

# Inhaled Anesthetics for Sedation in ICU: Widening Horizons!

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Sedation is an integral part of therapy for critically ill patients in the intensive care unit (ICU). Analgesia and sedation are prescribed to alleviate pain and anxiety, permit invasive procedures, prevent ventilator asynchrony and reduce stress, and thereby myocardial oxygen consumption.<sup>1</sup> Several International bodies have laid down guidelines that recommend analgo-sedation or analgesia-first sedation in critically ill patients to prevent pain, agitation, and delirium.<sup>2,3</sup> Intravenous sedatives like benzodiazepines (midazolam, lorazepam, and diazepam), propofol, and ketamine are commonly combined with opioids to achieve analgo-sedation and in addition, have an opioid-sparing effect.<sup>4</sup>

An ideal sedative drug must be free of side effects and should have rapid onset of action with a titratable dose–response relationship, with quick recovery time to facilitate easy weaning from mechanical ventilation.

Benzodiazepines are popular sedatives in the ICU, because of their wide availability, potency, and low cost. But there is evidence to demonstrate that continuous use of benzodiazepines in critically ill patients can lead to the accumulation of harmful metabolites due to impaired hepatorenal function resulting in oversedation, prolonged ventilator days and even mortality.<sup>5,6</sup> There are also concerns of delirium, tolerance, and long-term consequences like neuropsychiatric disorders.<sup>7</sup> Prolonged use of propofol as a sedative is associated with propofol infusion syndrome, hemodynamic instability, and hypertriglyceridemia. Dexmedetomidine has recently been considered as a better sedative drug offering light sedation with analgesia and is beneficial in preventing delirium.<sup>8</sup> But at a higher cost and with adverse effects like bradycardia and hypotension, and often the need for a second drug if deeper sedation is required.

Inhaled anesthetics (nitrous oxide, halothane, isoflurane, desflurane, and sevoflurane) are used for induction and maintenance of general anesthesia in the operating room. Halothane, isoflurane, desflurane, and sevoflurane are liquids at room temperature and need vaporizers to convert them to a gas before administration, as compared to nitrous oxide. Nitrous oxide and halothane have several serious side effects and are not commonly used for inhalation anesthesia.

The present-day popular anesthetics are isoflurane, desflurane, and sevoflurane, which are fluorinated hydrocarbons that have the advantage of rapid onset of action, high potency, with no tachyphylaxis, and rapid offset because of clearance through lung exhalation.<sup>9</sup> There is no accumulation of toxic metabolites in critically ill patients as compared to benzodiazepines. The inhaled anesthetics are also potent bronchodilators and anticonvulsants and have been traditionally used in the ICU for managing intractable bronchial asthma, status epilepticus, and in conditions that warrant higher sedation like drug abuse patients.<sup>10,11</sup>

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Inhaled anesthetics in addition to sedative properties have shown to have organ-protective effects on heart, lung, kidney, bowel, and brain by reducing proinflammatory cytokines and ischemia–reperfusion-mediated cellular injury.<sup>12–14</sup> But a recent meta-analysis on inhaled anesthetics in ICU did not show any benefit in decreasing ICU mortality and length of hospital stay.<sup>15</sup>

Inhaled anesthetics have a dose-dependent relationship between the inspired concentration of the drug, alveolar concentration, partial pressures of the drug in the brain, and its anesthetic effects. The breath-to-breath end-tidal concentration of the anesthetic agent can be monitored, which correlates well with the brain concentration and thereby help to titrate the dose.

With the therapeutic advantage and ease of dose monitoring, there has been a growing interest in the use of inhaled anesthetics for sedation in critically ill patients over the last few decades. The use of inhaled anesthetics to sedate critically ill patients is not new. In the 1950s, when positive pressure ventilation was initiated, nitrous oxide was used as a sedative for enabling long-term ventilation, until, in 1956, Lassen et al. reported severe bone-marrow suppression with its use.<sup>16</sup>

Despite the growing interest, there are several technical limitations in the use of inhaled anesthetics in ICU. Large anesthesia machines for administration with efficient scavenging systems are necessary to minimize air contamination, which can pose as a hazard to healthcare professionals. Advancement in technology has led to the development of the Anesthesia Conserving Device (AnaConDa™; Sedana Medical, Uppsala, Sweden) in 2001.<sup>17</sup> A more recent MIRUS™ system (Pall Medical, Dreieich, Germany) has been developed in 2013, which electronically titrates and delivers the gas.<sup>18</sup> The AnaConDa™ device has a carbon filter that absorbs and recycles more than 80% of the inhaled anesthetics. This enables low gas consumption and minimal environmental pollution. The AnaConDa™ is fixed between the endotracheal tube and the Y-piece of the ventilator circuit and can deliver isoflurane or

sevoflurane, but not desflurane as it has a low boiling point. The MIRUS™ system has several advantages over the AnaConDa™ device. Desflurane can also be used, and the gas can be titrated to a desired end-tidal concentration, and simultaneously monitor respiratory parameters.

Several randomized trials have been conducted comparing inhaled anesthetics to intravenous sedation, especially for short-term postoperative sedation.<sup>19,20</sup> A few studies were done for longer periods of sedation (>96 hours) on a mixed medical-surgical population.<sup>21</sup> All these trials demonstrated that inhaled anesthetic use showed quicker recovery from sedation and early extubation as compared to intravenous agents.

There are disadvantages on the use of these delivery devices. They are not widely available, are expensive, need to be changed every 24 hours, and recommendation for only off-label use in ICU for sedation. Unfamiliarity among intensivists and nursing personnel in operating these devices is another concern. These devices add to the dead space and can be used only if tidal volume is above 350 mL. Hence it cannot be used in pediatric cases, low-tidal volume ventilation, and when excessive secretions are present. The anesthetic agents can cause dose-dependent cerebral vasodilation, rise in intracranial pressure, hypotension, and there is a risk of malignant hyperthermia in genetically predisposed patients. Inorganic fluoride levels in the serum can rise, but studies have not reported nephrotoxicity in critically ill patients.<sup>22</sup> The concerns of air pollution and detrimental effects on caregivers with long-term use are also a concern, but studies have shown that air contamination with these new devices is negligible.<sup>21</sup> Efficient scavenging and room air conditioning with minimal ventilator disconnections can reduce the air pollution.

The inhaled anesthetics pose as an attractive option for expanding our sedative choice. But there is limited clinical data on its long-term use in critically ill patients. The study by Kulkarni et al. is the first from India to analyze the safety and feasibility of the use of the AnaConDa™ device for sedation in postoperative patients.<sup>23</sup> More research comparing inhaled anesthetics with intravenous sedation on patient-centered outcomes like mortality, duration of mechanical ventilation, organ protection, and cognitive effects, are necessary before expanding its application.

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