# 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