SPECIAL ARTICLES

DOI: https://doi.org/10.5114/ait/207183

Volatile anesthetics in the intensive care unit

Alexander Morrison-Nozik, Marcin Wąsowicz

Department of Anesthesia and Pain Medicine, Toronto General Hospital, Toronto, ON, Canada

Abstract

The use of volatile anesthetics as an alternative sedation modality in the intensive care unit (ICU) has gained traction over the last several years. Volatile agents such as sevoflurane and isoflurane possess favorable pharmacokinetic and pharmacodynamic properties that make them suitable choices for titration of sedation in patients requiring mechanical ventilation. Several studies have continued to demonstrate their efficacy and safety particularly when assessing wake-up times and times to extubation in contrast to various intravenous sedatives. Leveraging the pharmacodynamic properties of the volatile agents may also be beneficial in certain disease states. As there are devices currently available to enable delivery of volatile anesthetics to patients in the ICU, ongoing studies exist to determine how to best use this sedation modality. This review outlines the recent evidence and discusses perspectives on volatile-based sedation for critically ill patients.

Key words: volatile anesthetics, sedation, medications, mechanical ventilation, intensive care.

Anaesthesiol Intensive Ther 2025; 57: e165–e169

Received: 21.05.2025, **accepted:** 15.06.2025

CORRESPONDING AUTHOR:

Prof. Marcin Wąsowicz, Department of Anesthesia and Pain Medicine, Toronto General Hospital, Toronto, ON, Canada, e-mail: Marcin.Wasowicz@uhn.ca

Providing effective sedation in the intensive care unit (ICU) is a fundamental practice that requires constant titration depending on the clinical needs and status of each individual patient. While providing sedation is an important aspect of ICU care, whether it be in the long or short term, closely monitoring and following a patient's neurologic status off sedation is equally important. Current practice favors the use of intravenous medications such as propofol, dexmedetomidine, benzodiazepines, and opioids, to provide sedation, anxiolysis, analgesia, and amnesia. These agents are often administered as a continuous infusion and/or a bolus depending on the clinical scenario. Despite these medications being the mainstay for sedation in mechanically ventilated patients and for procedural sedation in the ICU, they are often associated with adverse hemodynamics, tolerance, delirium, tachyphylaxis, or withdrawal.

While still a relatively safe option, the adverse effects of using continuous propofol sedation in the ICU have been known to be associated with decreased systemic vascular resistance, hypertriglyceridemia, and propofol infusion syndrome [1, 2]. Likewise, with dexmedetomidine, despite its favorable use in the ICU with hyperactive delirium and minimal effects on ventilation, it is associated with hypotension, bradycardia, and tachyphylaxis [3, 4]. Benzodiazepines on the other hand, are associated with prolonged ICU stay, increased incidence of delirium, prolonged wake-up times, and dependence [5]. Thus, it is important to emphasize that other agents may be warranted for optimal delivery of sedation in the ICU setting.

Over the last 20 years there is emerging evidence that use of volatile agents for sedation in the ICU may be a favorable alternative in certain circumstances [6–10]. Some of their properties make them "an ideal" sedatives. The focus of this review is to highlight volatile anesthetic use as an alternative modality to sedation in mechanically ventilated patients.

PROPERTIES OF VOLATILE AGENTS

The most common inhaled volatile agents used for anesthesia and sedation are sevoflurane and isoflurane. Desflurane is not routinely used due to its high cost and need for a particular vaporizer given its physical properties. The pharmacokinetics and pharmacodynamics of volatile anesthetics have previously been reviewed in further detail [6]. How volatile anesthetics produce their anesthetic effects is suggested to be primarily based on modulation of protein-protein interactions at the neuronal synapse which promotes inhibitory action of neurotransmitters [11].

There are many attractive features of these agents that make them suitable and advantageous agents for sedation. Notably, they have rapid onset and rapid offset action as drug clearance is dependent on the patient's effective exhalation or minute ventilation [12]. In patients with impaired hepatic or renal

function prolonged clearance or toxicity has rarely been observed [13, 14]. As seen with use of benzodiazepines and dexmedetomidine, tachyphylaxis, resistance, or withdrawal effects with the use of volatile agents are not observed [15]. Regarding their end-organ effects, volatile anesthetic agents are known to cause bronchodilation [16], possess anticonvulsant effects [17], have the capability to elicit beneficial ischemic pre- and post-conditioning effects in the heart and brain [18, 19], and have been shown to ameliorate inflammatory effects after lung injury [20, 21].

Adverse and undesirable effects are also seen with volatile anesthetic use. These agents can cause a decrease in systemic vascular resistance causing hypotension with increasing dosages. There is also a concomitant increase in cerebral vasodilation when used in higher doses (MAC) increasing cerebral blood flow leading to a rise in intracranial pressure that may have negative implications in patients with hydrocephalus or needing neurocritical care [22]. Malignant hyperthermia is the most feared complication of volatile anesthetic use which causes fever, rigidity, acidosis, and hyperkalemia in patients with genetic predispositions and certain disease states [23]. Lastly, there is accumulating evidence that prolonged sedation with sevoflurane has been associated with nephrogenic diabetes insipidus [24, 25].

EVIDENCE FOR VOLATILE SEDATION

There is continuing and emerging evidence demonstrating the effectiveness of using volatile anesthetics for sedation [8]. The first published study by Sackey *et al*. [26] was a randomized controlled trial demonstrating that prolonged isoflurane use in the ICU is safe and is able to elicit shorter wake-up times when compared to patients receiving a midazolam infusion. When comparing isoflurane to midazolam the authors were able to demonstrate that patients receiving isoflurane had decreased time to begin following commands and subsequent decreased time to extubation. Furthermore, patients receiving volatile sedation did not show significant changes in fluoride concentrations or evidence of renal or hepatic impairment. Notably, no hemodynamic changes were observed in the volatile group.

Other studies support the use of volatile agents in mechanically ventilated patients and have demonstrated non-inferiority to patients receiving sedation with propofol. For example, an open-label, phase 3, multicenter randomized controlled trial showed that isoflurane promotes opioid dose reduction, spontaneous breathing, and decreased emergence times after stopping sedation when compared to patients receiving propofol [27]. When considering patients receiving sedation for prolonged periods such as more than 48 hours, there have also been favorable results. A prospective randomized controlled trial comparing patients who required at least 48 hours of sedation either receiving sevoflurane versus patients who received propofol or midazolam had comparable levels of sedation as compared by their Richmond Agitation-Sedation Scales (RASS) while the hemodynamic effects were unchanged. Furthermore, patients receiving sevoflurane were observed to have a significant decreased time to a spontaneous breathing trial as compared to receiving intravenous anesthetic agents [28].

Given the cardioprotective effects that have been ascribed to volatile agents, some groups have demonstrated their efficacy in sedation post-cardiac surgery. A prospective randomized controlled trial from our center randomized patients to receive post-operative sedation with either propofol or a volatile agent after coronary artery bypass graft surgery [29]. In patients that were administered volatile agents, extubation times were observed to be faster and there were no differences in postoperative pain scores, opioid consumption, RASS score, ICU or hospital length of stay, or mortality when compared with the propofol group. Likewise, Flinspach and others observed similar results in a prospective randomized single center trial when comparing volatile agents and propofol after valve surgery where patients receiving volatiles had faster times to eye opening, ability to follow commands, and extubation, while no differences in complications or hospital stay were observed between groups [30].

There may be additional applications or indications when volatile sedation may be appropriate. A retrospective case series has suggested that use of volatile sedation may be a reasonable approach after cardiac arrest during therapeutic hypothermia after achieving return of spontaneous circulation [31]. This could potentially be in part to leveraging the benefits of volatiles such as facilitation of early neurological assessment due to their pharmacokinetics and the post-conditioning cardioprotective properties that limit ischemia-reperfusion injury. Other areas of interest for volatile sedation in the ICU include use in patients with COVID-19 pneumonia and acute respiratory distress syndrome [20, 32–34], status epilepticus [17], and extracorporeal membrane oxygenation [35].

VOLATILE DELIVERY MODES

Volatile agents are classically known to be administered by anesthesiologists in the operating room for induction and maintenance of anesthesia. As these agents are in a liquid form at room tempe-

rature, they are housed in a vaporizer cassette which is inserted into the anesthetic machine. The anesthetic agents are vaporized by fresh oxygen and air flow through the vaporizer and then delivered to the patient via the ventilator attached to the anesthesia machine. This is not a practical approach in the ICU setting. To enable volatile delivery in the ICU for sedation, a vaporizing device must be used and connected to an ICU ventilator, and its management must be simplified. Additionally, in practical terms, it must not require a constant presence of an anesthesiologist. Several groups have previously described the important considerations for volatile agent delivery in the ICU environment [7, 9].

In contrast to intravenous agents, use of volatile agents in the ICU requires continuous end-tidal monitoring with a sampling line that provides the concentration of the agent with each breath which corresponds to the cerebral concentration (MAC level). This enables the clinician to enable a more precise level of sedation, preventing potential overdose or unfavorable hemodynamic effects. There are indeed vaporizers currently available to connect to modern ICU ventilators that are used. The two most common devices include the Anesthesia Conserving Device (AnaConDa or Sedaconda ACD-L; Sedana Medical, Danderyd, Sweden) and MIRUS (Pall Medical, Dreieich, Germany). As previously described [9], these devices can be connected to any ICU ventilator, possess the capability to re-vaporize exhaled gas for conservation and recycling of the agent, and limits dead space in order to provide lung protective ventilation. There is also the RIVAL (Thornhill Medical, Toronto, Canada) system which is a newer device with no restriction in tidal volumes allowing for more conservative low-flow lung protective ventilation. The AnaConDa or MIRUS devices are placed between the endotracheal tube and Y-piece of the circuit connected to the ventilator. As illustrated in previous work [6, 9], the AnaConDa system allows for the infusion of sevoflurane or isoflurane for vaporization and has a built-in carbon layer allowing for recycling of the expired agent. However, it must be used with a separate analyzer and gas scavenger. Using a MIRUS device allows for titration of end-tidal gas concentration, has an integrated analyzer, and can monitor ventilation settings. Attaching either system to the breathing circuit can increase dead space ventilation by approximately 50 mL.

Additionally, the use of volatile agents do require scavenging to limit exposure to anesthetic gas within the environment in which they are administered. In contrast to the operating room which is designed to limit excess volatile gas, the use of scavenging in the ICU is uncommon. Despite this, volatile agents can still be administered safely in an ICU setting by using a simple scavenging system that conforms to standards in most Western countries [36]. Furthermore, effective scavenging of these agents in an ICU setting has also been proven safe when administered for long term sedation or more than 48 hours [37].

CONCLUSIONS/FUTURE DIRECTIONS

There is emerging evidence that volatile agents are an effective and safe option for delivery of sedation to patients in the ICU setting whether it be in the long or short term. These agents are gaining traction as attractive alternatives to intravenous infusions such as propofol, dexmedetomidine, and benzodiazepines due to their predictable pharmacokinetics independent of renal or hepatic function and allowing for real time monitoring of anesthetic depth and breath-to-breath titration of dosage. Moreover, there appears to be favorability in terms of decreased time to follow commands and extubation in several studies when compared to intravenous sedatives. These findings have been corroborated in a meta-analysis comparing intravenous sedatives to volatile agents demonstrating reduction in times to extubation with no increase in short-term adverse outcomes [38]. However, further studies are warranted in order to determine adverse outcomes such as the evaluation of delirium and cognitive function in volatile versus intravenous agents [39].

In contrast, recent evidence from the SESAR trial has challenged the notion that sevoflurane is an effective alternative for sedation in critically ill patients [40]. Among patients with ARDS, when compared with intravenous propofol sedation, there were fewer number of ventilator free days, decreased 90-day survival, and a higher 7-day mortality was seen in the patient group that received sevoflurane sedation. Additional findings included higher norepinephrine doses, increases in serum lactate, increased acute kidney injury, and increased incidence of nephrogenic diabetes insipidus in patients receiving sevoflurane. Sevoflurane's impact on delirium was not assessed in this trial. While this trial controlled for patients with ARDS only, more evidence will be needed to determine the safety of volatile agents for sedation in other critical illnesses which will better inform decision making for sedation selection.

Despite the potential advantages of using volatile agents for sedation, this modality is not standard of care in ICU centers across North America. Limitations and barriers to the implementation of this sedation modality may be due in part to the multidisciplinary and multispecialty intensivist models in critical

care medicine as these agents are almost exclusively used by anesthesiologists. However, clinical trials are currently underway in the United States, particularly the INSPiRE-ICU trial which will determine the efficacy and safety of volatile agents compared to propofol sedation in patients requiring mechanical ventilation [41]. As more evidence is obtained, future studies are warranted to determine the benefits of volatile sedation in particular subsets of patients and disease states requiring ICU care allowing the intensivist to select the most appropriate modality.

ACKNOWLEDGEMENTS

1. Assistance with the article: None.
2. Financial support and sponsorship: None.
3. Conflicts of interest: None.
4. Presentation: None.

REFERENCES

1. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41: 263-306. DOI: 10.1097/CCM.0b013e3182783b72.
2. Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. Crit Care 2009; 13: R169. DOI: 10.1186/cc8145.
3. Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. Drugs 2015; 75: 1119-1130. DOI: 10.1007/s40265-015-0419-5.
4. Kim CS, McLaughlin KC, Romero N, Crowley KE. Evaluation of dexmedetomidine withdrawal and management after prolonged infusion. Clin Ther 2024; 46: 1034-1040. DOI: 10.1016/j.clinthera.2024.09.006.
5. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018; 46: e825-e873. DOI: 10.1097/CCM.0000000000003299.
6. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Volatile anesthetics. Is a new player emerging in critical care sedation? Am J Respir Crit Care Med 2016; 193: 1202-1212. DOI: 10.1164/rccm.201512-2435CP.
7. Wąsowicz M, Jerath A. Expanding the use of volatile anesthetic agents beyond the operating room. Can J Anaesth 2014; 61: 905-908. DOI: 10.1007/s12630-014-0211-0.
8. O'Gara B, Boncyk C, Meiser A, Jerath A, Bellgardt M, Jabaudon M, et al. Volatile anesthetic sedation for critically ill patients. Anesthesiology 2024; 141: 163-174. DOI: 10.1097/ALN.0000000000004994.
9. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Opportunity knocks? The expansion of volatile agent use in new clinical settings. J Cardiothorac Vasc Anesth 2018; 32: 1946-1954. DOI: 10.1053/j.jvca.2017.12.035.
10. Meiser A, Laubenthal H. Inhalational anaesthetics in the ICU: theory and practice of inhalational sedation in the ICU, economics, risk-benefit. Best Pract Res Clin Anaesthesiol 2005; 19: 523-538. DOI: 10.1016/j.bpa.2005.02.006.
11. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med 2003; 348: 2110-2124. DOI: 10.1056/NEJMra021261.
12. Preckel B, Bolten J. Pharmacology of modern volatile anaesthetics. Best Pract Res Clin Anaesthesiol 2005; 19: 331-348. DOI: 10.1016/j.bpa.2005.01.003.
13. Röhm KD, Mengistu A, Boldt J, Mayer J, Beck G, Piper SN. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: a comparison with intravenous propofol sedation. Anesth Analg 2009; 108: 1848-1854. DOI: 10.1213/ane.0b013e3181a1988b.
14. Taylor B, Scott TE, Shaw J, Chockalingam N. Renal safety of critical care sedation with sevoflurane: a systematic review and meta-analysis. J Anesth 2023; 37: 794-805. DOI: 10.1007/s00540-023-03227-y.
15. Breheny FX, Kendall PA. Use of isoflurane for sedation in intensive care. Crit Care Med 1992; 20: 1062-1064. DOI: 10.1097/00003246-199207000-00027.
16. Mondoñedo JR, McNeil JS, Amin SD, Herrmann J, Simon BA, Kaczka DW. Volatile anesthetics and the treatment of severe bronchospasm: a concept of targeted delivery. Drug Discov Today Dis Models 2015; 15: 43-50. DOI: 10.1016/j.ddmod.2014.02.004.
17. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. Arch Neurol 2004; 61: 1254-1259. DOI: 10.1001/archneur.61.8.1254.
18. Kikuchi C, Dosenovic S, Bienengraeber M. Anaesthetics as cardioprotectants: translatability and mechanism. Br J Pharmacol 2015; 172: 2051-2061. DOI: 10.1111/bph.12981.
19. Li L, Zuo Z. Isoflurane postconditioning induces neuroprotection via Akt activation and attenuation of increased mitochondrial membrane permeability. Neuroscience 2011; 199: 44-50. DOI: 10.1016/j.neuroscience.2011.10.022.
20. Jabaudon M, Boucher P, Imhoff E, Chabanne R, Faure JS, Roszyk L, et al. Sevoflurane for sedation in acute respiratory distress syndrome. a randomized controlled pilot study. Am J Respir Crit Care Med 2017; 195: 792-800. DOI: 10.1164/rccm.201604-0686OC.
21. Englert JA, Macias AA, Amador-Munoz D, Pinilla Vera M, Isabelle C, Guan J, et al. Isoflurane ameliorates acute lung injury by preserving epithelial tight junction integrity. Anesthesiology 2015; 123: 377-388. DOI: 10.1097/ALN.0000000000000742.
22. Oshima T, Karasawa F, Okazaki Y, Wada H, Satoh T. Effects of sevoflurane on cerebral blood flow and cerebral metabolic rate of oxygen in human beings: a comparison with isoflurane. Eur J Anaesthesiol 2003; 20: 543-547. DOI: 10.1017/s0265021503000863.
23. Miranda AD, Donovan LA, Schuster LL, Gerber DR. Malignant hyperthermia. Am J Crit Care 1997; 6: 368-374; quiz 375-376.
24. Kraus MB, Leuzinger K, Reynolds E, Gallo de Moraes A, Smith J, Sharpe EE, et al. Diabetes insipidus related to sedation in the intensive care unit: a review of the literature. J Crit Care 2023; 75: 154233. DOI: 10.1016/j.jcrc.2022.154233.
25. Dupuis C, Robert A, Gerard L, Morelle J, Laterre PF, Hantson P. Nephrogenic diabetes insipidus following an off-label administration of sevoflurane for prolonged sedation in a COVID-19 patient and possible influence on aquaporin-2 renal expression. Case Rep Anesthesiol 2022; 2022: 3312306. DOI: 10.1155/2022/3312306.
26. Sackey PV, Martling CR, Granath F, Radell PJ. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med 2004; 32: 2241-2246. DOI: 10.1097/01.ccm.0000145951.76082.77.
27. Meiser A, Volk T, Wallenborn J, Guenther U, Becher T, Bracht H, et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomised controlled, non-inferiority trial. Lancet Respir Med 2021; 9: 1231-1240. DOI: 10.1016/S2213-2600(21)00323-4.
28. Soukup J, Michel P, Christel A, Schittek GA, Wagner NM, Kellner P. Prolonged sedation with sevoflurane in comparison to intravenous sedation in critically ill patients – a randomized controlled trial. J Crit Care 2023; 74: 154251. DOI: 10.1016/j.jcrc.2022.154251.
29. Jerath A, Beattie SW, Chandy T, Karski J, Djaiani G, Rao V, et al.; Perioperative Anesthesia Clinical Trials Group. Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. Crit Care Med 2015; 43: 1062-1069. DOI: 10.1097/CCM.0000000000000938.
30. Flinspach AN, Raimann FJ, Kaiser P, Pfaff M, Zacharowski K, Neef V, Adam EH. Volatile versus propofol sedation after cardiac valve surgery: a single-center prospective randomized controlled trial. Crit Care 2024; 28: 111. DOI: 10.1186/s13054-024-04899-y.
31. Hellström J, Öwall A, Martling CR, Sackey PV. Inhaled isoflurane sedation during therapeutic hypothermia after cardiac arrest: a case series. Crit Care Med 2014; 42: e161-166. DOI: 10.1097/CCM.0b013e3182a643d7.
32. Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation for COVID-19 pneumonia and ARDS. Intensive Care Med 2020; 46: 1563-1566. DOI: 10.1007/s00134-020-06154-8.
33. Blondonnet R, Simand LA, Vidal P, Borao L, Bourguignon N, Morand D, et al. Design and rationale of the sevoflurane for sedation in acute respiratory distress syndrome (SESAR) randomized controlled trial. J Clin Med 2022; 11: 2796. DOI: 10.3390/jcm11102796.
34. Beck-Schimmer B, Schadde E, Pietsch U, Filipovic M, Dübendorfer-Dalbert S, Fodor P, et al. Early sevoflurane sedation in severe

COVID-19-related lung injury patients. A pilot randomized controlled trial. Ann Intensive Care 2024; 14: 41. DOI: 10.1186/s13613-024-01276-4.
35. Rand A, Zahn PK, Schildhauer TA, Waydhas C, Hamsen U. Inhalative sedation with small tidal volumes under venovenous ECMO. J Artif Organs 2018; 21: 201-205. DOI: 10.1007/s10047-018-1030-9.
36. Pickworth T, Jerath A, DeVine R, Kherani N, Wąsowicz M. The scavenging of volatile anesthetic agents in the cardiovascular intensive care unit environment: a technical report. Can J Anaesth 2013; 60: 38-43. DOI: 10.1007/s12630-012-9814-5.
37. Wong K, Wasowicz M, Grewal D, Fowler T, Ng M, Ferguson ND, et al. Efficacy of a simple scavenging system for long-term critical care sedation using volatile agent-based anesthesia. Can J Anaesth 2016; 63: 630-632. DOI: 10.1007/s12630-015-0562-1.
38. Jerath A, Panckhurst J, Parotto M, Lightfoot N, Wasowicz M, Ferguson ND, et al. Safety and efficacy of volatile anesthetic agents compared with standard intravenous midazolam/propofol sedation in ventilated critical care patients: a meta-analysis and systematic review of prospective trials. Anesth Analg 2017; 124: 1190-1199. DOI: 10.1213/ANE.0000000000001634.
39. Cuninghame S, Jerath A, Gorsky K, Sivajohan A, Francoeur C, Withington D, et al. Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis. Br J Anaesth 2023; 131: 788. DOI: 10.1016/j.bja.2023.07.009.
40. Jabaudon M, Quenot JP, Badie J, Audard J, Jaber S, Rieu B, et al. Inhaled sedation in acute respiratory distress syndrome: the SESAR randomized clinical trial. JAMA 2025; 333: 1608-1617. DOI: 10.1001/jama.2025.3169.
41. Boncyk C, Devlin JW, Faisal H, Girard TD, Hsu SH, Jabaley CS, et al. INhaled Sedation versus Propofol in REspiratory failure in the Intensive Care Unit (INSPiRE-ICU1): protocol for a randomised, controlled trial. BMJ Open 2024; 14: e086946. DOI: 10.1136/bmjopen-2024-086946.