



The impact of the coronavirus pandemic on sedation in critical care: volatile anesthetics in the ICU

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Purpose of review

To reflect on the impact of the coronavirus pandemic on sedation for mechanically ventilated patients.

Recent findings

Shortages of intravenous sedatives during coronavirus pandemic renewed interest in using widely available inhaled anaesthetics for sedation of critically ill patients. Universally used for surgical anaesthesia, inhaled anaesthetics may offer therapeutic advantages in patients with acute lung injury with good sedation profiles, rapid clearance and lower lung inflammation in pilot trials. However, enabling ICU sedation with inhaled anaesthetics required technological and human resource innovation during the chaos of the global pandemic. The disruption of standard sedation practices is challenging during normal operations, yet pandemic facilitated innovation in this field by fostering cross-discipline collaboration supported by healthcare professionals, hospitals, research institutes and regulators.

Summary

Although further research is needed to establish the role of inhaled anaesthetics in critical care sedation toolkit, maintaining the spirit of innovation ignited during the recent coronavirus pandemic would require ongoing collaboration and streamlining of processes among healthcare, research and regulatory institutions.

Keywords

critical care, intensive care, sedation, ventilator, volatile

INTRODUCTION

As we enter a new phase of the coronavirus pandemic, reflecting on the many lessons and opportunities presented for respiratory care is valuable to prepare for future health crises, and to advance daily clinical care and research endeavours. Over 20% of coronavirus victims suffered from acute respiratory distress syndrome needing lifesaving therapies in ICUs that led to enormous resource and infrastructure challenges. However, the crisis arguably created the perfect incubator for new ideas and accelerated innovation in diagnostics, therapeutics and vaccine development, and implementation. This review provides a reflection on innovation in critical care with a focus on sedation medicine for mechanically ventilated patients.

WHERE WE WERE

COVID-19 pandemic caused an unprecedented worldwide increase in the number of patients requiring respiratory supports including mechanical ventilation. As it often occurs in the times of crisis,

the stress of the pandemic exposed previously concealed bottlenecks in our ability to provide mechanical ventilatory support. Fears of ventilator shortages augmented by the lay press [1] prompted numerous ventilator projects [2], including public-private partnerships and development of open-source ventilators to meet needs in resource-limited settings [3,4]. However, access to ventilators is not sufficient to enable provision of well tolerated mechanical ventilation. Trained personnel, appropriate infrastructure and sedative medications to enable tolerance of

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KEY POINTS

- Inhaled anaesthetics can be used for sedating mechanically ventilating patients and aided the drug shortage crisis seen during COVID-19.
- Early clinical studies have suggested inhaled anaesthetics can provide sedation and possibly other clinical benefits (faster patient awakening, lower pulmonary inflammation).
- Larger trials assessing the efficacy of inhaled anaesthetics on clinically meaningful endpoints are underway.
- Further evaluation of where inhaled anaesthetics fit in the intensivists sedation tool box is required.

invasive mechanical ventilation are all critical components that were in short supply during the pandemic [5].

To address some of these shortages, hospitals and healthcare jurisdictions innovated by utilizing shared skills among healthcare providers to stretch human resources. Creation of supervised ICU physician pyramid-staffing models preserved expert physicians for managing ventilators for the sickest patients, while other healthcare providers took over the rest of the ICU care (e.g. anaesthesiologists, surgeons and interventional radiologists leading airway and procedural teams, and physiotherapists leading dedicated proning teams) [6]. Addressing infrastructure shortages ranged from re-purposing operating rooms and cardiac catheterization laboratories into make-shift ICUs to creation of field, new mobile healthcare units and hospitals [7,8]. However, one of the major challenges that emerged early in 2020, was an acute shortage of intravenous sedatives that are essential for provision of well tolerated mechanical ventilation [9].

The need for sedation is largely guided by two factors: enabling patient tolerance of an endotracheal tube and other invasive procedures, and suppressing a patient's drive to breathe in order to limit tidal volumes and reduce ventilator-induced lung injury. Low supply of sedative agents along with many other drugs stemmed from disruption of drug supply chains in China and India that are pivotal in the production of the active ingredients of many agents [10]. Drug shortages are not a new phenomenon [11], but the universal surge in demand for the same sedative therapeutics, rapid change in drug purchasing patterns, scaling up and shipping problems led to major drug shortage crises [12]. The increased demand for sedatives was in part fuelled by higher sedative needs and longer duration of

sedation in COVID-19 patients compared with other intubated respiratory failure patients [13]. In the absence of innovative solutions, the risk of triaging access to mechanical ventilation was becoming a stark reality [14]. Hospitals and healthcare jurisdictions responded by creating preservation policies to conserve select drugs for ventilated patients, developing pharmacy networks to share resources and avoid drug stockpiling. Although effective in the shorter-term, preservation policies are ultimately limited by available drug supplies and rely on eventual restoration of supply chains given many sedatives are generic agents with few alternative options. Hospitals were also advising practitioners to use second-line or third-line sedatives (e.g. barbiturates). Although these agents induce hypnosis, many alternative (often older) sedatives are associated with common adverse patient outcomes, including prolonged coma, delayed weaning and liberation from mechanical ventilation, hypotension and delirium. Clinicians and hospital leaders were looking for alternative readily available sedative solutions. Given some ICU clinicians' familiarity with using inhaled volatile anaesthetics for medical refractory asthma and seizures, and several published early trials of using these agents for ICU sedation [15–17], COVID-19 created an opportunity to implement a new inhaled anaesthetic sedation pathway [18].

REPURPOSING INHALED ANESTHETICS AS ALTERNATIVE ICU SEDATIVES

Inhaled anaesthetics are readily available alternatives to intravenous agents that can provide sedation to facilitate mechanical ventilation in ICU patients with respiratory failure. These ether-based compounds have reliably provided well tolerated levels of surgical hypnosis in operating rooms worldwide for many decades [18]. Global interest in utilizing inhaled anaesthetics for ICU sedation during the pandemic grew from their wide availability across hospitals, low cost and ability to provide good depth of sedation in patients with high sedative drug requirements. Several ICU trials showed that inhalational based sedation offers several unique advantages over traditional intravenous agents such as benzodiazepines, propofol and opioids [15–17]. Inhalational anaesthetics can be rapidly titrated to standard bedside sedation scores and ventilation mechanics, while also enabling real-time tracking of inspired and expired gas concentrations that correlate with the brain anaesthetic levels [19]. This additional information provides bedside assessment of actual blood levels that individual patients need to meet their sedation

requirements, and enables tracking of sedative elimination during drug weaning, which is a new practice deviation from simple titration of syringe driver pump infusion rates for intravenous sedatives.

Beyond sedation, inhaled anaesthetics have favourable pharmacokinetic and therapeutic properties that could provide unique benefits for critically ill patients. In contrast to intravenous sedatives, inhaled anaesthetics have no active metabolites and are cleared primarily by exhalation, which prevents their build up in settings of hepatorenal dysfunction commonly accompanying critical illness. Inhaled anaesthetics are potent bronchodilators, which facilitates secretion clearance and gas exchange, and they are often used as rescue medications in patients with the most severe forms of respiratory failure such as status asthmaticus [12]. Finally, inhaled anaesthetics may reduce inflammation and pulmonary epithelial injury, which translated into improved oxygenation and a trend towards shorter duration of ventilation in pilot randomized controlled trial of patients with acute respiratory distress syndrome [20].

CHALLENGES WITH USING INHALED ANAESTHETICS IN THE ICU

Although inhaled anaesthetics are used daily in the operating rooms, they were used sporadically in the ICUs for rescue scenarios until recently due to technical and practical challenges. In contrast to anaesthesia machines in the operating rooms, ICU ventilators generally differ by not having integrated vaporizer to support administration of volatile agents, using nonrebreathing circuits instead of circle circuits that wastes exhaled drug, lacking exhaled gas scavenging systems to prevent environmental contamination and lacking carbon-dioxide absorbents to capture exhaled carbon dioxide and minimize re-breathing. Due to these limitations, the delivery of inhaled anaesthetics in the ICUs was usually accomplished by 'borrowing' the anaesthesia machine from the operating room, and the associated oversight of this 'foreign' technology by operating room personnel, such as anaesthesiologists, anaesthesia assistants and operating room respiratory therapists. As a result, most of the ICU staff were not involved in the practical aspects of inhaled anaesthetics delivery.

Recent development of miniature vaporizers and portable scavenging systems have addressed many technical challenges of delivering inhaled anaesthetics in the ICU. Available miniature vaporizers with reflectors that facilitate high efficient recycling (>80%) of exhaled anaesthetics enable delivery of these agents with existing ICU circuits

using lower volumes of volatile agent [18]. Use of portable gas scavenging systems connected to expiratory ports of existing ICU ventilators keeps environmental levels lower than current regulatory requirements, and newer scavenging systems enable recycling of adsorbed agents for patient re-use [21,22].

Although some equipment challenges of delivering inhaled anaesthetics in the ICU have been addressed, the practical challenges related to new drug, device and healthcare process implementation remain. Inhaled anaesthetic drug delivery and titration in the operating room is the prerogative of anaesthesiologists and anaesthesia assistants. Dispensing of intravenous sedatives in the ICU is the purview of pharmacists who are generally unfamiliar with inhaled anaesthetics. Sedation drug delivery and titration of intravenous agents is accomplished by bedside nurses who lack experience in delivering inhaled medications. The need for complex vaporizing and scavenging equipment necessitates participation of respiratory therapists. Whether these same professionals can assume the responsibility to enable the use of inhaled anaesthetics in the ICU was not clear. Successful integration of these agents into clinical practice required disrupting existing workflows and overcoming prevailing intravenous sedation inertia. A challenging task at the best of times, it seemed insurmountable in the midst of a global pandemic that was wreaking havoc on established clinical workflows in overburdened, understaffed and under-resourced hospitals. Fortunately, in Canada, drug repurposing studies using inhaled anaesthetics began several years prior to COVID with early testing of safety, protocol development and understanding delivery implementation [15,23[¶]]. Development of local policies and protocols for drug and equipment management are vital for successful implementation, and will differ depending on national regulations and preferred local hospital practices [23[¶],24^{¶¶}]. Given that modern ICUs are more frequently staffed by intensive care physicians from nonanaesthesia backgrounds, development of new care teams and multidisciplinary staff education are crucial to initiate any new processes of care and tailor use of sedatives to the clinical goals of care for individual patients [24^{¶¶}].

BEYOND THE PANDEMIC: FUTURE OF INNOVATION IN ICU SEDATION

Inhaled anaesthetics have shown to be excellent alternatives at providing effective sedation and overcoming the emergency drug shortages faced during the pandemic. Early trials have shown inhaled

anaesthetics may reduce pulmonary inflammation, improve oxygenation and shorten time to extubation with good end-organ safety [16,20,25]. These studies are largely single-centre, vary in outcome ascertainment and are underpowered to detect clinically important outcomes. Future research must assess whether inhaled agents can positively impact global patient and health systems outcomes such as duration of mechanical ventilation, ICU and hospital stays, mortality and quality of life using standardized instruments at clinically reasonable time points. Cognitive function is an important patient-centred outcome and up to 80% of ventilated adult ICU patients experience delirium in the hospital [26], with many experiencing longer lasting neurocognitive changes [27]. Sedation plays a vital role in neurological recovery and trials are underway to study the effect of inhaled anaesthetics on ICU delirium [28]. Although volatile anaesthetics are relatively inexpensive, there are considerable differences in equipment needed to administer intravenous and inhaled sedation. Well conducted cost-effectiveness analyses would be welcomed by hospital administrators who are considering whether a shift in practice is needed to deliver better value-based care for our critically ill patients in high and middle-low resource practice settings.

Inhaled anaesthetics have shown to be clinically useful in managing patients with severe asthma, seizures and high drug needs with polypharmacy [29,30]. The role of inhaled anaesthetics within ICU sedation toolbox next to benzodiazepines, propofol, opioids, dexmedetomidine and other adjuncts requires deeper consideration. The place of different sedatives and how best to use each agent in patients with varied diagnoses, baseline chronic health status, genotype and risk of neurological decline needs further study. Depth of sedation and ventilation needs vary along the patients' clinical journey. Inhaled anaesthetics have the advantage of real-time monitoring of blood drug concentrations to guide sedation depth and titration. This can be combined with other methods that monitor the effect of sedative agents on patient's brain activity (such as electroencephalography) to optimize patient sedation in the ICU. Enabling personalized sedation using these methods in the future may optimize patient exposure to sedatives, identify when to switch sedative agents and potentially improve clinical outcomes, including ventilator synchrony, neurocognitive outcomes, and duration of ventilation and hospital stay, with the latter preserving ICU capacity and resources during future pandemics and crises. Integrating automated sedation drug choice, delivery, brain monitoring and ventilation strategy into a smart ventilator/monitoring system may be a useful design to aid better

patient-ventilator synchrony, timing of weaning and spontaneous breathing trials.

For conducting research, the pandemic brought pivotal and welcome changes in streamlining administrative processes. Granting agencies, regulatory bodies, ethic boards and legal teams coalesced to support rapid reviews and approvals to expedite innovative work. Sustaining this process is challenging, yet vital to ensure continued need for innovation in critical care and the long timeframe needed to complete many studies. Establishing pathways for transparent private-public partnerships would encourage industry partners to participate in research and innovation projects, while developing evidence-based frameworks for open-source innovation will democratize responsible healthcare delivery [31]. Embedding research into clinical practice can expedite the ability to initiate pragmatic multi-centre trials [32]. In the UK, the National Health Service funds research infrastructure in participating hospitals that includes research nurses and routine collection of key clinical outcomes. In direct demonstration of the effectiveness of such an approach, the RECOVERY trial showed benefit of dexamethasone in hospitalized COVID-19 patients after enrolling over 6000 patients in less than 4 months [33].

The pandemic sought clinicians and researchers to work respectfully at the intersection of disciplines. A strength of our own research group includes clinician-scientist anaesthesiologists, critical care physicians, neuroscientists and allied health with broad methodological expertise. We aimed to instil a spirit of effective collaboration and equity across disciplines to avoid regression to respective academic silos. The interdisciplinary nature of research has and continues to be fostered by our own membership in established national research networks, such as the Canadian Critical Care Trials Group [34].

CONCLUSION

Innovations in new processes of sedation care, administrative regulations, clinical care delivery and collaborative teams have been a positive hallmark of the pandemic. Continuing these changes at an individual, local hospital and wider health system levels will help make this turn-point into a lasting legacy.

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Conflicts of interest

The authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. New York Times. There aren't enough ventilators to cope with the coronavirus. 26th March 2020. <https://www.nytimes.com/2020/03/18/business/coronavirus-ventilator-shortage.html>. [Accessed 22 August 2022].
 2. COVID-19 ventilator projects and resources with FAQs. <https://github.com/Publnv/covid19-vent-list>. [Accessed 20 August 2022].
 3. Mora S, Duarte F, Ratti C. Can Open Source Hardware Mechanical Ventilator (OSH-MVs) initiatives help cope with the COVID-19 health crisis? Taxonomy and state of the art. *HardwareX* 2020; 8:e00150.
 4. Ranney ML, Griffith V, Jha AK. Critical supply shortages: the need for ventilators and personal protective equipment during the Covid-19 pandemic. *N Engl J Med* 2020; 382:e41.
 5. Dave C, Cameron P, Basmaji J, *et al*. Frugal innovation: enabling mechanical ventilation during Coronavirus disease 2019 pandemic in resource-limited settings. *Crit Care Explor* 2021; 3:e0410.
 6. Kumaraiah D, Yip N, Ivascu N, Hill L. Innovative ICU physician care models: Covid-19 pandemic at NewYork-Presbyterian. *N Engl J Med DOI*:10.1056/CAT.20.0158; 2020.
 7. Sunnybrook Health Sciences Centre. Sunnybrook's Mobile Health Unit (MHU). <https://sunnybrook.ca/content/?page=mobile-health-unit> 2021.
 8. BBC. Coronavirus:10 days of hospital building in 60 s. 2 February 2020. <https://www.bbc.com/news/av/world-asia-china-51348297>.
 9. FDA drug shortages. <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm> [Accessed 14 April 2020].
 10. Lau B, Tadrous M, Chu C, *et al*. COVID-19 and the prevalence of drug shortages in Canada: a cross-sectional time-series analysis from April 2017 to April 2022. *CMAJ* 2022; 194:E801–E806.
 11. Chabner BA. Drug shortages: a critical challenge for the generic-drug market. *N Engl J Med* 2011; 365:2147–2149.
 12. Gaudette E. COVID-19's limited impact on drug shortages in Canada. *Can Public Policy* 2020; 1:S307–S312.
 13. Flinspach AN, Brooke H, Zacharowski K, *et al*. High sedation needs of critically ill COVID-19 ARDS patients: a monocentric observational study. *PLoS One* 2021; 16:e0253778.
 14. Netters S, Dekker N, van de Wetering K, *et al*. Pandemic ICU triage challenge and medical ethics. *BMJ Support Palliat Care* 2021; 11:133–137.
 15. Jerath A, Beattie SW, Chandy T, *et al*. Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. *Crit Care Med* 2015; 43:1062–1069.
 16. 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.
 17. Hellstrom J, Owall A, Bergstrom J, Sackey PV. Cardiac outcome after sevoflurane versus propofol sedation following coronary bypass surgery: a pilot study. *Acta Anaesthesiol Scand* 2011; 55:460–467.
 18. 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.
 19. Jerath A, Parotto M, Wasowicz M, Ferguson ND. Opportunity knocks? The expansion of volatile agent use in new clinical settings. *J Cardiothorac Vasc Anesth* 2017; 32:1946–1954.
 20. 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.
 21. Wong K, Wasowicz M, Grewal D, *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.
 22. Pickworth T, Jerath A, DeVine R, *et al*. The scavenging of volatile anesthetic agents in the cardiovascular intensive care unit environment: a technical report. *Can J Anaesth* 2013; 60:38–43.
 23. 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.
- Multicentre pilot trials assessing use of inhaled volatile anesthetics for ICU patients needing sedation for more than 24 h with key data on cardiorespiratory mechanics, sedation goals, antipsychotic drug use.
24. Jerath A, Ferguson ND, Cuthbertson B. Inhalational volatile-based sedation ■ for COVID-19 pneumonia and ARDS. *Intensive Care Med* 2020; 46:1563–1566.
- A review on practical use inhaled anesthetics during COVID-19 with information on implementation and protocols.
25. 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.
 26. Wilcox ME, Girard TD, Hough CL. Delirium and long term cognition in critically ill patients. *BMJ (Clinical research ed)* 2021; 373:n1007.
- An overview of current issues in critical care delirium and longer-term cognition.
27. Honarmand K, Lalli RS, Priestap F, *et al*. Natural history of cognitive impairment in critical illness survivors. A systematic review. *Am J Respir Crit Care Med* 2020; 202:193–201.
 28. Bailly P, Egretreanu P-Y, Ehrmann S, *et al*. Inhaled (inhaled sedation in ICU) trial protocol: a multicentre randomised open-label trial. *BMJ Open* 2021; 11:e042284.
 29. 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.
 30. 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.
 31. Dave C, Sivajohan A, Basmaji J, Slessarev M. Evidence-based considerations for the design of an open-source ventilator: a systematic review. *Crit Care Explor* 2022; 4:e0723.
 32. Murthy S, Fowler RA, Laupacis A. How Canada can better embed randomized trials into clinical care. *Can Med Assoc J* 2020; 192:E928–E929.
 33. Horby P, Lim WS, Emberson JR, *et al*. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384:693–704.
 34. Canadian Critical Care Trials Group (CCCTG). <http://www.ccctg.ca>. [Accessed October 2014].