SYSTEMATIC REVIEW

OPEN

Inhaled Volatiles for Status Asthmaticus, Epilepsy, and Difficult Sedation in Adult ICU and PICU: A Systematic Review

Kevin Gorsky, MD[1]

Sean Cuninghame, MD[2]

Kesikan Jayaraj, RN[3]

Marat Slessarev, MD, PhD, FRCPC[2,4]

Conall Francoeur, MD[5]

Davinia E. Withington, BM, FRCA, MRCP(UK)[6]

Jennifer Chen[7]

Brian H. Cuthbertson, MBBS, PhD[1,8,12,13]

Claudio Martin, MD[2]

Martin Chapman, MD, FRCPC[1,8]

Saptharishi Lalgudi Ganesan, MBBS, MD, DM, FACNS[4,9]

Nicole McKinnon, MD, PhD[10]

Angela Jerath, MD, MSc, FANZCA, FRCPC[1,11,12,13]

on behalf of the SAVE-ICU Study Investigators

OBJECTIVES: Inhaled volatile anesthetics support management of status asthmaticus (SA), status epilepticus (SE), and difficult sedation (DS). This study aimed to evaluate the effectiveness, safety, and feasibility of using inhaled anesthetics for SA, SE, and DS in adult ICU and PICU patients.

DATA SOURCES: MEDLINE, Cochrane Central Register of Controlled Trials, and Embase.

STUDY SELECTION: Primary literature search that reported the use of inhaled anesthetics in ventilated patients with SA, SE, and DS from 1970 to 2021.

DATA EXTRACTION: Study data points were extracted by two authors independently. Quality assessment was performed using the Joanna Briggs Institute appraisal tool for case studies/series, Newcastle criteria for cohort/case–control studies, and risk-of-bias framework for clinical trials.

DATA SYNTHESIS: Primary outcome was volatile efficacy in improving predefined clinical or physiologic endpoints. Secondary outcomes were adverse events and delivery logistics. From 4281 screened studies, the number of included studies/patients across diagnoses and patient groups were: SA (adult: 38/121, pediatric: 28/142), SE (adult: 18/37, pediatric: 5/10), and DS (adult: 21/355, pediatric: 10/90). Quality of evidence was low, consisting mainly of case reports and series. Clinical and physiologic improvement was seen within 1–2 hours of initiating volatiles, with variable efficacy across diagnoses and patient groups: SA (adult: 89–95%, pediatric: 80–97%), SE (adults: 54–100%, pediatric: 60–100%), and DS (adults: 60–90%, pediatric: 62–90%). Most common adverse events were cardiovascular, that is, hypotension and arrhythmias. Inhaled sedatives were commonly delivered using anesthesia machines for SA/SE and miniature vaporizers for DS. Few (10%) of studies reported required non-ICU personnel, and only 16% had ICU volatile delivery protocol.

CONCLUSIONS: Volatile anesthetics may provide effective treatment in patients with SA, SE, and DS scenarios but the quality of evidence is low. Higher-quality powered prospective studies of the efficacy and safety of using volatile anesthetics to manage SA, SE, and DS patients are required. Education regarding inhaled anesthetics and the protocolization of their use is needed.

KEYWORDS: critical care; sedation; status asthmaticus; status epilepticus; volatile anesthetics

Inhaled volatile anesthetic agents are widely used in operating rooms to provide safe and effective deep hypnosis for surgery (1, 2). Volatile agents are being used in critical care settings to provide sedation, but widespread use is limited by a lack of familiarity with these agents and specific drug delivery requirements (3, 4). However, adult and pediatric intensivists will consider using inhaled volatiles to "rescue" medical emergencies unresponsive to standard treatments such as status asthmaticus (SA), status epilepticus (SE),

DOI: 10.1097/CCE.0000000000001050

KEY POINTS

Question: Evaluate the efficacy, safety, and feasibility of using inhaled volatile anesthetics for status asthmaticus, status epileptics, and difficult sedation in adult ICU and PICU patients.

Finding: In a systematic review of 116 studies with 755 patients, inhaled volatiles showed good clinical and physiologic improvement in all three medical conditions.

Meaning: Inhaled volatiles provide useful therapeutic properties for managing adult and pediatric critically ill patients with status asthmaticus, status epileptics, or difficult sedation needs.

and patients with high and/or difficult sedation (DS) needs (3).

Inhaled volatile agents possess sedative and antiseizure properties by augmenting central inhibitory gamma-aminobutyric acid (GABAa) pathways (5). Volatile agents also provide therapeutic relief of bronchospasm through the relaxation of bronchial smooth muscle using a variety of mechanisms that include lowering intracellular calcium levels that lead to bronchodilatation (6, 7). SA and epilepticus are severe conditions that may benefit from inhaled volatiles to help improve gas exchange and achieve burst suppression respectively (3). Volatile agents may also manage DS scenarios with resistance to conventional IV sedatives such as patients with coronavirus disease, burns, or illicit drug use. In complex sedation, volatile agents possess several advantages over IV agents including less drug tolerance and better drug titration to a desired depth of sedation using bedside gas monitoring (3, 8, 9). For patients at risk of drug accumulation impacting patient awakening and neurologic assessment (e.g., prolonged infusions, multiple sedatives), inhaled volatiles provide fast clearance through simple pulmonary exhalation with no systemic active metabolites (3, 10, 11). Whether inhaled volatile agents should be used, as first-line therapy for these conditions requires further evaluation. Before further study, this systematic review aims to evaluate the effectiveness, safety, and feasibility of inhaled volatile use for SA, SE, and DS in both adult ICU and PICU patients.

METHODOLOGY

This protocol was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, published and registered with the International Prospective Register of Systematic Reviews CRD42021233083 (12, 13).

Study Eligibility

Inclusion criteria: 1) ventilated adult (≥ 18 yr) or pediatric (< 18 yr) patients and 2) volatiles used for SA and refractory bronchospasm, SE and refractory myoclonic activity/movement disorders, and DS. Patients with DS were defined as those with challenging sedation requirements (i.e., two or more sedative agents and unable to meet sedation target), or expected prolonged sedation greater than 24 hours with switch to, or initial administration of inhaled volatile anesthetic, or concern of adverse effects from or buildup of active metabolites from IV sedatives. Studies in the DS group were not limited by underlying patient diagnosis, 3) volatile agents halothane, enflurane, isoflurane, sevoflurane, and desflurane or inhalational nitrous oxide (given combined use in early studies), 4) general and specialized ICUs (cardiac, burns, neurosurgical, trauma), 5) case reports, case series, observational studies, and trials, and 6) published in English or French from 1970 to 2021.

Exclusion criteria: 1) No clear indication for use of volatile agent, 2) volatiles used for other clinical scenarios (e.g., cardioprotection), 3) older volatiles no longer used (i.e., diethyl ether, chloroform, ethyl chloride, cyclopropane), 4) abstract only, and 5) editorials without original data.

Outcomes

Primary outcome studied the efficacy of volatile agents in the three clinical scenarios as defined by: 1) SA—breaking bronchospasm (i.e., clinical and physical examination improvements, decreased wheeze on auscultation, improved air entry, and/or features of improved compliance with ventilation), improving oxygenation or ventilation parameters, improving lung mechanics, de-escalation of medical therapies and weaning from the ventilator (i.e., reduction in driving pressures for appropriate ventilation); 2) SE—terminating seizure activity defined by the cessation of

epileptiform activity clinically or achieving burst suppression on electroencephalography, and de-escalation of other antiseizure drugs given for burst suppression; and 3) DS—achieving adequate sedation or target sedation score and weaning of other IV sedatives.

Secondary outcomes included assessment of prevolatile ICU care (i.e., adjunctive medications used and time to commence volatile therapy), volatile use (i.e., duration, concentration of inhaled volatile agent and/or minimum alveolar concentration), and postvolatile care (i.e., duration of ventilation and ICU length of stay [LOS]). We assessed safety by including short-term adverse effects during ICU care, for example, cardiovascular (arrhythmias, hypotension, need for vasoactive drug support), ventilation/gas exchange, neurocognitive changes (new-onset seizures, delirium), neurologic changes on neuroimaging, hepatorenal (hepatitis, acute kidney injury, fluoride levels), and other systemic effects (hematological, metabolic, etc.). When available, we recorded longer-term outcomes after hospital discharge, for example, neuropsychiatric or neurocognitive disorders. Feasibility including barriers to volatile implementation was assessed by method (equipment used), presence of a drug protocol, and additional personnel required for volatile drug delivery. Attitudes toward volatile use among practitioners were captured when available. For all included papers, patient characteristics (age, sex), ICU LOS, and mortality were described. Our original protocol aimed to report the severity of illness (e.g., Sequential Organ Failure Assessment) but full-text review revealed this was rarely reported and thus omitted from the results.

Quality assessment was performed using the Joanna Briggs Institute (JBI) appraisal tool for case studies/series (1), Newcastle criteria for cohort and case–control studies (14), and risk-of-bias (Rob 2) framework for randomized controlled trials (RCTs) (15).

Electronic Search

Literature searches were conducted in MEDLINE, Cochrane Central Register of Controlled Trials, and Embase electronic databases, and performed by a medical information specialist trained in search strategies; see **Supplemental Figure 1** (http://links.lww.com/CCX/B309) for search details. Additional studies were identified by cross-referencing review articles, examining references of relevant studies, search "clinicaltrials.gov" (the National Institutes of Health) and World Health Organization International Clinical Trials Registry Platform for unpublished trials. Authors were not contacted for unpublished data.

Study Selection and Extraction

Seven reviewers (K.G., A.J., D.W., M.S., C.F., S.C., and K.J.) screened abstracts. Two independent individuals reviewed all studies and conflicts were resolved by a third reviewer. Full-text editions were obtained for all eligible studies. Data extraction was performed using a standardized extraction tool in Excel and confirmed by a second independent reviewer.

Analysis

Data were stratified by patient group (adult vs. pediatric patients) and diagnosis (S.A., S.E., or D.S.). Continuous data were summarized using median (range) and categorical data using frequency (percentage). No meta-analysis was performed given the lack of randomized data and the low quality of the small patient number within the included studies.

RESULTS

From 4281 studies, the number of reported studies (k)/number of patients (n) meeting study inclusion was 116 of 755 (**Fig. 1**). From 116 studies, 65 examined SA (adult 38/121, pediatric 28/142), 21 SE (adult 18/37, pediatric 5/10), and 30 DS (adult 21/355, pediatric 10/90) (**Supplemental Tables 1** and **2** and **Supplemental References**, http://links.lww.com/CCX/B309) for included studies. Of 116 studies, 69 were case reports, 38 case series, 5 cohort studies, 1 case–control study, and 3 RCTs. Most SA and SE studies were single-patient case reports, whereas adult and pediatric DS were a mix of study types with a median of seven and six patients per study, respectively. Most studies were from academic hospitals in North America (40%) and Europe (32%). The majority of included studies (k = 107) were case reports and series that met appropriate JBI criteria for inclusion were level 4 or low Grading of Recommendation, Assessment, Development and Evaluation quality of evidence (**Supplemental Table 3, *A*** and ***B*,** http://links.lww.com/CCX/B309). The three clinical trials, cohort, and case–control studies showed an overall

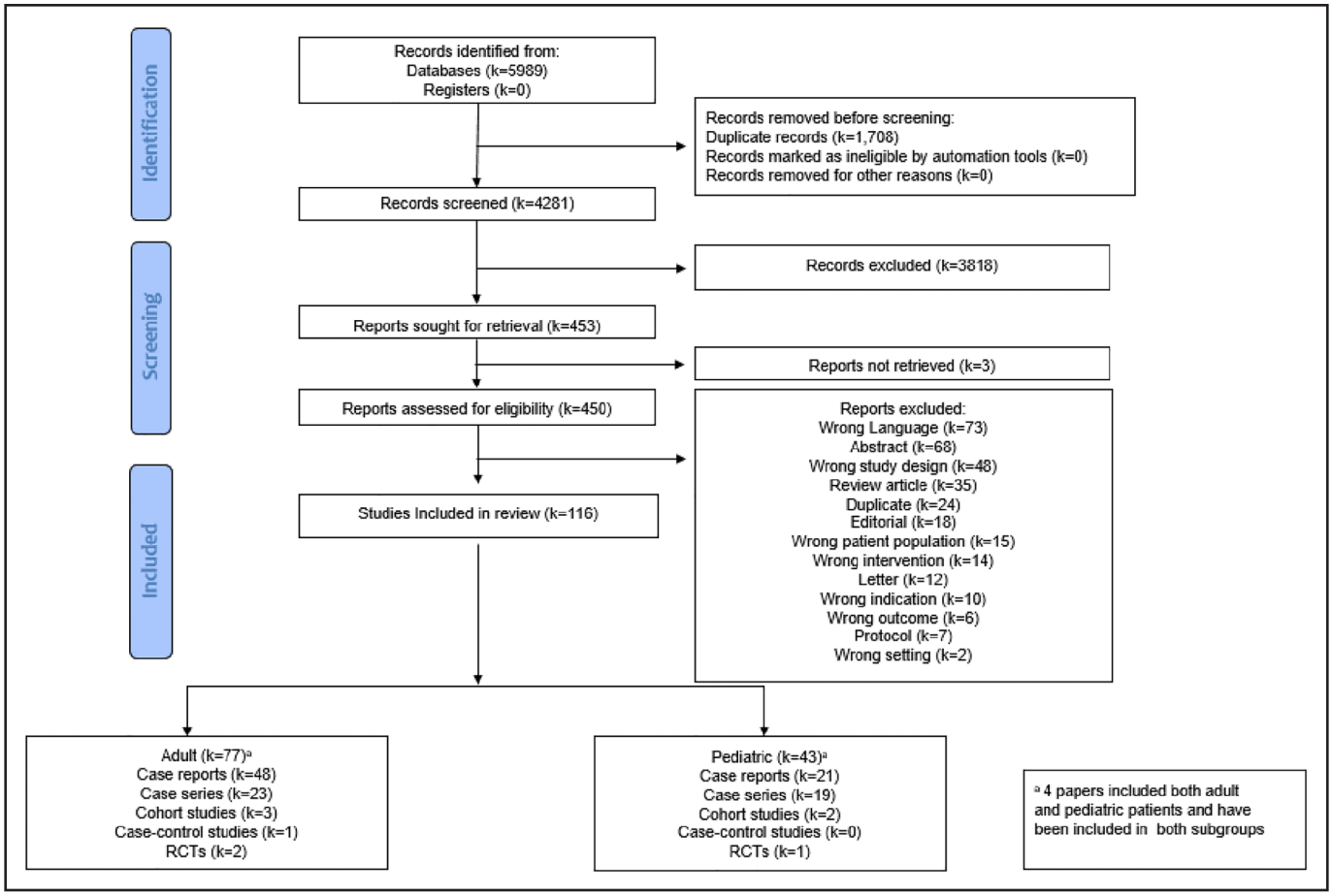

Figure 1. Consort diagram describing number of studies screened and included in the final analysis. RCT = randomized controlled trial.

low Rob 2 (**Supplemental Table 3*C*–*E***, http://links.lww.com/CCX/B309).

Status Asthmaticus

In 38 of 121 (*k*/*n*) adult studies, the median age was 37 years with 64% female patients. Halothane and sevoflurane were the commonest used volatile agents and were initiated within the first ICU admission day for a median of 1 day (**Supplemental Table 2**, http://links.lww.com/CCX/B309). Before initiating volatile therapy, studies reported predominantly using β-agonists (97% of studies), steroids (94%), methylxanthines (65%), and paralytics (63%) (**Table 1**). Median duration of ventilation and ICU LOS were 5 days (0.5–39) and 7 days (0.5–45), respectively, with low ICU mortality (0%). The proportion of patients where volatiles assisted de-escalation of adjunctive therapies was 94% (*k*/*n*, 21/32), improved clinical status in 95% (*k*/*n*, 33/83), reduced ventilator mechanics in 92% (*k*/*n*, 34/100), and better gas exchange in 89% (*k*/*n*, 28/56) (**Supplemental Fig. 2**, http://links.lww.com/CCX/B309). Most adverse events were cardiac issues (e.g., hypotension, arrythmias) particularly with halothane therapy and long-term (weeks–months) myo-neuropathic changes or resolution (**Supplemental Fig. 3**, http://links.lww.com/CCX/B309). Studies failed to report whether adverse events were related to volatile use, other agents, or patient factors.

In 28 of 142 pediatric studies (*k*/*n*), the median age was 8 years with 40% females (Supplemental Table 2, (http://links.lww.com/CCX/B309). Isoflurane (45%) was the commonest agent started within the first ICU admission day and maintained for a median of 1.5 days (0.05–16). Most children also received β-agonists and steroid therapy (Table 1). The proportion of patients where volatile anesthetics assisted de-escalation of adjunctive therapies was 80% (*k*/*n*, 23/45), improved clinical status 95% (*k*/*n*, 24/63) and ventilator mechanics in 97% (*k*/*n*, 25/94), and better gas exchange in 97% (*k*/*n*, 26/95) (Supplemental Fig. 2, http://links.lww.com/CCX/B309). Clinical improvement was seen within a median time of 1 hour (0.1–144) after commencing volatile therapy. The median duration of

TABLE 1.
Adjunctive Medications and Therapies Used Before Initiating Volatile Anesthetic

Adjunctive Medications Used Before Volatile Anesthetic	Percent of Studies (%)	*k*/*n*	Percent of Studies (%)	*k*/*n*
	Adult		Pediatric	
	Status Asthmaticus		Status Asthmaticus	
Methylxanthines	65	35/117	86	28/142
Heliox	14	36/118	7	28/142
Beta-agonists (inhaled/IV)	97	35/117	100	28/142
Steroids (IV/oral/inhaled)	94	35/117	96	28/142
Anticholinergics	32	35/117	39	28/142
Ketamine	32	35/117	50	28/142
Magnesium	38	35/117	43	28/142
Antibiotics	38	35/117	30	27/141
Paralysis	63	36/118	50	26/140
Other[a]	95	21/67	100	11/34
	Status Epilepticus		Status Epilepticus	
Antiepileptics	89	18/37	100	5/10
Benzodiazepines (bolus)	94	17/30	80	5/10
Benzodiazepines (infusion)	33	15/19	40	5/10
Ketamine	20	15/19	40	5/10
Propofol	38	16/26	20	5/10
Barbiturate[b]	100	17/30	100	5/10
Other[c]	100	7/13	100	3/5
	Difficult Sedation		Difficult Sedation	
Propofol	75	16/238	60	10/90
Benzodiazepines	94	16/238	80	10/90
Ketamine	33	15/166	40	10/90
Opioids	73	15/178	100	10/90
Dexmedetomidine	23	13/124	30	10/90
Antipsychotics	15	13/124	10	10/90
Propranolol	0	13/124	0	10/90
Barbiturate	8	13/124	20	10/90
Other[d]	100	4/19	100	6/69

k = number of studies; *n* = number of patients.

[a]Other interventions include propofol (*k* = 4), bicarbonate (*k* = 5), additional IV beta-agonist (*k* = 9), hypothermia (*k* = 1), bronchoalveolar lavage (*k* = 2), benzodiazepines (*k* = 12), cromolyn (*k* = 2), opioids (*k* = 10), digitalis (*k* = 1), gamma-hydroxybutyrate barbiturate (*k* = 2), and extracorporeal membrane oxygenation (*k* = 1).

[b]Barbiturates included thiopentone and phenobarbitone.

[c]Other interventions include local anesthetics (*k* = 3), opioids (*k* = 1), paraldehyde (*k* = 3), paralytics (*k* = 2), etomidate (*k* = 1), steroids (*k* = 2), ketogenic diet (*k* = 1), and IV immunoglobulins (*k* = 1).

[d]Other interventions include clonidine (*k* = 3) various paralytics (*k* = 6) and epidural (*k* = 1).

ventilation and ICU LOS were 4 days (0.3–38) and 7 days (2–30), respectively. Cardiac events were the commonest complication (35% patients, *k*/*n*, 26/140) followed by other events such as raised fluoride levels and acute kidney injury (Supplemental Fig. 3, http://links.lww.com/CCX/B309).

Status Epilepticus

In 18 of 37 *(k/n)* adult studies, the median age was 32 years with 45% females. Patients spent a median (range) of 4 days (1, 2–7) in the ICU before commencing volatile therapy, which lasted for 3 days (0.2–34). Studies administered multiple antiseizure medications before volatiles including barbiturates (100%), benzodiazepines (94%), and antiepileptics (88%) (Table 1). Most patients (78%) received isoflurane therapy. Volatiles prevented seizure recurrence in 54% of patients (*k/n*, 16/28), achieved de-escalation of other therapies in 62% (*k/n*, 17/29), aided burst suppression in 100% (*k/n*, 9/18), clinical or epileptiform improvement in 95% (*k/n*, 16/22), and 89% (*k/n*, 12/18), respectively. The median (range) time to volatile efficacy was 0.1 hours (0.1–0.25) (*n/k*, 6/6). The most frequently reported adverse events were cardiac complications (i.e., hypotension and arrythmias) in 77% of patients (*k/n,* 14/30). Overall, ICU mortality was low (median 0%) with long ICU stays (median 50 d).

In 5 of 10 pediatric studies (*k/n*) the median age was 5 years with 73% females. Isoflurane was the most common agent in 80% of patients. The median (range) ICU time before initiating volatile therapy was 20 days (reported in 1 study) and used for 3 days (2–85). Pediatric patients also showed a high use of barbiturates, benzodiazepine but a lower use of ketamine and compared with adult SE patients (Table 1). Like adults, ICU mortality was low (median 0%), with long ICU LOS at 31 days (5–81). The proportion of patients where volatiles were effective at preventing seizure recurrence was 60% (*k/n*, 5/10), achieved de-escalation of other therapies in 40% (*k/n*, 5/10), burst suppression in 86% (*k/n*, 3/10), clinical and EEG improvement in 90% (*k/n*, 5/10) and 100% (*k/n*, 5/10) respectively. A single study reported clinical benefits within an hour of initiating therapy. Cardiac complications were the most frequently reported adverse events (86% patients, *k/n* 3/7), followed by neurologic complications (33% patients, *k/n* 3/3) such as neurophysiologic changes consistent with neuron loss, motor and cognitive deficits, and persistent low consciousness levels (Supplemental Fig. 3, http://links.lww.com/CCX/B309).

Difficult Sedation

In 21 of 355 adult studies (*k/n*), the median age was 55 years with 34% female adults. This cohort included medical-surgical patients who required sedation for greater than 24 hours with various diagnoses including burns, postcardiac arrest therapeutic hypothermia, extracorporeal circuits, and COVID-19. The median (range) duration of ICU stay before starting volatiles was 3 days (0–17). Most patients (76%) received isoflurane for a median of 4 days (0.5–32). The commonest adjunct sedatives were propofol, benzodiazepines, and opioids before commencing volatiles (Supplemental Table 2, http://links.lww.com/CCX/B309). The median ICU mortality was 11% (0–100%), duration of ventilation of 18 days (1.5–46), and LOS of 25 days (2–46) (Supplemental Table 2, http://links.lww.com/CCX/B309). Volatiles were efficacious at achieving de-escalation of adjunct sedatives in 90% of patients (*k/n*, 6/40), improved ventilator synchrony in 60% (*k/n*, 1/5), clinical status in 54% (*k/n,* 7/28), and sedation scores in 82% (*k/n*, 14/204) (Supplemental Fig. 2, http://links.lww.com/CCX/B309). The median time to improvement in any clinical outcomes was 1 hour (0.01–4). The commonest adverse events were cardiac in 43% of patients (*k/n*, 8/122), and longer-term complications like cognitive impairment and nephrogenic diabetes insipidus with sevoflurane (Supplemental Fig. 3, http://links.lww.com/CCX/B309).

In 10 of 90 pediatric studies (*k/n*), the median age was 3 years with 46% females. Median time in ICU before commencing volatiles and duration of volatile use were longer than adult patients at 10 days (4–30) and 8 days (2–32), respectively. The commonest adjuncts used were opioids, benzodiazepine, and propofol (Table 1). Duration of mechanical ventilation and ICU LOS were 10 days (5–60) and 27 days (9–106), respectively (Supplemental Table 2, http://links.lww.com/CCX/B309). The proportion of patients where volatiles achieved de-escalation of adjunctive sedatives was 62% (*k/n*, 7/37), improved ventilator synchrony in 0% (*k/n*, 0/0), clinical status in 89% (*k/n*, 5/25), and sedation scores in 90% (*k/n*, 4/38). Clinical improvement was seen within a median of 2 hours (1–12) after commencing volatiles. Cardiac events were the most frequently reported problem (54% patients, *k/n* = 7/69) followed by neurologic events (e.g., withdrawal, delirium, tremor, hallucinations) (Supplemental Fig. 3, http://links.lww.com/CCX/B309).

Delivery and Implementation

Volatiles were commonly initiated in the ICU with traditional vaporizers or anesthesia machines in SA and SE patients, while miniature vaporizer systems were

more common in DS patients (**Supplemental Table 4**, http://links.lww.com/CCX/B309). There was limited description of delivery processes; only 10–20% of studies described the need for non-ICU (anesthesiology) personnel to support volatile administration and the use of a delivery protocol. Descriptive comments within studies indicated that volatiles worked well for the three conditions with rapid clinical improvement, but staff experienced difficulties accessing anesthesia workstations to deliver agents.

DISCUSSION

To our knowledge, this is the first systematic review summarizing the efficacy, safety, and feasibility of volatile use in the ICU for the conditions of SA, SE, and DS. We purposefully included both adult and pediatric patients given that these diagnoses affect all patients and comparison between age groups highlights similarities and differences in practice between adult and PICUs. Overall, the results showed that volatile use rapidly improved patients' clinical status with the de-escalation of other medical therapies and improvement in physiologic endpoints.

Several reports described adverse events most notably in the cardiovascular, hepatorenal, and neurologic categories. Since the studies were nonrandomized and volatile therapy was used in-extremis to rescue life-threatening emergencies, it remains uncertain whether these complications are attributable to commencing volatile agents, the primary disease process, or other patient-related risk factors. Furthermore, we anticipate our cohort may be sicker, as evidenced by the longer ICU stays (7 d SA, up to 50 d in SE) compared with the usual median stay of 1.5–1.7 days in large cohort studies (16, 17). These results should also be taken into context with randomized clinical trial data that investigated volatile agents in ICU patients (18–23). These trials administered volatile agents for hours to days and showed good safety profiles with equivalent hemodynamic profiles, vasoactive drug use, and hepatorenal function compared with IV sedatives. Adult trials have shown fluoride (a constituent of volatile agents), increases in blood plasma with longer use, but this has not been associated with nephrotoxicity (19, 22). Several studies noted volatile use was associated with nephrogenic diabetes insipidus. This is a rare complication, particularly of sevoflurane use through the potential lowering of renal aquaporin-2 receptors that help to concentrate urine (24, 25). Evidence examining the neurocognitive and long-term effects of ICU volatile use is limited, but current data show equivalent effects on ICU delirium (22, 26).

To maximize the breadth of this review, we spanned five decades of literature that have seen changes in volatile drugs and delivery systems. Earlier studies were more likely to use halothane with anesthetic workstations or in-line vaporizers with a ventilator. Contemporary studies use sevoflurane and isoflurane with miniature vaporizer technologies designed for volatile delivery outside operating rooms (3, 23, 27). Despite our wide time frame, the information gained on volatile implementation remains relevant, as these agents are infrequently used by intensivists. Several reasons may underpin the low utilization of these agents including a lack of familiarity with the pharmacology of these agents, managing drug titration, additional equipment, and personnel needs. Although our included studies under-report the challenges of implementing volatiles, the use of drug protocols and multidisciplinary training of ICU teams may safeguard the use of these agents and delivery systems as noted in larger studies (21, 22, 28).

To date, most clinical trials examining the use of volatiles in the ICU have shown good quality of sedation with potentially better outcomes like faster patient awakening, extubation times, lower inflammation, and opioid use (11, 23, 29). There are also several ongoing clinical trials that will continue to grow evidence in this area (NCT05327296, NCT05312385, NCT04341350, NCT04415060, etc.). Our results show volatiles were commenced on average 1–3 days after ICU admission, with clinical benefits apparent within a few hours of initiation. Hence, this review supports considering the clinical benefits of volatile anesthetics earlier in the care of ventilated SA, SE, and DS patients. Further research in these medical conditions is needed to evaluate if earlier volatile use translates into better outcomes like shorter mechanical ventilation, ICU and hospital stays, and improved survival.

We acknowledge several notable limitations. First, the review is built on collating lower-quality evidence using largely case reports and series. A lack of clinical trials in the three conditions likely reflects the complexity of conducting research during these emergency situations. Case reports/series data are highly

variable in their reporting approach, outcomes, and content. To ensure transparency, we reported on outcomes that are clinically relevant and well described within this literature, including both the number of studies and patients for each endpoint, and assessed the Rob 2 using current measurement tools for different study types. However, we identify that underreporting impacts the depth of our results. In addition, the actual effectiveness of volatiles may be less as case reports and series are inherently associated with a publication bias. Halothane—an older volatile agent that is no longer used in many countries was included in this review. This was to ensure the inclusivity of an agent that is still available in some countries and may be useful in resource-limited settings. Although we wanted to summarize precise oxygenation, ventilator, and sedation target parameters for SA patients, it was not possible to do this given the heterogeneous or incomplete reporting of these variables in primary studies.

CONCLUSIONS

Volatile anesthetics may provide effective treatment in patients with SA, SE, and DS scenarios but current evidence is low quality. Future work should examine whether earlier use of volatile agents for SA, SE, and DS scenarios improves patient and health system outcomes.

ACKNOWLEDGMENTS

The authors thank London Health Sciences Centre Clinical Librarian, Alla Iansavitchene for her assistance with performing the literature search.

1 *Department of Anesthesiology and Pain Management, University of Toronto, Toronto, ON, Canada.*

2 *Department of Medicine, University of Western Ontario, London, ON, Canada.*

3 *Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*

4 *Western Institute for Neuroscience, Western University, London, ON, Canada.*

5 *Department of Pediatrics, Laval University Faculty of Medicine, QC, Canada.*

6 *Department of Anesthesiology, McGill University Faculty of Medicine, Montreal, QC, Canada.*

7 *Department of Medical Biophysics, University of Western Ontario, London, ON, Canada.*

8 *Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

9 *Department of Pediatrics, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada.*

10 *Department of Critical Care Medicine, The Hospital for Sick Children, Toronto, ON, Canada.*

11 *Cardiovascular Program, ICES, Toronto, ON, Canada.*

12 *Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada.*

13 *Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

The SAVE-ICU Study Investigators are as follows: Sunnybrook Health Sciences Centre: Martin Chapman, Damon Scales, Julie Nardi, Beth Linseman, Phil Lau, Boris Yakubov, and Eily Shaw; Centre hospitalier de l'Universite de Montreal (CHUM), Montreal, Canada: Francois Carrier, Emmanuel Charbonney, Michaël Chassé, Martin Girard, Antoine Halwagi, Guillaume Plourde, and Han Ting Wang; Centre hospitalier universitaire de Sherbrooke (CHUS): Frédérick D'Aragon, Maxime Tissot-Therrien, François Lamontagne, Dominique Bérard; Centre intégré universitaire de santé et de services sociaux du Nord-de-Ille-de-Montréal (Sacre Coeur): Yiorgos Alexandros Cavayas, Martin Albert, Francis Bernard, Karim Serri, David Williamson, Virginie Williams, Patricia Martinez Barrios, and Sabrina Araujo De Franca; Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec City, Canada: Etienne J. Couture, Adreanne Côté, Mathieu Simon, Pierre-Alexis Lépine, Dave Gleeton; London Health Sciences Centre: John Basmaji, Marat Slessarev, Ahmed Hegazy, Tracey Bentall, and Eileen Campbell; Michelle Stephens; Tim Winterburn; McGill University Health Centre: Roupen Hatzakorzian, Kosar Khwaja, Peter Goldberg, Jason Shahin, and Jeremy Richard Grushka; The Ottawa Hospital: Jonathan Hooper, Sherissa Microys, Hilary Meggison, David Leilipovitz, Jessica Haines, Irene Watpool, Rebecca Porteous, Stephanie Dunster, and Sylvie Bourbonnais; Toronto General Hospital: Ewan Goligher, Lorenzo Del Sorbo, Niall Ferguson, Philip Graham, Michael Long, Tina Yan, Denise Morris, Maria Kobylecky, Hesham Abdelhady, Tina Romagnuolo; Toronto Western Hospital: Bourke Tillman, Ian Randall, and Elizabeth Wilcox; University of Alberta Hospital: Michael Jacka, Oleksa Rewa, Vincent Lau, Sean Bagshaw, and Nadia Baig.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Gorsky was involved in the study concept, design study protocol, data extraction, data analysis, data interpretation, drafting the first article, and critical revision of the article. Drs. Cuninghame, Francoeur, and Withington were involved in data extraction, data analysis, data interpretation, drafting of the first article, and critical revision of the article. Dr. Jayaraj and Mr. Chen were involved in data extraction, data interpretation, and article revision. Dr. Slessarev was involved in the conception, design study protocol, data analysis, data interpretation, drafting first article, and critical revision of the article. Drs. Cuthbertson, Martin, Ganesan, and McKinnon were involved in data interpretation and critical revision of the article. Dr. Jerath was involved in the conception, design study protocol, data analysis, data interpretation, drafting first article, and critical revision of the article.

Funding for this project was supported by Canadian Institute for Health Research (Drs. Jerath, Slessarev, Martin, and Cuthbertson), Government of Ontario (Drs. Jerath, Slessarev, Martin, and Cuthbertson), Alternate Funding Plan, Ministry of Ontario (Drs. Jerath and Cuthbertson), Merit Award, Department of Anesthesiology and Pain Medicine, University of Toronto (Drs. Jerath and Cuthbertson).

Drs. Jerath and Cuthbertson are supported by the Merit Award, Department of Anesthesiology and Pain Medicine, University of Toronto. Drs. Jerath, Slessarev, Martin, and Cuthbertson have received grant funding from the Canadian Institute of Health Research and the Ontario Government.

The authors have no interests to declare related to the production of this manuscript. Drs. Slessarev and Jerath have an ongoing clinical trial examining the effects of inhaled anesthetics on cognitive outcomes in critically ill adults.

For information regarding this article, E-mail: Angela.Jerath@mail.utoronto.ca

REFERENCES

1. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Case Reports. Joanna Briggs Institute 2017. Available at: http://joannabriggs.org/research/critical-appraisal-tools.html. Accessed June 1, 2021
2. Hudson AE, Hemmings HC: 3—Pharmacokinetics of inhaled anesthetics. In: *Pharmacology and Physiology for Anesthesia*. Second Edition. Hemmings HC, Egan TD (Eds). Philadelphia, Elsevier, 2019, pp 44-69
3. Jerath A, Parotto M, Wasowicz M, et al: Volatile anesthetics. Is a new player emerging in critical care sedation? *Am J Respir Crit Care Med* 2016; 193:1202–1212
4. Blondonnet R, Quinson A, Lambert C, et al: Use of volatile agents for sedation in the intensive care unit: A national survey in France. *PLoS One* 2021; 16:e0249889
5. Campagna JA, Miller KW, Forman SA: Mechanisms of actions of inhaled anesthetics. *N Engl J Med* 2003; 348:2110–2124
6. Vaschetto R, Bellotti E, Turucz E, et al: Inhalational anesthetics in acute severe asthma. *Curr Drug Targets* 2009; 10:826–832
7. Mondonedo JR, McNeil JS, Amin SD, et al: Volatile anesthetics and the treatment of severe bronchospasm: A concept of targeted delivery. *Drug Discov Today Dis Models* 2015; 15:43–50
8. Payen JF, Chanques G, Mantz J, et al: Current practices in sedation and analgesia for mechanically ventilated critically ill patients: A prospective multicenter patient-based study. *Anesthesiology* 2007; 106:687–695; quiz 891
9. Mehta S, Burry L, Fischer S, et al; Canadian Critical Care Trials Group: Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med* 2006; 34:374–380
10. Mesnil M, Capdevila X, Bringuier S, et al: Long-term sedation in intensive care unit: A randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med* 2011; 37:933–941
11. Jerath A, Panckhurst J, Parotto M, 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
12. Gorsky K, Cuninghame S, Chen J, et al: Use of inhalational anaesthetic agents in paediatric and adult patients for status asthmaticus, status epilepticus and difficult sedation scenarios: A protocol for a systematic review. *BMJ Open* 2021; 11:e051745
13. Gorsky K, Jerath A, Slessarev M, et al: Rescue use of volatile anaesthetic agents in paediatric and adult ICU patients for status asthmaticus, status epilepticus and difficult sedation scenarios: A systematic review. National Institute for Health Research: International prospective register of systematic review; PROSPERO CRD42021233083. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=233083. Accessed February 11, 2024
14. Wells G, Shea B, O'Connell D, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 11, 2024
15. Sterne JAC, Savović J, Page MJ, et al: RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898
16. Hay A, Bellomo R, Pilcher D, et al: Characteristics and outcome of patients with the ICU admission diagnosis of status epilepticus in Australia and New Zealand. *J Crit Care* 2016; 34:146–153
17. Gupta D, Keogh B, Chung KF, et al: Characteristics and outcome for admissions to adult, general critical care units with acute severe asthma: A secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care* 2004; 8:R112–R121
18. Hellstrom J, Owall A, Sackey PV: Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery. *SCJ* 2012; 46:262–268
19. Rohm KD, Mengistu A, Boldt J, et al: 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
20. Rohm KD, Wolf MW, Schollhorn T, et al: Short-term sevoflurane sedation using the anaesthetic conserving device after cardiothoracic surgery. *Intensive Care Med* 2008; 34:1683–1689
21. Jerath A, Beattie SW, Chandy T, 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
22. Jerath A, Wong K, Wasowicz M, et al: Use of inhaled volatile anesthetics for longer term critical care sedation: A pilot randomized controlled trial. *Crit Care Explor* 2020; 2:e0281
23. Meiser A, Volk T, Wallenborn J, et al; Sedaconda study group: 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 Respirat Med* 2021; 9:1231–1240
24. Morita K, Otsuka F, Ogura T, et al: Sevoflurane anaesthesia causes a transient decrease in aquaporin-2 and impairment of urine concentration. *Br J Anaesth* 1999; 83:734–739

25. Maussion E, Combaz S, Cuisiner A, et al: Renal dysfunction during sevoflurane sedation in the ICU. *Eur J Anaesthesiol* 2019; 36:375–385

26. Cuninghame S, Jerath A, Gorsky K, et al; Sedating with Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects on Ventilatory Parameters and Survival study investigators: Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: A systematic review and meta-analysis. *Br J Anaesth* 2023; 131:314–327

27. Soukup J, Scharff K, Kubosch K, et al: State of the art: Sedation concepts with volatile anesthetics in critically Ill patients. *J Crit Care* 2009; 24:535–544

28. Jerath A, Ferguson ND, Cuthbertson B: Inhalational volatile-based sedation for COVID-19 pneumonia and ARDS. *Intensive Care Med* 2020; 46:1563–1566

29. Jabaudon M, Boucher P, Imhoff E, 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