

Safety and Feasibility of AnaConDa™ to Deliver Inhaled Isoflurane for Sedation in Patients Undergoing Elective Postoperative Mechanical Ventilation: A Prospective, Open-label, Interventional Trial (INSTINCT I Study)

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ABSTRACT

Aim: Sedation is essential during invasive mechanical ventilation, and conventionally intravenous analgesic and sedative drugs are used. Sedation with inhaled anesthetics using anesthesia conserving device (ACD) is an alternative. There is no data on the safety and ease of use of AnaConDa™ from India.

Materials and methods: After IEC approval and informed consent, we used AnaConDa™-S for Isoflurane sedation in 50 hemodynamically stable (need for <0.5 µg/kg/min of Noradrenaline infusion), ASA I and II patients aged 18–80 years, undergoing elective mechanical ventilation for up to 24 hours after elective oncosurgeries. Patients with mental obtundation (GCS <14), or if pregnant, were excluded. The primary outcome was time spent between RASS scores of -3 and -4, while secondary outcomes were incidence of delirium, technical problems with AnaConDa™, and adverse systemic effects of isoflurane. Bolus doses of isoflurane 0.2–0.5 mL were given if the Richmond agitation sedation scale (RASS) score was not achieved.

Results: Fifty patients received isoflurane infusion for a median of 720 (IQR 630–900) minutes, and all remained in the target sedation range. Median time to awakening [19 (IQR, 5–85) minutes], to follow simple verbal commands [20 (IQR 5–180) minutes], and extubation after stopping the infusion of isoflurane was quick [100 (10–470) minutes]. All patients remained hemodynamically stable. None of the patients had delirium.

Conclusion: Target sedation levels were achieved with initial boluses of isoflurane using AnaConDa™-S. Isoflurane sedation delivery using AnaConDa™-S is safe and feasible.

Keywords: Anesthesia conserving device, Delirium, Inhaled sedation, Mechanical ventilation, Richmond agitation sedation scale score.

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HIGHLIGHTS

- Sedation is essential for mechanically ventilated patients. Most Indian ICUs use IV sedation.
- We used AnaConDa™ for delivery of inhaled isoflurane sedation in 50 patients.
- AnaConDa™ was easy to use without technical problems.
- Sedation target was easy to achieve, titrate and maintain in all patients without adverse effects.

INTRODUCTION

Effective sedation and analgesia are indispensable to reduce pain, anxiety, and agitation during mechanical ventilation, invasive diagnostic, and therapeutic interventions. Current SCCM guidelines for analgesia and sedation in ICU favor the use of intravenous medications and make a conditional recommendation for intravenous propofol or dexmedetomidine.¹ In an ISCCM survey, most intensivists used midazolam and fentanyl in Indian ICUs, and very few were using propofol or dexmedetomidine.² While dexmedetomidine offers quick onset and offset, it is costly and can cause hypotension, nausea, bradycardia, atrial fibrillation, and hypoxia.^{3,4} Propofol, while excellent for short-term sedation, can cause hypotension due to vasodilation and myocardial depression.

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It can also cause respiratory depression and hypertriglyceridemia, and rarely Propofol infusion syndrome. Benzodiazepines delay extubation by decreasing sleep, inducing fatigue, causing delirium, and prolonging ventilation duration.⁵

The volatile anesthetics, isoflurane, and sevoflurane are extensively used for anesthesia in millions of patients every year. They have a proven safety record and are mainly excreted by the respiratory system. Only 0.2% of isoflurane and 2–5% of sevoflurane are metabolized. For many years they have been used for sedation in critically ill patients in Europe. The 2010 German Guideline suggests the use of inhaled sedation as an alternative to intravenous sedation. It also suggests that inhaled agents be used when rapidly wake-up or quick recovery of cognitive functions or mobilization is required.⁶ A recent French survey showed that most intensivists (80% of respondents) were familiar with inhaled ICU sedation, but its use was limited to <20% of their patients.⁷

Louis Gibeck, who developed the heat and moisture exchanger (HME), modified it later to reduce the consumption of inhaled anesthetics. In addition to antibacterial and antiviral filters, the ACD (AnaConDa™) has an evaporator rod, and a proprietary carbon felt, which adsorbs exhaled isoflurane (or sevoflurane), and releases it during the next inspiration, conserving the anesthetics (Fig. 1).⁸ AnaConDa™-S is specifically recommended for those being ventilated with low tidal volumes, e.g., ALI/ARDS.

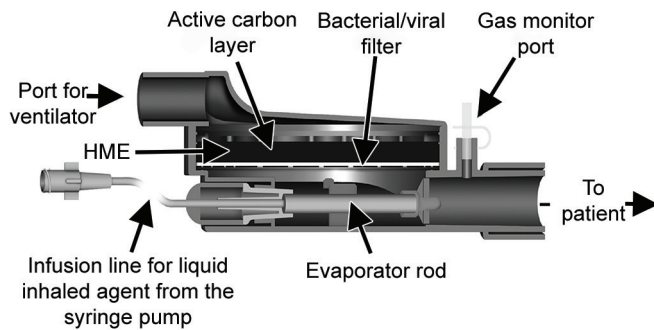


Fig. 1: Cross-section of AnaConDa™

Enlund et al. demonstrated that the available ACD (called Alfa-Reflector) reduced the consumption of the volatile agents by 40%.⁹ Sackey et al. described the use of AnaConDa™ for prolonged ICU sedation.¹⁰ Since the use of inhaled sedation has not been described in India, we investigated the ease of its use and safety in ventilated adults.

MATERIALS AND METHODS

This prospective, interventional, open-label, single-arm study was carried out in our tertiary referral center, after obtaining IEC approval and CTRI registration, from January 2021 to February 2022. The IEC allowed consent from the Legally Authorized Representatives (LAR), followed by consent from the patients when they were awake. We included adults (18–80 years) weighing 50–120 kgs who needed sedation for 12–24 hours while being ventilated after elective oncosurgeries. Patients who were hemodynamically unstable (need for >0.5 µg/kg/min of Noradrenaline infusion) or with mental obtundation (GCS <14), pregnant or breast-feeding patients, and those with contraindications to use of HME filter (excessive secretions or pulmonary hemorrhage likely to block the filter or with a need to reduce dead space) were excluded from the study. The AnaConDa™ devices, for the study, were supplied by Sedana Medicals, Sweden, as per agreement under Investigator Initiated Trial Grant. Before undertaking the study, members of our team had used AnaConDa™ in eight different patients for a period ranging from 1 to 5 days, over a period of 2 months.

After arrival in ICU, and being put on the ventilator, an intravenous Fentanyl infusion (0.5–1.5 µg/kg/min) titrated to achieve analgesia was commenced. The AnaConDa™ device was attached between the Y-piece of the ventilator and the catheter mount (Fig. 2). The agent line of the AnaConDa™ was connected to a 50 mL syringe mounted in the syringe pump, in which isoflurane was already drawn. The agent monitoring line of AnaConDa™ was connected to the Anesthesia Gas Monitor (Philips IntelliVue MP50), while both the ventilator expiratory port and AGM outlet were connected to the FlurAbsorb™.

Once the assembly was complete, after checking the RASS score, and if <2, an initial bolus of 1.5–2 mL of Isoflurane was injected

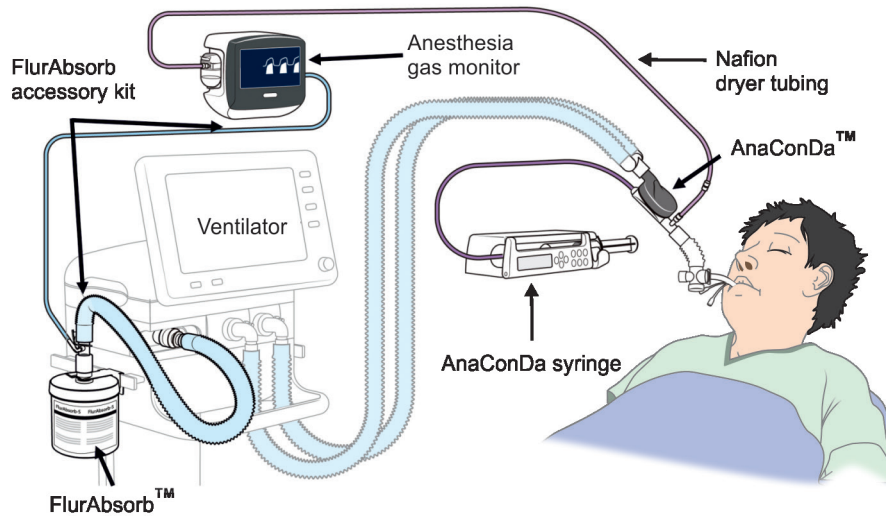


Fig. 2: AnaConDa™ set-up

using the bolus function of the syringe pump into AnaConDa™, and the RASS score was again checked. If required, additional boluses of 0.3–0.5 mL Isoflurane were given. Once a RASS score of -3 was achieved, an infusion of Isoflurane at 1.5–2.5 mL was commenced and titrated to keep the RASS score between -3 and -4, which was assessed hourly. Additional boluses of Isoflurane 0.2–0.5 mL were given till RASS was within the target range and no intravenous sedative agents were given. Inspired, end-tidal, and minimum alveolar concentration of isoflurane were monitored throughout the study. The infusion rates of isoflurane, fentanyl, and the number of boluses of isoflurane, fentanyl, and rescue drugs were recorded. The primary outcome was time spent between RASS scores of -3 and -4, while secondary outcomes were incidence of delirium [as assessed by confusion assessment method (CAM-ICU)], technical problems during the use of AnaConDa™, and adverse systemic, i.e., renal and hepatic effects of isoflurane, if any.

When the attending intensivists decided that patient was ready to wean off, isoflurane infusion was stopped, but the device was left in the circuit, as we did not want an abrupt cessation of sedation. Following this, the time for awakening after the termination of sedation, to follow simple verbal commands (such as tongue protrusion, eye opening and closing, and handgrip), and time to extubation was noted. Patients were extubated once they were fully awake. In other patients; not deemed ready for extubation, at the end of 24 hours, intravenous sedation was commenced.

We recorded the infusion rate, the number of dose adjustments required, and the no. of boluses of isoflurane and fentanyl. If the desired RASS score was not achieved solely with isoflurane, we also noted the amount of intravenous conventional sedatives required to sedate patients over the duration of ventilation. Instances of hypotension (SBP <90 mm Hg), if any were recorded. Whenever the RASS score was >-3, patients were assessed for delirium using the CAM-ICU scale. Instances of agitation, airway accidents, and other mishaps (such as accidental extubation, pulling out of lines, and catheters), along with equipment-related problems, were recorded. Preoperative renal and hepatic function tests (Sr. urea, creatinine, bilirubin, AST, and ALT) and postoperative day 3 or 5 values were recorded.

Statistics

We selected a convenience sample of 50 patients. Simple descriptive statistics were used to analyze the data.

RESULTS

Demographics

The mean age of patients was 50 (±12) years, and the mean height and weight were 160 (±9.12) cm and 61.14 (± 9.4 kgs), respectively. There were equal no. of males and females, with 23 ASA I patients and 27 ASA II patients. The mean (±SD) admission APACHE II score was 10.94 (±3.6). There were four reformed tobacco chewers and two chronic alcoholic patients. Most patients had undergone extensive supramajor oncosurgeries (Table 1) with significant blood loss (median 2025.00, range 200–21,000 mL). The median duration of surgeries was [median 660.00, (IQR 180.00–1140.00) minutes]. At the time of admission, 20 patients were on noradrenaline infusion.

Sedation Efficacy

The median isoflurane infusion rate required was 2 (1.5–6) mL/hour to meet the sedation goal. The median time to awakening, to follow simple commands, and the time to extubation was 19

Table 1: Type of surgeries undertaken

Name of the procedures	No. of procedures
Cytoreductive surgery + heated intraperitoneal chemotherapy (CRS + HIPEC)	19
Total pelvic exenteration and reconstruction	9
Supramajor thoracic surgeries	6
Other supramajor abdominal surgeries	5
Supramajor head and neck surgeries with or without microvascular free flap transfer	9
Other supramajor oncosurgeries	2
Total procedures	50

Table 2: Duration of infusion, time to awakening, time to respond to simple commands, and extubation after stopping the isoflurane infusion

	Mean ± SD (mins)	Median (IQR) (mins)
Duration of isoflurane infusion	764 ± 87	720 (630–900)
Time to awakening after stopping sedation	30 ± 25	19 (5–85)
Time to hand grip after stopping sedation	34 ± 33	20 (5–180)
Time to extubation after stopping sedation	141 ± 117	100 (10–470)

(5–85) minutes, 20 (5–180) minutes, and 100 (10–470) minutes (Table 2). Only two patients needed additional boluses of isoflurane, once target sedation was achieved. Some patients did require additional boluses of fentanyl (Table 3). Most patients remained within the target RASS range (-4, range -3 to -4), and none developed delirium (Table 4). Some of the patients were not extubated in spite of being awake and able to respond to simple verbal commands such as hand lift and finger grip (Table 4). In 14 patients who were awake by 20 minutes and following simple commands, extubation was delayed [240 (range 210–470) minutes] due to other considerations, such as high opioid requirements or poor breathing pattern due to diaphragmatic stripping and/or splinting caused by large upper abdominal incisions. Six patients who continued to require ventilatory support were extubated after 24 hours, of these two, were extubated on the 4th and 5th postoperative days.

Safety of Inhaled Sedation

Two patients (3rd and 5th patients) at the beginning of the study developed ventilator asynchrony approximately 90 minutes after starting inhaled sedation, and we found that the AnaConDa™ was positioned lower than ETT (not at 45° angle, as recommended). This had caused the tracheal secretions to enter the AnaConDa™ device. This was rectified, bolus of isoflurane (1.5 mL) was repeated, and infusion was recommenced at a higher rate. There were no further issues after this. One patient became awake and self-extubated as soon as the sedation was stopped, this might have been because the device was removed from the circuit, (instead of being left in the circuit as planned) which causes near-immediate termination of sedation.

Twenty patients were shifted to ICU with noradrenaline infusion. Three of these patients had one episode each of hypotension (SBP <90 mm Hg) after receiving Isoflurane bolus, while one patient



Table 3: Isoflurane and fentanyl dosage to maintain target RASS scores

Time (hours)	Isoflurane infusion rate (mL/hr)		Fentanyl infusion rate (mL/hr)	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
1	2.27 ± 0.85	2 (1–5)	3.52 ± 1.16	3 (2–7)
4	2.032 ± 0.67	2 (1–4)	3.46 ± 1.07	3 (2–7)
8	2.072 ± 0.69	2 (1–4)	3.52 ± 1.43	3 (2–7)
12	2.1 ± 0.79	2 (0.5–4)	3.32 ± 1.36	3 (2–7)
14 (45 patients)	2.1 ± 0.74	2 (1–3.5)	3 ± 1.1	3 (2–5)
15 (23 patients)	2 ± 0.7	2 (1–3.5)	3.5 ± 1.2	3 (2–5)
16 (22 patients)	2 ± 0.6	2 (1–3.5)	2.9 ± 1.3	3 (1–5)
17 (18 patients)	2 ± 0.7	2 (1–3.5)	3.4 ± 1.1	3 (2–5)
18 (17 patients)	2 ± 0.7	2 (1–3.5)	3.25 ± 1.1	3 (2–5)
19 (15 patients)	2.1 ± 0.7	2 (1–3.5)	3.4 ± 1.1	3 (2–5)
20 (14 patients)	2.1 ± 0.8	2 (1–3.5)	3.6 ± 1	3 (3–5)

Table 4: Median RASS scores and need for isoflurane and fentanyl boluses

Time (hours)	RASS score median (range)	No. of pts. who needed isoflurane boluses*	No. of pts. who needed fentanyl boluses
4	-4 (-4 to -2)	1	4
8	-4 (-4 to -1)	4	5
12	-4 (-4 to 0)	2	4
16	-4 (-4 to -2)	0	2
20	-3 (-4 to -2)	0	2
24	0 (-4 to -2)	0	1

*Does not include the initial bolus

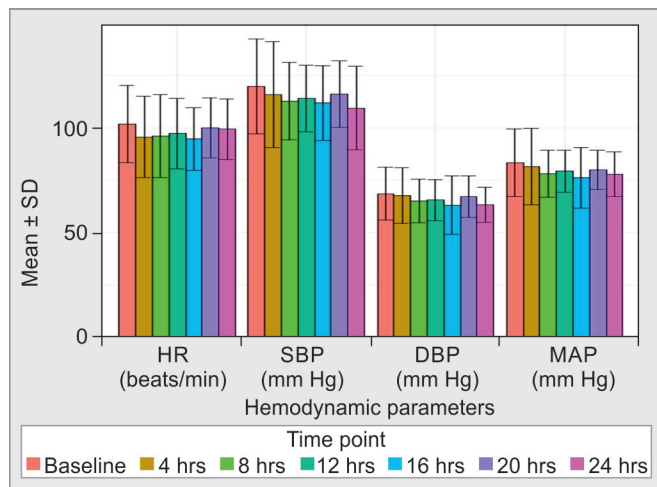


Fig. 3: Hemodynamic parameters over 24 hours

had two episodes of hypotension. All episodes were transient (5–10 minutes) and the blood pressure normalized with minimal increase in the dose of noradrenaline, and the dose was reduced to the previous dose (before the occurrence of hypotension) within 10 minutes. Otherwise, these patients and all other patients remained hemodynamically stable (Fig. 3). After volume replacement, we were able to discontinue vasopressor infusion in all patients. There were no renal or hepatic adverse effects; barring 16 patients who had a transient increase in bilirubin, AST, and ALT levels (Table 5). These values had normalized before ICU discharge from the hospital. One patient had a hemorrhagic shock after a graft in

the hepatic artery gave way causing catastrophic bleeding, was readmitted to ICU, and died in spite of surgical exploration. Others were discharged alive from the hospital.

DISCUSSION

In this, first Indian study of using AnaConDa™-S to deliver inhaled sedation in the ICU, we found that the device AnaConDa was easy to use. Achieving and maintaining the sedation target was straightforward. There did not seem to be any adverse hemodynamic or systemic effects. Patients woke up quickly and were able to follow simple verbal commands after sedation was stopped. We were able to extubate most patients in a short time. In a few patients with surgical issues, extubation was delayed, though they woke up quickly and had to be re-sedated.

The most attractive feature of the newer inhaled anesthetic agents is the ease of titration to achieve the sedation target and the almost on-off nature of sedation. The patients get sedated remarkably quickly and wake up almost immediately after the infusion is stopped. Though the non-anesthetist may be wary of using an unfamiliar agent and fear possible hemodynamic instability, it is easy to learn to titrate the inspired concentration of inhaled agent as per the clinical effect. Initially, this can be safely done by monitoring the inhaled and exhaled concentrations of isoflurane or sevoflurane using an airway gas monitor (AGM) and carefully observing hemodynamic effects, alongside the sedation levels. We feel that once the intensivist becomes familiar with the usage, there is no need to use the AGM. After all, all intravenous sedative drugs, particularly when infused with opioids, have the potential to produce hemodynamic instability due to their sympatholytic effects. We continue to use them while titrating

Table 5: Baseline and postoperative renal and hepatic parameters

Parameters	Preop	Postop D1	Postop D3 or 5*	p-value
Sr. urea mg/dL	24.02 ± 14.33	19.28 ± 9.18	25.1 ± 9.52	0.76, 0.08
Sr. creatinine mg/dL	0.74 ± 0.22	0.60 ± 0.20	0.63 ± 0.19	1.0, 0.8
Sr. bilirubin mg/dL	0.49 ± 0.25	1.09 ± 0.85	0.88 ± 0.87	2.0, 0.00
AST IU/L	25.57 ± 5.94	102.6 ± 68.72	54.66 ± 36.36	0.03, 0.02
ALT IU/L	24.57 ± 7.78	83.2 ± 50.96	52.83 ± 56.32	0.03, 0.12

ALT, alanine aminotransferase; AST, aspartate aminotransferase; *Whichever was available, since performing these tests was not part of the protocol

their sedative and hemodynamic effects without continuously monitoring the blood levels of these drugs. Also, in contrast to the inhaled anesthetics, the context-sensitive half-life of intravenous sedative agents increases due to prolonged infusion due to accumulation, which causes an increase in wake-up time. These wake-up times and extubation times need to be compared with IV sedation in a randomized trial, in a similar group of patients.

The first two trials describing the use of inhaled sedation in the critically ill were published in 1989 and 1992, but both used Siemens isoflurane vaporizer 952 (Siemens-Elma AB, Sweden) along with the Siemens-Elma Servo 900B ventilator to deliver Isoflurane, and not an ACD.^{11,12} Using the anesthetic vaporizer in the ICU can be cumbersome; hence, probably the idea did not become very popular. Sackey et al. can be credited with demonstrating the utility and ease of use of the AnaConDa™ device to deliver isoflurane in the critically ill.¹⁰ They randomized 40 patients who needed sedation for >96 hours to receive isoflurane or midazolam. They found that the time to follow the verbal command (10 vs 130 minutes, $p = 0.003$) and to extubation (10 vs 250 minutes, 95% CI, 9–35; $p < 0.001$) was shorter in patients sedated with isoflurane. Inorganic fluoride levels were generally low in patients receiving isoflurane, with the highest level being 64 $\mu\text{mol/L}$ in one of the three patients who had values over 50 $\mu\text{mol/L}$. The renal and liver functions remained normal in all, except for three patients who needed renal replacement therapy, but there was no correlation of creatinine clearance with the inorganic fluoride levels. In another small study of 15 patients, inhaled sedation was found to be easy to administer, safe, and effective. The costs were similar, particularly when compared to sedating patients who needed large doses of midazolam, with shorter awakening times, and with inhaled sedation.¹³

Bellgardt et al. retrospectively compared the effect of intravenous and inhaled sedation on hospital and one-year survival.¹⁴ The patients were ventilated for at least 96 hours and sedated with a midazolam–propofol combination or isoflurane. The hospital (40 vs 63%, $p = 0.005$) and one-year survival (50 vs 70%, $p = 0.013$) was higher in the isoflurane group. Even after adjusting for various confounders such as age, comorbidities, and severity of illness, the patients who received isoflurane were less likely to die during the hospital stay (aOR 0.35; 95% CI 0.18–0.68, $p = 0.002$) and during the first year (aOR 0.41; 95% CI 0.21–0.81, $p = 0.010$). Though the authors admit to the limitations of retrospective nature and short duration of the study, and importantly, the imbalance in the age groups at baseline, the survival benefit was sustained, even after adjustment for age.

Why should the use of inhaled agents improve survival? This is probably owed to the many beneficial effects of the inhaled anesthetics. Yildirim et al. compared the extent of ischemia- and reperfusion-mediated free-radical injury, oxidative stress, and effects on end products of lipid peroxidation and nitric oxide in patients undergoing CABG under the inhaled or intravenous

anesthetics.¹⁵ In spite of stable hemodynamics, the rise in troponin I was higher in the propofol compared to sevoflurane and isoflurane groups. The atrial NO production was significantly lower in atrial tissue after propofol. This and animal studies suggest the cardioprotective effects of inhaled anesthetics.^{16,17}

In 19 neurocritical care patients, Bösel et al. found that prolonged sedation using inhaled isoflurane can be safely used in patients with low or moderately elevated ICP, provided caution is exercised to maintain adequate mean arterial pressure (MAP) and cerebral perfusion pressure (CPP).¹⁸ This was because, 1 hour after starting inhaled sedation, there was a small rise (2.1 mm Hg, $p = 0.1$) in the ICP and also a minimal drop in MAP leading to a reduction in the CPP. All the beneficial effects of inhaled isoflurane may have led to the improved survival of the patients in the trial by Bellgardt et al.¹⁴ They also suggested that the decreased survival in the intravenous sedation group could have been due to adverse effects of benzodiazepines. Benzodiazepines have been shown to be associated with a higher incidence of delirium in critically ill adults, and delirium was an independent predictor of mortality in another study.^{19,20} A multicenter cohort study found that early deep sedation using mainly midazolam for mechanically ventilated patients was independently associated with the hospital (HR 1.11, 95% CI 1.05–1.18, $p < 0.001$) and 6-month mortality (HR 1.09, 95% CI 1.04–1.15, $p = 0.002$).²¹

In our study, we observed a mild but significant rise in Sr. bilirubin and AST and ALTs (Table 5). We attribute this to the extensive surgeries involving partial liver resections or need for intraoperative massive transfusions or hypotension requiring vasopressor support [16 patients, blood loss 5535 ± 5185 mL, median 3700 (IQR 1100–21,000) mL].

The initial concerns about the safety of ICU staff who were tending to critically ill patients receiving prolonged inhaled sedation seem unfounded. In multiple studies, the environmental levels of isoflurane or sevoflurane were found to be within safe limits (0.1–0.2 ppm), much lower than safe levels recommended internationally.^{22,23} Berton et al. performed a bench study and also a small study in anesthetized patients.²⁴ They found that since there was a standard Luer lock connector on the inhaled agent syringe earlier, it could be connected to any other port. The Luer lock system has been now modified so that inhaled agent line from the AnaConDa™ can only be connected to the AnaConDa™ syringe.

More centers need to gain experience in the management of patients being sedated with inhaled sedation. Our center has a possible advantage while handling this technique since Anesthesia and the Critical Care divisions are part of the same department. Many of the residents and consultant staff have anesthesiology backgrounds and are therefore used to administering inhaled anesthetic agents and monitoring their hemodynamic effects and inhaled and exhaled concentrations. Other units with staff from varied backgrounds, particularly those who are not from

anesthesiology, may take some time to get used to handling the anesthetic agents. The other difficulty might be having access to an AGM. Here again, being part of the same department, we had access to the technology, which other centers may not have. While inhaled sedation infusion rate can be titrated against the desired sedation levels, in the same way, we titrate intravenous sedatives (without measuring their blood levels), it is advisable at least in the beginning to monitor inhaled and exhaled levels of anesthetic agents. The main limitation of our study is that it is a single-center study.

Apart from the cardioprotective properties mentioned above, most halogenated inhaled anesthetics including Isoflurane are potent bronchodilators. Isoflurane has other beneficial effects on the gas exchange due to attenuation of pulmonary, systemic inflammation, reduction in alveolar edema, and proinflammatory properties.²⁵ Isoflurane preconditioning and postconditioning have been shown to offer neuroprotection. Human and animal studies suggest that hepatic and renal function is well preserved after the use of sevoflurane and isoflurane, in spite of a small rise in inorganic fluoride ions after the use of sevoflurane.^{26–28} Future studies should concentrate on evaluating whether these beneficial properties of inhaled agents in general and isoflurane in particular, can have positive effects on outcomes of patients with cardiorespiratory impairment.

CONCLUSION

Target sedation levels were achieved with initial boluses of isoflurane using AnaConDa™-S. Isoflurane sedation delivery using AnaConDa™-S is safe and feasible.



ACKNOWLEDGMENTS

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ABBREVIATION

INSTINCT-INhaled SedaTion IN CriTically ill patients

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