Volatile Agents in Medical and Surgical Intensive Care Units: A Meta-Analysis of Randomized Clinical Trials

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Objective: **To comprehensively assess published randomized peer-reviewed studies related to volatile agents used for sedation in intensive care unit (ICU) settings, with the hypothesis that volatile agents could reduce time to extubation in adult patients.**

Design: **Systematic review and meta-analysis of randomized trials.**

Setting: **Intensive care units.**

Participants: **Critically ill patients.**

Interventions: **None.**

Measurements and Main Results: **The BioMedCentral, PubMed, Embase, and Cochrane Central Register databases of clinical trials were searched systematically for studies on volatile agents used in the ICU setting. Articles were assessed by trained investigators, and divergences were resolved by consensus. Inclusion criteria included random allocation to treatment (volatile agents versus any intravenous comparator, with no restriction on dose or time of administration) in patients requiring mechanical ventilation in the ICU. Twelve studies with 934 patients were included in the meta-analysis. The use of halogenated agents reduced the time to extubation (standardized mean difference = −0.78 [−1.01 to −0.55] hours; p for effect <0.00001; p for heterogeneity = 0.18; I^2 = 32% in 7 studies with 503 patients). Results for time to extubation were confirmed in all subanalyses (eg, medical and surgical patients) and sensitivity analyses. No differences in length of hospital stay, ICU stay, and mortality were recorded.**

Conclusions: **In this meta-analysis of randomized trials, volatile anesthetics reduced time to extubation in medical and surgical ICU patients. The results of this study should be confirmed by large and high-quality randomized controlled studies.**

KEY WORDS: volatile agents, anesthesia, intensive care, sedation, mechanical ventilation, critically ill

SEDATION IN THE intensive care unit (ICU) has important implications for survival of critically ill patients. In fact, there is increasing evidence that the avoidance of deep sedation can improve patients' outcome by reducing the incidence of delirium and undesired prolonged recovery time, leading to a shorter period of mechanical ventilation (MV), thus reducing its complications, the ICU length of stay, and the mortality rate.[1,2] This topic is included in a short list of strategies, with a documented effect on survival in critically ill patients.[3]

Different sedatives and hypnotics commonly are used for the management of discomfort, fear, anxiety, agitation, and delirium of patients in the ICU. According to recent guidelines, modern sedatives include propofol, dexmedetomidine, midazolam, and different combinations of analgesic, hypnotic, and antipsychotic drugs.[4]

Volatile agents have a documented beneficial effect on clinically relevant outcomes in the perioperative cardiac surgical setting, with a possible reduction in mortality in coronary artery bypass grafting patients.[5] Although not included in guidelines for sedation of patients in the ICU, the use of volatile agents can offer several advantages in this setting. First, they can be considered as advantageous additional sedative drugs to be alternated with the usual standard care, which may reduce the necessity of MV because of the agents' fast washout and their possible role in reducing awakening time, allowing for earlier extubation. Moreover, they may be considered life-saving agents in the treatment of severe diseases, such as refractory asthma and epilepsy.[6-8] In addition, initial evidence has demonstrated that their anti-inflammatory activity[9] could translate into a better outcome in cases of sepsis, even if this evidence is limited to the experimental setting.[10,11]

To assess whether the use of halogenated anesthetics could offer advantages to ICU patients in terms of time to extubation, the authors performed a meta-analysis of all the randomized clinical trials ever published on halogenated agents in this setting.

METHODS

Search Strategy

Pertinent studies were independently searched in PubMed, BioMedCentral, Embase, and the Cochrane Central Register of clinical trials (updated June 1, 2015) by 4 investigators (MBR, CDV, MB, GB). The full PubMed search strategy aimed to include any randomized controlled trials ever performed on volatile agents in the ICU setting and is presented in Supplemental Material (available online at: cicm.org.au/journal.php). Moreover, the authors contacted international experts and used backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) for further studies. No language restriction was imposed.

Study Selection

References obtained from database and literature searches first were examined independently at a title/abstract level by 4

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1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2016.02.021

investigators (MBR, CDV, MB, GB) and then, if potentially pertinent, retrieved as complete articles. Divergences were resolved by consensus. The following inclusion criteria were used for potentially relevant studies: random allocation to treatment (volatile agents versus any intravenous comparator with no restrictions on dose or time of administration) and studies involving patients who required MV in a surgical or medical ICU. The exclusion criteria were nonadult patients, duplicate publications (in this case, the authors referred to the first article published and retrieved data from the article with the longest follow-up available), and lack of data on all of the following: time to extubation, ICU stay, hospital stay, and mortality. Two investigators (GL, LP) independently assessed compliance to selection criteria and selected studies for the final analysis. Divergences were resolved by consensus.

Data Extraction and Study

Data were extracted independently by 4 investigators (MBR, CDV, MB, GB).[12-23] If a trial reported multiple comparisons,[12] the comparators were aggregated as a single control group. At least 2 separate attempts at contacting corresponding authors were made in cases of missing data. The primary endpoint of this study was the time to extubation (hours). Secondary end-points were lengths of ICU and hospital stays (days) and mortality rate at the longest available follow-up. Adverse effects also were collected.

Internal Validity and Risk of Bias Assessment

The internal validity and risk of bias of included trials were appraised by 2 independent reviewers according to the latest version of the "risk of bias assessment tool" developed by The Cochrane Collaboration[24] (see Supplemental Material). Divergences were resolved by consensus. Publication bias was assessed by visually inspecting funnel plots.

Data Analysis and Synthesis

Computations were performed with RevMan version 5.2 (Cochrane, London, United Kingdom). Hypothesis of statistical heterogeneity was tested using Cochran Q test, with statistical significance set at the 2-tailed 0.10 level, whereas extent of statistical consistency was measured with I^2, defined as $100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Binary outcomes from individual studies were analyzed to compute individual and pooled risk ratios, with pertinent 95% confidence interval (CI), by means of inverse variance method and with a fixed-effect model in case of low statistical inconsistency ($I^2 < 25\%$) or with random-effect model (which better accommodates clinical and statistical variations) in case of moderate or high statistical inconsistency ($I^2 > 25\%$). Standardized mean differences (SMDs) and 95% CIs were computed for continuous variables using the same models just described. To evaluate whether the small study effect had an influence on the treatment effect estimate, in case of evidence of between-study heterogeneity ($I^2 > 25$), the results of both fixed- and random-effect models were compared.

Subanalyses on setting, type of administered halogenated agent, and comparator were performed. Sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining data set (producing a new analysis for each study removed) and by analyzing only data from studies with low or moderate risk of bias.

Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing. Unadjusted p values are reported throughout the article. This study was performed in compliance with The Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24-26]

RESULTS

Study Characteristics

Database searches, snowballing, and contacts with experts yielded a total of 343 articles. The flowchart used for the selection of the final 12 manuscripts[12-23] is detailed in Figure 1.

After excluding 320 nonpertinent titles or abstracts, the authors retrieved in complete form and assessed 23 studies according to the selection criteria. Eleven studies were further excluded because of the prespecified exclusion criteria (see Fig 1). The references of the excluded manuscripts and the cause of exclusion are presented in the Supplemental Material. The final 12 included manuscripts randomly assigned 934 patients to the following treatment groups: 452 to volatile agents and 482 to control agents (see Tables 1-3). Clinical heterogeneity was mostly due to setting, administered volatile agent, and control treatment. Indeed, 5 trials used a halogenated anesthetic in a general ICU setting [16-20] and 7 trials used volatile agents in a surgical ICU, either cardiac or noncardiac.[12-14,16,17,19,21]

Sevoflurane was used in 7 trials,[12,13,16,18,19,21,23] isoflurane in 3 trials,[15,20,22] isoflurane or sevoflurane in 1 trial,[14] and desflurane in 1 trial.[21] Propofol was the comparator in 9 study arms[12-14,16-19,21,23] and midazolam in 3[15,20,22] (see Table 1).

Study quality appraisal indicated that trials were of low-medium quality (see Supplemental Material); in particular 1 of them had a low risk of bias,[21] whereas 7 had a moderate risk of bias.[12,13,17-21,23]

Quantitative Data Synthesis

The overall analysis showed that the use of halogenated agents was associated with a significant reduction in time to extubation (SMD = −0.78 [−1.01 to −0.55] hours; p for effect < 0.00001; p for heterogeneity = 0.18; $I^2 = 32\%$ in 7 studies with 503 patients) (Fig 2; Table 4).

The results on reduction in time to extubation were confirmed in all performed subanalyses (see Table 2). Results were confirmed at sensitivity analyses performed by sequentially removing each study and reanalyzing the remaining data set. Visual inspection of the funnel plot did not identify a skewed or asymmetric shape, excluding the presence of small publication bias (Fig 3).

No differences in ICU stay, hospital length of stay, and mortality were observed (see Table 4 and Figure 4). No differences in adverse events among groups were observed.

DISCUSSION

To the best of the authors' knowledge, this was the first meta-analysis performed on the use of halogenated anesthetics for the sedation of patients in the ICU setting. This study

Table 1. Description of the 12 Trials Included in the Meta-Analysis

First Author	Year	Journal	Setting	Outcome of the Study	Population	Patients After Surgery	Patients With Respiratory Insufficiency	Patients With Sepsis
Orriach JL[12]	2013	J Crit Care	Post–cardiac surgery ICU	To evaluate whether there are beneficial effects when sevoflurane is maintained in the postoperative period in terms of myocardial protection	Postoperative cardiac surgery patients	100%	0%	0%
Hellström J[13]	2012	Scand Cardiovasc J	Post–cardiac surgery ICU	Primary end point: time from drug termination to extubation and to adequate verbal response Secondary end points: adverse recovery events, memory reported in the ICU, ICU and hospital stays	Postoperative cardiac surgery patients	100%	0%	0%
Jerath A[14]	2015	Crit Care Med	Post–cardiac surgery ICU	Primary outcome: assessing whether volatile agents provide significant preconditioning and postconditioning myocardial protective effects by a reduction in postoperative troponin levels Secondary outcomes: extubation times, sedation and pain scores, analgesia requirement, shivering, postoperative nausea and vomiting, and ICU and hospital stays	Postoperative cardiac surgery patients	100%	NA	NA
Kong KL[15]	1989	BMJ	General ICU	Achievement of a predetermined level of sedation for as much of the time as possible	Patients requiring mechanical ventilation	85%	NA	3%
Marcos-Vidal JM[16]	2014	Heart Lung Vessel	Post–cardiac surgery ICU	To assess whether sevoflurane has benefits on myocardial infarction (troponin T levels)	Postoperative cardiac surgery patients	100%	NA	NA
Meiser A[17]	2003	Br J Anaesth	Mixed surgery ICU	Emergence time	Patients requiring mechanical ventilation	100%	0	NA
Mesnil M[18]	2011	Intensive Care Med	General ICU	Primary end points: wake-up times and extubation delay from termination of sedative administration	Patients expected to require more than 24 hours sedation	0%	15%	10%
Röhm KD[19]	2008	Intensive Care Med	Post–cardiac surgery ICU	Primary end points: extubation time from termination of sedation Secondary end points: recovery times, consumption of anesthetics, end-tidal sevoflurane concentrations, lengths of ICU and hospital stay, and side effects	Postoperative cardiac surgery patients	100%	NA	NA
Sackey PV[20]	2004	Crit Care Med	General ICU	To test the efficacy and patient safety of anesthetic conserving device	Patients requiring mechanical ventilation	22.50%	12.50%	27.50%
Soro M[21]	2012	Eur J Anaesthesiol	Post–cardiac surgery ICU	Primary end point: increase in myocardial biomarkers Secondary end points: hemodynamic events, ICU and hospital lengths of stay	Postoperative cardiac surgery patients	100%	0%	0%
Spencer EM[22]	1992	Intensive Care Med	General ICU	Efficacy and safety of isoflurane as a sedative compared with midazolam for a period more than 24 hours	Patients requiring mechanical ventilation	73.30%	NA	NA
Steurer MP[23]	2012	Crit Care	General ICU	Primary outcome: cardiac injury in first postoperative day Secondary outcomes: oxygenation index 4 hours after initiating postoperative sedation in ICU and in postoperative day 1, incidence of postoperative pulmonary complications during hospitalization, duration of ICU and hospital stays, need for antiemetics	Postoperative cardiac surgery patients	100%	0%	0%

Abbreviations: ICU, intensive care unit; NA, not available.

Table 2. Characteristics of the 12 Trials Included in the Meta-Analysis

First Author	Year	Patients Receiving Volatiles (n)	Control Patients (n)	Volatile Agent	Dose of Volatile Agent	Location Volatile Started	Device	Comparator	Dose of Comparator Drug	Episodes of Hypotension	Episodes of Tachycardia
Orriach JL[12]	2013	20	40	Sevoflurane	MAC 0.5-0.7	Operating room	AnaConDa (Sedana Medical, Kildare, Ireland)	Propofol	1-1.5 μg/mL with TCI	No differences between groups	No differences between groups
Hellström J[13]	2012	50	50	Sevoflurane	End-tidal 0.5%-1%	ICU	AnaConDa	Propofol	2 mg/kg/h plus/minus bolus of 20-50 mg	NA	NA
Jerath A[14]	2015	67	74	Isoflurane or sevoflurane	MAC 0.1-0.3	Operating room	AnaConDa	Propofol	10-25 μg/kg/min	Volatile group: higher prevalence hypotension	NA
Kong KL[15]	1989	30	30	Isoflurane	End-tidal 0.1%-0.6%	ICU	Servo 900B + Isoflurane Vaporizer 952 (Maquet, Rastatt, Germany)	Midazolam	0.01-0.20 mg/kg/h	No differences between the 2 groups	NA
Marcos-Vidal JM[16]	2014	67	62	Sevoflurane	End-tidal 0.5%-1%	ICU	AnaConDa	Propofol	1-4 mg/kg/h	NA	NA
Meiser A[17]	2003	28	28	Desflurane	End-tidal 3%, plus steps of up to 0.5%	ICU	Cicero Dräger (Dräger, Lübeck, Germany) + TEC 6 Vaporizer (GE Healthcare, Little Chalfont, United Kingdom)	Propofol	4 mg/kg/h changed in steps of up to 40 mg every 15 min; bolus of 40 mg allowed	No differences between the 2 groups	NA
Mesnil M[18]	2011	20	20	Sevoflurane	End-tidal 0.5% (dose adjustments were possible within steps of 0.1%)	ICU	AnaConDa	Propofol	2 mg kg/h	NA	NA
Röhm KD[19]	2008	35	35	Sevoflurane	End tidal 0.5%-1%	Operating room	AnaConDa	Propofol	2-4 mg/kg/h	NA	NA
Sackey PV[20]	2004	20	20	Isoflurane	End-tidal 0.5%	ICU	AnaConDa	Midazolam	0.02-0.05 mg/kg/h	3 episodes of hypotension in the isoflurane group and 2 episodes in the midazolam group	NA
Soro M[21]	2012	36	39	Sevoflurane	End-tidal 0.5%-1%	Operating room	AnaConDa	Propofol	1-4 mg/kg/h	No differences between groups	No differences between groups
Spencer EM[22]	1992	22	24	Isoflurane	End-tidal 0.1%-0.6%	ICU	Servo 900B + Isoflurane Vaporizer 952	Midazolam	0.02-0.20 mg/kg/h	No differences between groups	NA
Steurer MP[23]	2012	57	60	Sevoflurane	MAC 0.5	ICU	AnaConDa	Propofol	0.5-4 mg/kg/h	NA	NA

Abbreviations: ICU, intensive care unit; MAC, minimum alveolar concentration; NA: not available TCI, target controlled infusion.

Table 3. Details on Devices, Scavenge Systems Used, and Costs

First Author	Year	Device	Scavenging and Monitoring	Costs
Orriach J[12]	2013	AnaConDa (Sedana Medical, Kildare, Ireland)	NA	NA
Hellström J[13]	2012	AnaConDa	Approximately 90% of exhaled anesthetic agent adsorbed to an active carbon filter in the AnaConDa and recycled to the patient with the next breath. Scavenging is performed actively or passively from the ventilator and the gas analyzer.	NA
Jerath A[14]	2015	AnaConDa	Atmospheric pollution was minimized by active scavenging of volatile agents using 2 canisters of Deltasorb (Blue-Zone Technologies Ltd, Concord, Ontario, Canada) linked in series from the ventilator expiratory port to wall outlet suction. Deltasorb contains a diamond lattice of silica zeolite (Delatzite), which selectively adsorbs volatile agents and reduces environmental emissions.	NA
Kong KL[15]	1989	Servo 900B + Isoflurane Vaporizer 952 (Maquet, Rastatt, Germany)	Discharged outside	NA
Marcos-Vidal JM[16]	2014	AnaConDa	AnaConDa scavenging system	NA
Meiser A[17]	2003	Cicero Dräger (Dräger, Lübeck, Germany) + TEC 6 Vaporizer (GE Healthcare, Little Chalfont, United Kingdom)	Discharged outside	Pure drug costs for 24 h of sedation: $80.23 for propofol and $107.34 for desflurane
Mesnil M[18]	2011	AnaConDa	The ICU ventilators (Evita XL; Drägerwerk AG, Lübeck, Germany) in the single-bed rooms were connected to the hospital waste gas system wall outlet. Atmospheric contamination was measured in rooms of patients exposed to sevoflurane using passive lapel dosimeter sampling placed at 1 m from the ventilator. These dosimeters were later analyzed using gas chromatography.	NA
Röhm KD[19]	2008	AnaConDa	A charcoal membrane integrated within the AnaConDa absorbs volatile anesthetics during exhalation (to 90%) and then releases it by evaporation into the inspired gas during inspiration. Any exhaled sevoflurane that fails to condense on the filter is released through the expiratory outlet of the ventilator to an active coal scavenging system (Novasorb) to prevent environmental pollution.	Pure drugs costs: sevoflurane: $17.06 ± $10.70; propofol: $14.12 ± $6.50; sevoflurane sedation costs that included use of the AnaConDa were significantly higher in the sevoflurane group due to the cost of the device itself
Sackey PV[20]	2004	AnaConDa	Active evaquation system	NA
Soro M[21]	2012	AnaConDa	To prevent environmental pollution with sevoflurane, ventilators were fitted with a Scat exhaled gas scavenging system (Temel SA, Valencia, Spain)	NA
Spencer EM[22]	1992	Servo 900B + Isoflurane Vaporizer 952	Cardiff Aldasorbers (NorVap, North Yorkshire, United Kingdom)	Isoflurane $115.10 for 24 h
Steurer MP[23]	2012	AnaConDa	A CONTRAfluran active charcoal filter (ZeoSys GmbH, Berlin, Germany) was used on the expiratory valve of the ventilator to minimize environmental contamination with sevoflurane.	NA

Abbreviations: ICU: Intensive Care Unit; NA: not available.

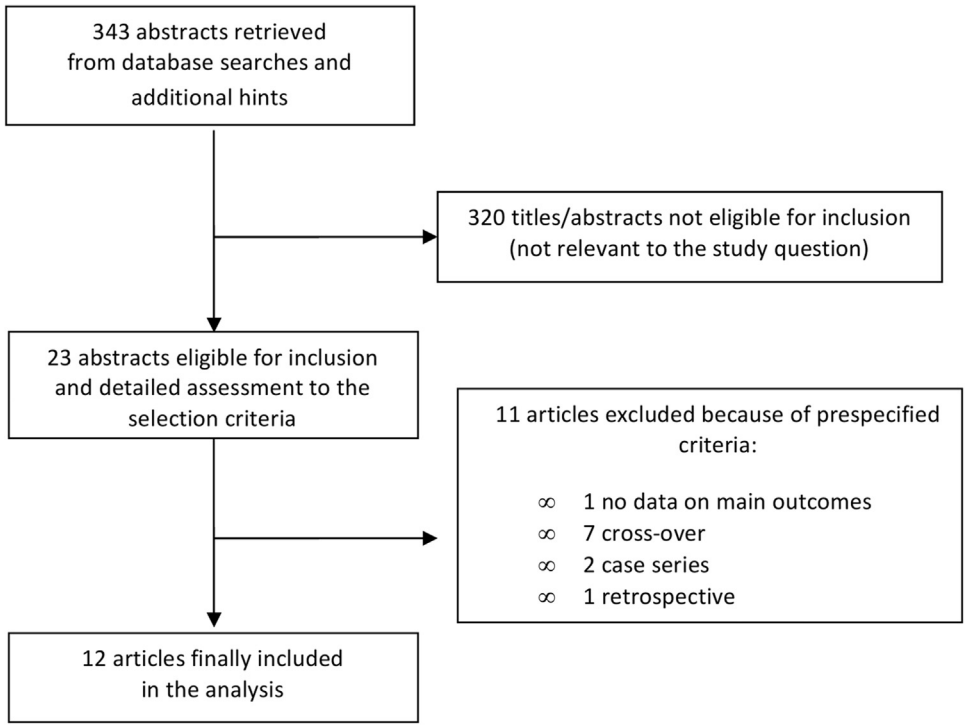

Fig 1. Flowchart used to select the final 12 manuscripts.

proved, with sufficiently robust evidence, that the use of volatile agents could help reduce the extubation time of mechanically ventilated patients, both in post-cardiac surgery and general medical/surgical ICU settings compared with patients who received standard continuous infusion of propofol or midazolam. The implications of these findings can be considered extremely important because early extubation can expedite the ICU discharge and the overall length of hospital stay, thus resulting in a clear cost savings. Nonetheless, no differences in the lengths of ICU or hospital stay and the mortality rate were found.

Several studies suggested the superiority of inhaled anesthetics for sedation in ICU patients compared with intravenous agents because inhaled anesthetics improve cognitive recuperation and memory scores after sedation.[15,17,22,27-29] Notably, inhalation anesthetics allow a shorter and more "predictable" emergence time; it has been shown that the end-tidal fraction of volatile anesthetics, which is monitored easily, can provide a good indication of a drug's concentration in the target organ.[30] The favorable pharmacokinetics of inhaled anesthetics and their stable washout time also may be useful for patients requiring both daily neurologic assessment and MV. Clinical positive experience with different inhaled agents has been reported in the last 2 decades, both in adults and children,[8,31-33] and several reviews have been published on this topic.[12,34-38]

In other settings, such as the perioperative period of cardiac surgery, volatile agents have improved clinically relevant outcomes, with a possible reduction in mortality in patients

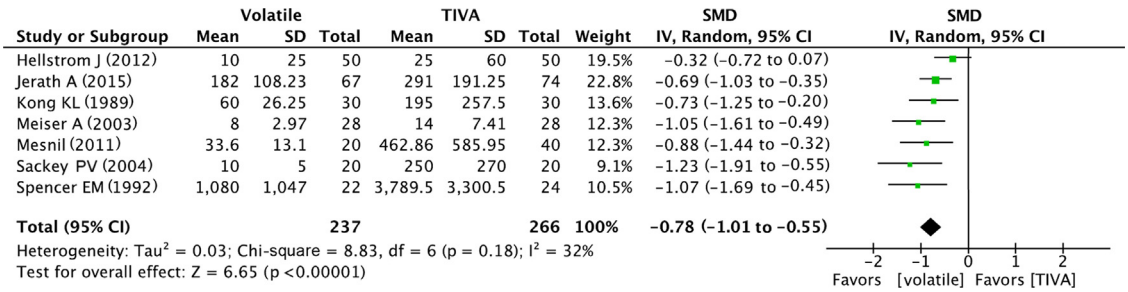

Fig 2. Forest plot for time to extubation. The plot displays the study, sample size, standardized mean difference (SMD), confidence interval (CI), and p value. The *square* shown for each study is the mean difference for individual trials, and the corresponding *horizontal line* is the 95% CI. The *diamond* is the pooled SMD with the CI. The different sizes of squares indicate the weight of the individual trials in the analysis, taking into account sample size and standard deviations. TIVA, total intravenous anesthesia.

Table 4. Outcomes and Sensitivity Analysis

Outcome	Included Trials (n)	Patients Receiving Volatiles (n)	Control Patients (n)	SMD OR RR	95% CI	p Value for Effect	p Value for Heterogeneity	I^2 (%)
	12	452	482					
Time to extubation (h)	7	237	266	−0.78	−1.01 to −0.55	<0.0001	0.18	32%
Post-cardiac surgery ICU	2	139	148	−0.64	−1.01 to −0.27	0.0007	0.12	54%
General ICU	4	92	114	−0.94	−1.23 to −0.65	<0.00001	0.67	0%
Sevoflurane	2	70	90	−0.51	−0.83 to −0.19	0.002	0.11	61%
Isoflurane	3	72	74	−0.96	−1.31 to −0.62	<0.00001	0.48	0%
Propofol as comparator	4	165	192	−0.66	−0.88 to −0.45	<0.00001	0.15	43%
Midazolam as comparator	3	72	74	−0.96	−1.31 to −0.62	<0.00001	0.48	0%
Sensitivity (including only studies with low or medium risk of bias)	4	118	138	−0.73	−0.99 to −0.47	<0.00001	0.05	61%
Sensitivity (removing 1 study at time)				All 95% CIs of SDM <0 and p < 0.05				
ICU stay, days	6	228	266	−0.21	−0.48; 0.06	0.13	0.06	53%
Hospital length of stay, days	4	141	164	−0.40	−0.86; 0.05	0.08	0.01	73%
Mortality	9	308	340	1.52	0.69; 3.36	0.30	0.94	0%
Sensitivity (removing 1 study at time)				All 95% CIs of SDM<0 and p < 0.05				

Abbreviations: CI, confidence interval; ICU, intensive care unit; NA, not applicable; OR, odds ratio; RR, relative risk; SMD, standardized mean difference.

undergoing coronary artery bypass grafting.[5] In addition to preconditioning, active postconditioning also has been described and its role still is the object of study, especially in patients with or at high risk of coronary artery disease.[39] A recent meta-analysis also suggested that volatile anesthetics may provide renal protection in this surgical setting.[40] In regard to toxicity of the degradation products of halogenated anesthetics, different studies have shown that there is a rapid, transient increase in the measured serum fluoride concentration, with no clinical relevance and no deterioration of renal function (measured inorganic fluoride levels were set well below the renal toxic level), even after prolonged application.[41,42] Moreover, different studies have examined pollution of volatile agents and have demonstrated that these agents can be administered safely also in the ICU setting using a simple scavenging system, which allows the environmental concentrations of the volatile agent to be maintained below the harmful threshold, thus guaranteeing the safety of healthcare workers.[43,44]

Inhalation anesthetics can be considered a feasible and safe alternative to standard intravenous sedation of critically ill patients in the ICU setting. In particular, they can play a life-saving role in case of severe diseases, such as refractory asthma and epilepsy.[6-8] In an experimental asthma animal model, volatile agents demonstrated effectiveness in reducing airways resistance, atelectasis, and bronchoconstriction; moreover, sevoflurane down-regulates inflammatory, fibrogenic, and angiogenic mediators and modulates oxidant-antioxidant imbalance.[6] Several studies and case reports have proven the beneficial clinical effects of inhaled anesthetics for asthmatic patients, especially children (see Supplemental Material). Although asthma is far less common than it was 20 years ago, some relatively recent estimates reported that 1 to 2 million patients per year present to emergency departments for asthma-related symptoms.[45] Moreover, although rare, death from asthma is estimated to be around 5,000 cases per year in the United States.[46]

Because technology supports progress in science, some specialized industries have developed new, easy-to-use, safe devices that allow for sedation with inhaled anesthetics for use with ICU patients. Both AnaConDa (Sedana Medical, Kildare, Ireland) and MIRUS (Technologie Institut Medizin GmbH, Andernach, Germany), for example, are electronically controlled anesthesia gas delivery systems that can be used in all common ventilation circuits with environmental scavengers. Furthermore, ventilators for ICUs also now are available that include in their structure the possibility of administering volatile agents.

Study Limitations

Limitations of meta-analysis are well-known,[47,48] and the authors are aware that this study included small, medium-low quality randomized clinical trials with high heterogeneity of settings. In fact, only 1 of the included studies was blinded, which could have introduced biases in the interpretation of results. Nonetheless, this was the first meta-analysis on the use of halogenated anesthetics in the ICU setting and, according to randomized evidence, demonstrated the superiority of volatile agents in reducing time to extubation of critically ill patients compared with standard care performed with intravenous

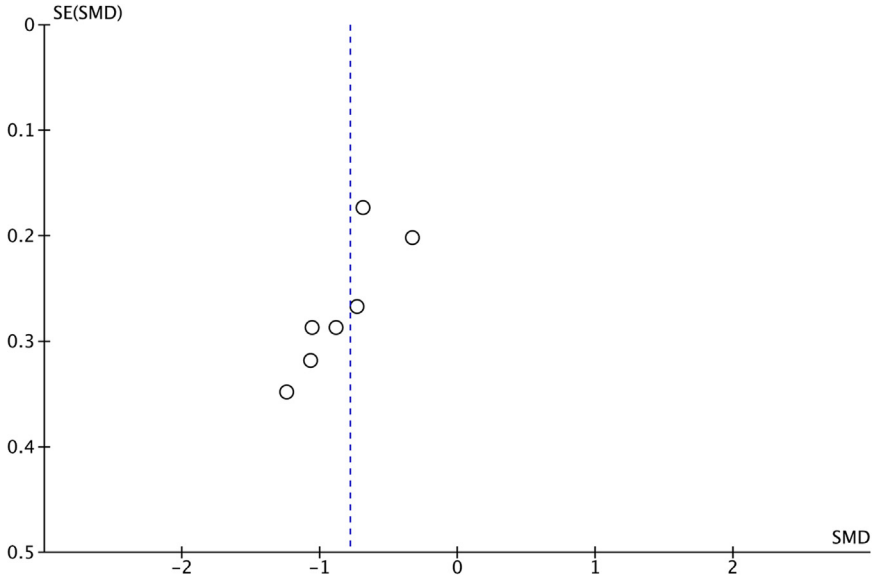

Fig 3. Funnel plot for time to extubation. SMD, standardized mean difference.

sedatives. Nonetheless, the authors acknowledge that the statistically significant reduction in time to extubation might have little clinical relevance. In fact, in daily clinical practice, when working with drugs such as midazolam or propofol, physicians often coordinate the termination of the drug to allow for extubation at an expected time. Another limitation of this study was that most of the included studies did not report data on relevant outcomes such as cognitive dysfunction, delirium, major morbidity, and/or mortality. In addition, no data on rescue sedative drugs in cases of inefficient/insufficient sedative levels in different situations were available in the original manuscripts. Moreover, comparisons with other intravenous drugs, such remifentanil and dexmedetomidine, are lacking. In fact, dexmedetomidine reduced ICU stay, time to extubation, and the incidence of delirium in critically patients.[49,50]

CONCLUSIONS

Volatile anesthetics reduce time to extubation in medical and surgical patients admitted to the ICU according to a meta-analysis of randomized trials. Large, high-quality randomized clinical trials are mandatory to confirm these positive results. Further research should focus on long-term clinically relevant outcomes such as delirium, cognitive dysfunction, major morbidity, and mortality.

APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1053/j.jvca.2016.02.021.

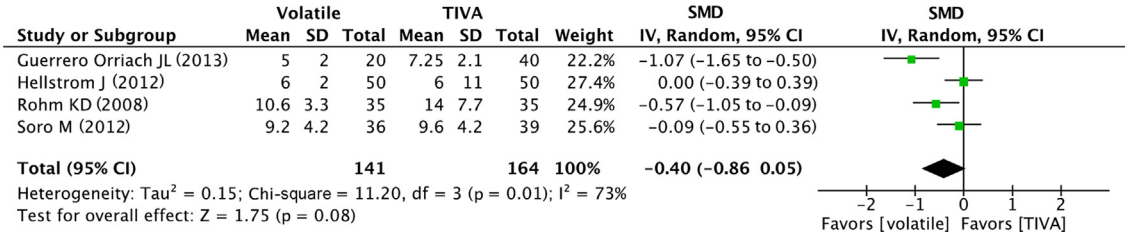

Fig 4. Forest plot for hospital length of stay. The plot displays the study, sample size, standardized mean difference (SMD), confidence interval (CI), and p value. The *square* shown for each study is the mean difference for individual trials, and the corresponding *horizontal line* is the 95% CI. The *diamond* is the pooled SMD with the CI. The different sizes of squares indicate the weight of the individual trials in the analysis, taking into account sample size and standard deviations. TIVA, total intravenous anesthesia; SMD, standardized mean difference.

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