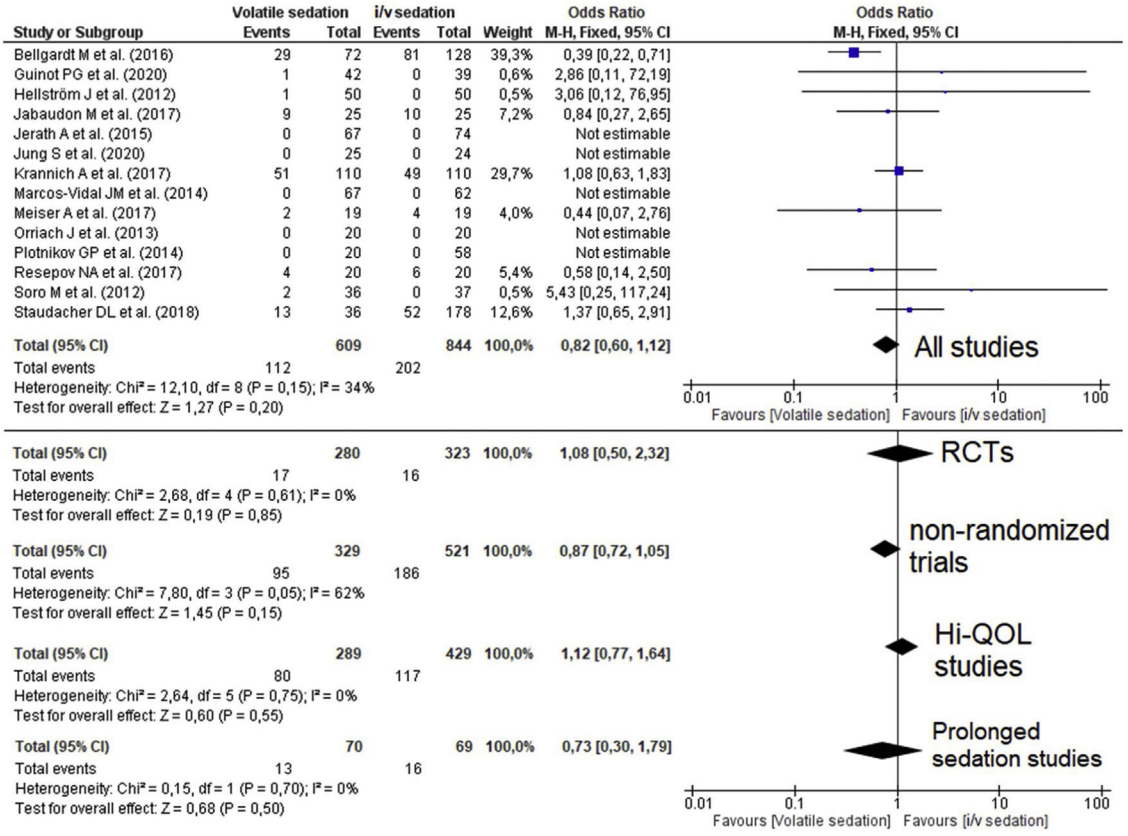

Figure 2 Forest plot for hospital mortality representing the odd's ratio for volatile vs. intravenous sedation effects on all-cause mortality for the included studies. The plot displays the study, sample size, odds ratio (OR), confidence interval (CI), and *p*-value. The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled OR with CI. Hi-QOL – studies with low–moderate risk of bias.

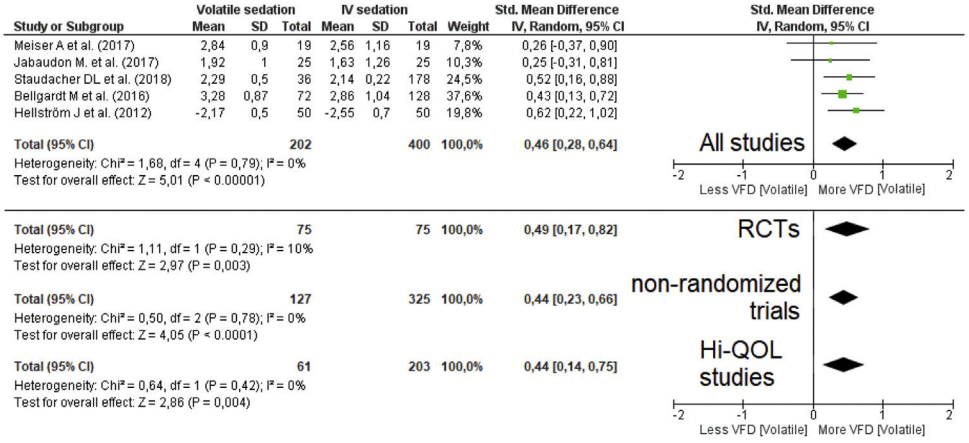

Figure 3 Forest plot for ventilator-free days. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and *p*-value. The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI. Hi-QOL – studies with low–moderate risk of bias.

admission ($p = 0.003$).[4] Patients in VA group had 0.71 ng ml^{-1} (95% CI: 0.23 to 1.2) lower troponin levels according to a meta-analysis by Spence et al. (2017).[45]

According to the results of our research there was no impact of VA on catecholamine requirements, which was confirmed in the sensitivity analysis and in the review of studies with prolonged sedation, however the evidence was of very low quality. The impact of VA and i/v anesthetics on this outcome has not been assessed in other meta-analyses to date.

No relationship was found between the type of sedation and length of ICU stay and in hospital LOS in current

Table 2 Outcomes and sensitivity analysis.

Outcome	Trials	*N*, VA	*N*, i/v	SMD/OR	95% CI	*p*-value for overall effect	*p*-value for heterogeneity	I^2, %	*p*-value for publication bias
MortalityS									
All studies	14	609	844	0.82	0.60–1.12	0.20	0.15	34	$p = 0.19$
RCTs	8	280	323	1.08	0.50–2.32	0.85	0.61	0	$p = 0.02$
Non-randomized trials	6	329	521	0.87	0.72–1.05	0.15	0.05	62	$p = 0.86$
Studies with low–moderate bias	7	289	429	1.12	0.77–1.64	0.55	0.75	0	$p = 0.60$
Prolonged sedation	3	70	69	0.73	0.30–1.79	0.50	0.70	0	$p = 0.001$
Duration of mechanical ventilation									
All studies	9	371	616	−0.46	−0.88–(−0.04)	0.03*	<0.001	88	$p = 0.49$
RCTs	5	134	181	−0.60	−1.31–0.10	0.09	<0.001	88	$p = 0.85$
Non-randomized trials	4	237	435	−0.31	−0.87–0.26	0.29	<0.001	90	$p = 0.86$
Studies with low–moderate bias	5	191	333	−0.52	−0.72–(−0.33)	<0.001*	0.09	54	$p = 0.44$
Prolonged sedation	3	64	73	−0.11	−0.45–0.22	0.51	0.70	0	$p = 0.31$
Troponin level at 1 postoperative day									
All studies	4	179	171	−0.52	−0.84–(−0.20)	0.001*	0.10	52	$p = 0.49$
RCTs	3	112	109	−0.50	−0.98–(−0.03)	0.04*	0.06	65	$p = 0.35$
Studies with low–moderate bias	2	62	59	−0.61	−1.56–0.34	0.21	0.02	82	$p < 0.001$
Ventilator-free days									
All studies	5	202	400	0.46	0.28–0.64	<0.001*	0.79	0	$p = 0.40$
RCTs	2	75	75	0.49	0.17–0.82	0.003*	0.29	10	$p < 0.001$
Non-randomized trials	3	127	325	0.44	0.23–0.66	<0.001*	0.78	0	$p = 0.59$
Studies with low–moderate bias	2	61	203	0.44	0.14–0.75	0.004*	0.42	0	$p < 0.001$
Time to extubation									
All studies	4	177	191	−1.59	−2.26–(−0.91)	<0.001*	<0.001	87	$p = 0.06$
Awakening time									
All studies	3	122	280	−1.30	−2.54–(−0.06)	0.04*	<0.001	95	$p = 0.41$
RCTs	2	86	102	−1.99	−3.92–(−0.06)	0.04*	<0.001	94	$p < 0.001$
LOS in ICU									
All studies	13	588	794	0.01	−0.17–0.18	0.93	0.008	55	$p = 0.88$
Hospital LOS									
All studies	9	367	589	−0.06	−0.35–0.23	0.69	<0.001	76	$p = 0.03$
Catecholamine requirements									
All studies	9	362	550	1.13	0.79–1.61	0.50	0.41	3	$p = 0.43$

Abbreviations: VA: volatile anesthetics, i/v: intravenous anesthetics, CI: confidence interval; ICU: intensive care unit; LOS: length of stay; RCT: randomized controlled trial; OR: odds ratio; SMD: standardized mean difference.
* Significant overall effect.

Table 3 Certainty of evidence from RCTs for studied outcomes (Grade approach).

Outcome	No. of participants and RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrades	Overall quality of evidence
Mortality statement								
No effect on ICU patients	525, 7 RCTs	Not serious (0)	Serious (−1)	Not serious (0)	Very serious (−2)	Serious (−1)	None	⊕OOO Very low
Duration of mechanical ventilation (DMV) statement								
Volatile anesthetics do not reduce DMV in ICU patients	315, 5 RCTs	Serious (−1)	Very serious (−2)	Not serious (0)	Very serious (−2)	Not serious (0)	None	⊕OOO Very low
Troponin level at 1 p/o day statement								
Volatile anesthetics reduce troponin level after cardiac surgery	221, 3 RCTs	Not serious (0)	Serious (−1)	Not serious (0)	Serious (−1)	Not serious (0)	None	⊕⊕OO Low
Ventilator-free days (VFD) statement								
Volatile anesthetics increase VFD in ICU patients	150, 2 RCTs	Serious (−1)	Very serious (−2)	Not serious (0)	Not serious (0)	Serious (−1)	None	⊕OOO Very low
Time to extubation (TE) Statement								
Volatile anesthetics reduce TE in ICU patients	368, 4 RCTs	Serious (−1)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	None	⊕⊕⊕O Moderate
Awakening time (AT) statement								
Volatile anesthetics reduce AT in ICU patients	188, 2 RCTs	Serious (−1)	Serious (−1)	Not serious (0)	Serious (−1)	Not serious (0)	None	⊕OOO Very low
LOS in ICU statement								
No effect on ICU patients	532, 7 RCTs	Not serious (0)	Serious (−1)	Not serious (0)	Not serious (0)	Not serious (0)	None	⊕⊕⊕O Moderate
Hospital LOS statement								
No effect after cardiac surgery	455, 5 RCTs	Not serious (0)	Serious (−1)	Not serious (0)	Serious (−1)	Not serious (0)	None	⊕⊕OO Low
Catecholamine requirements statement								
No effect on ICU patients	520, 6 RCTs	Serious (−1)	Not serious (0)	Serious (−1)	Serious (−1)	Not serious (0)	None	⊕OOO Very low

Abbreviations: RCT, randomized controlled trial; p/o, postoperative; ICU, intensive care unit; LOS, length of stay.
Key: 0, no evidence downgrade; −1, serious limitation; −2, very serious limitation; +1, evidence upgrade. Baseline evidence level for RCTs: high.

meta-analysis. This fact has also been confirmed in other studies. Thus, in a meta-analysis of Landoni et al. (2016) no relationship was found between VA and ICU LOS ($p = 0.13$) and hospital LOS ($p = 0.08$).[17] Similar results were obtained in meta-analyses of Jerath et al. (hospital LOS: $p = 0.74$), Kim et al. (ICU LOS: $p = 0.513$; hospital LOS: $p = 0.059$) and Spence et al. (ICU LOS: $p = 0.65$; hospital LOS: $p = 0.11$).[4,41,45]

We were the first to use the GRADE approach to assess the quality of the evidence regarding the effect of sedation on mortality. Increase of ventilator free days due to volatile sedation firstly depicted in current meta-analyses and it seems to be a new and important piece of information that have been brought to our knowledge. It looks like that the next strength of our meta-analysis is that we performed very thorough sensitivity analyses, looking at both RCT alone and low-risk of bias studies.

Authors acknowledge that this study also has some limitations. All RCTs included in the meta-analysis were single center studies and therefore external validity is limited. The meta-analysis was performed mostly from studies included surgical patients so the cohort of medical critically ill patients is poorly represented. The sample sizes of the included studies were small and only four studies used long-term sedation (12 h or longer). Clinical heterogeneity (inconsistency) of studies (mixed surgery, varying depth of sedation, different time points for measuring outcomes) and risks of bias also reduced the level of evidence. We failed to spot any difference in effect on the investigated parameters between isoflurane and sevoflurane been used for inhaled sedation. Thus, some of the results may have been insufficient. We also have not considered the type of anesthetic used in the surgery room. Finally, we were unable to analyze other factors such as laboratory parameters, cognitive status and major morbidity as most of the included studies did not report these data.

Conclusion

Volatile anesthetics had no effect on hospital mortality (very low evidence), however they reduced duration of mechanical ventilation, troponin level, time to extubation, and the time to awakening in medical and surgical ICU patients. Thus, it seems like, despite of new data, brought by current meta-analysis, further large high-quality randomized controlled studies are to be performed to provide more knowledge towards this still unclear challenge due to the low power of published studies.

Author contributions

Conceived and designed the análisis: VL, GL, NE, MY, LB, KK, OG, AK

Collected the data: NE, MY, LB, KK

Contributed data or analysis tools: GL

Performed the analysis: MY, KK

Wrote the paper: VL, GL, NE, MY, LB, KK, OG, LO, AK

All authors have approved the final article.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medin.2022.03.007.

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