Inhaled sedation and opioid reduction – October 2022

	Reference	Methodology or type of publication	Results	Conclusion
ISOFLURANE				
Randomized Controlled Trials	**Meiser A et al., 2021.** 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, randomized controlled, non-inferiority trial. Lancet Respir Med. Nov;9(11):1231-1240.	RCT to evaluate the efficacy and safety of isoflurane (n=150; age: 65.8 ± 11.8 years) delivered via Sedaconda ACD (3ml/h ± 1.5%) for up to 54 h of sedation compared with propofol (n=151; age: 64·3 ± 12·9 years; 20mg/ml ± 0.5) in invasively ventilated adults in the ICU.	Opioid dose intensity was significantly lower for isoflurane than for propofol on day 1 (0.23 (0.12–0.33) vs 0.32 (0.22–0.43)) mg/kg/h morphine equivalent dose, p=0.0032 and for the overall sedation period (0.22 (0.12–0.34) vs 0.32 (0.21–0.42)) mg/kg/h morphine equivalent dose, p=0.0036.	Isoflurane facilitated opioid dose reduction by 29% without any indications of increased pain. The effect could possibly be explained by the antinociceptive effects of the inhaled anesthetics on the spinal cord.
	Jerath A et al., 2015. Perioperative Anesthesia Clinical Trials Group. Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial. Crit Care Med. May;43(5):1062-1069.	RCT involved 141 patients undergoing coronary artery bypass graft surgery to evaluate the differences in extubation times in patients who were anesthetized and sedated with either propofol (n=74; age: 63 ± 10 years; 1 mg/kg/h) or isoflurane/ sevoflurane (n=67; age: 65 ± 9 years; 0.5–5 ml/h).	Fentanyl dose for patients on volatile anesthetics was 1022.4 ± 380.1 µg vs 1116.7 ± 320.1 µg for patients on propofol. However, the difference was not statistically significant (p=0.22). Also, there was no significant difference in pain scores.	Opioid consumption was lower in patients receiving volatile sedation but the difference was not significant.
	Sackey PV et al., 2004. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. Crit Care Med. Nov;32(11):2241-2246.	RCT with 40 ventilator-dependent ICU patients, expected to need >12 hrs sedation. Patients were randomized to sedation with isoflurane (end-tidal concentration of 0.5% (1.0 –3.5 mL/hr); age: 60 (39–80) years) via the Anesthetic Conserving Device or midazolam infusion (0.02–0.05 mg/kg/hr; 60 (19-80) years). The study duration was 96 h or until extubation.	Opiate requirement (mg/hr) was 2.7 ± 2.0 and 4.2 ± 3.8 in the isoflurane and midazolam groups, respectively. However, there was no statistical difference.	Though there was no statistical difference, the opioid-sparing action of isoflurane has been demonstrated in this study.

Retrospective studies	**Kermad A et al., 2021.** Comparison of isoflurane and propofol sedation in critically ill COVID-19 patients-a retrospective chart review. J Anesth. Oct;35(5):625-632.	Retrospective study to compare isoflurane delivered via AnaConDa (end-tidal concentration 0.96 ± 0.41 Vol%) to propofol (2.2 ± 1.0 mg/kg) sedation in 20 invasively ventilated COVID-19 patients (age 64 (60–68) years) with ARDS. Mixed sedation days were excluded.	Compared to propofol, isoflurane sedation decreased the use of muscle relaxants (11% vs 21%, p<0.001), polypharmacy (7% vs 31%; p<0.001) and opioid doses in morpine equivalent doses (720 (720–960) mg/24 h vs 1080 (720-1620) mg/24h; p<0.001)). Richmond Agitation Sedation Scale (RASS scores) were also significantly lower under isoflurane sedation (− 4.0 (− 4.0 to − 3.0) vs − 3.0 (− 3.6 to − 2.5); p<0.01).	Isoflurane provided sufficient sedation with less use of neuromuscluar blocking agents, less polypharmacy, and lower opioid doses compared to propofol in COVID-19 ARDS patients.
	Ferrière N et al., 2021. Shortage of anesthetics: Think of inhaled sedation! J Crit Care. Jun;63:104-105.	Retrospective study, 11 endotracheally intubated and ventilated COVID-19-ARDS patients (age: 58.1 ± 12.4 years; sedated with midazolam (6.4 ± 1.4 mg/h) and sufentanil (17.3 ± 5.0 gamma/h) for a median duration of 82 h, were switched to isoflurane delivered via AnaConDa (minimum 1 ml/h).	Sufentanil consumption decreased significantly after switching to isoflurane (17.3 ± 5.0 vs. 10.6± 4.0 gamma/h; p=0.005) while reaching the same sedation goals evaluated with the RASS and Behavioral Pain Scale.	Isoflurane can decrease opioid consumption while the same sedation goal was reached.
	Grasselli G et al., 2021. Volatile Sedation for Acute Respiratory Distress Syndrome Patients on Venovenous Extracorporeal Membrane Oxygenation and Ultraprotective Ventilation. Crit Care Explor. 2021 Jan 8;3(1):e0310.	A retrospective study with 74 ARDS patients (age: 50 (43-56) years) sedated with isoflurane (started on day 3 with a median duration of 7 (14-13) days) via the AnaConDa system during venovenous ECMO. The sedation level, hemodynamics, and laboratory tests were compared between isoflurane and the iv sedation (propofol and midazolam) phases before and after the isoflurane sedation period.	Opioid dosing was significantly reduced during isoflurane sedation compared with iv sedation (fentanyl: 1.41 ± 0.57 vs 1.63 ± 0.54 µg/kg/hr (p<0.001); remifentanil: 0.07 ± 0.04 vs 0.14 ± 0.07 µg/kg/min (p=0.005)).	A reduction in the dose of opiates was recorded when sedation was shifted from intravenous sedation to inhaled sedation
	Meiser A et al., 2018. Inhalation sedation in subjects with ARDS undergoing continuous lateral rotational therapy. Respir Care. Apr;63(4):441-447.	A retrospective study with 38 critically ill surgical subjects (mean age 48.9 ± 16.9 years) with ARDS treated with continuous lateral rotational therapy. 19 subjects were sedated with propofol or midazolam (56.3 ± 21.4	Remifentanil dose (µg/kg/min) before isoflurane sedation was 0.19 ± 0.10 compared to 0.22 ± 0.09 (p=0.39) before propofol/midazolam sedation. 6 h after isoflurane, remifentanil dose was 0.10 ± 0.04 vs 0.23 ± 0.10 after propofol/midazolam (p=0.007). Finally remifentanil dose after 24 h of isoflurane sedation was	Opioid consumption was significantly decreased in patients with isoflurane after 6 and 24 h.

		years) and compared with 19 subjects (48.9 ± 16.9 years) sedated with isoflurane (3–10 mL/h) using the AnaConDa-system.	0.09 ± 0.04 vs 0.25 ± 0.09 after propofol/midazolam (p<0.001). Sufentanill dose (µg/kg/min) before isoflurane sedation was 0.46 ± 0.66 compared to 0.68 ± 0.59 (p=0.64) before propofol/midazolam sedation. 6 h after isoflurane, sufentanil dose was 0.29 ± 0.45 vs 0.68 ± 0.58 after propofol/midazolam (p=0.20). Finally sufentanil dose at 24 h was 0.29 ± 0.45 vs 0.52 ± 0.55 after propofol/midazolam sedation (p=0.38).	
	Staudacher DL et al., 2018. Isoflurane or propofol sedation in patients with targeted temperature management after cardiopulmonary resuscitation: A single-center study. J Crit Care. Jun;45:40-44.	A retrospective cohort study comparing isoflurane sedation (n=36; age: 69 (57.3–76.0) years; end-tidal concentration: 0.5 to 1.0%) delivered via AnaConDa to propofol (n=178; age: 73 (61.0–79.5) years sedation in comatose patients with return of spontaneous circulation after cardiopulmonary resuscitation undergoing targeted temperature management (TTM).	The sufentanil dose given to patients in the isoflurane group was significantly lower when compared to the propofol group (p<0.001).	The opioid dose was significantly lower in the isoflurane group compared to propofol.
	Meiser A et al., 2017. Inhaled Sedation in Patients With Acute Respiratory Distress Syndrome Undergoing Extracorporeal Membrane Oxygenation. Anesth Analg. Oct;125(4):1235-1239.	Retrospective case report of 6 patients with simplified acute physiology scores between 31 and 55 suffering from ARDS with the need for ECMO was sedated with isoflurane (delivered via AnaConDa system at 1-3 mL/h; end-tidal concentration 0.5 to 0.7 vol%) within 24h after ECMO initiation.	After 24 hours of isoflurane sedation, opioid consumption was decreased in all cases. Remifentanil, µg/kg/min - **Case 1** - 0.12 before ACD, 0.093 at 1 h and 0.046 at 24h. **Case 5** - 0.17 before ACD, 0.074 at 1 h and 0.054 at 24h. **Case 6** - 0.097 before ACD, 0.097 at 1 h and 0.056 at 24h. Sufentanil, µg/kg/h - **Case 2** - 0.2 before ACD, 0.04 at 1 h and 0.04 at 24h. **Case 3** - 0.38 before ACD, 0.38 at 1 h and 0.19 at 24h. **Case 4** - 0.004 before ACD, 0.04 at 1 h and 0.03 at 24h.	Opioid consumption could be reduced, and only very low doses of isoflurane were needed (1 mL/h to 3 mL/h). Nevertheless, all patients remained deeply sedated as demonstrated by RASS scores of −4 to −5.

	Bösel J et al., 2012. Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa: effects on cerebral oxygenation, circulation, and pressure. Intensive Care Med. 2012 Dec;38(12):1955-1964.	RCT with 19 ventilated patients with intracerebral hemorrhage (n=12), subarachnoid hemorrhage (n=4), and ischemic stroke (n=3) were switched from propofol or midazolam to isoflurane sedation (MAC 0.56 ± 0.12 after the switch) for an average of 3.5 days.	Remifentanil dosing: 0.11 ± 0.05 µg/kg/min before switching to IV sedation compared to 0.07 ± 0.04 µg/kg/min 1-6 h after switching from IV sedation (difference from baseline of -0.03 ± 0.04; p=0.046). 7-12h after switching from IV sedation, the mean dose was 0.05 ± 0.06 (difference from baseline of 0.06 ± 0.06; p=0.021). Sufentanil dosing: 0.81 ± 0.58 (µg/kg/h) before switching to IV sedation compared to 0.65 ± 0.40 1-6h after switching from IV sedation (difference from baseline of -0.17 ± 0.41; p=0.144). 7-12h after switching from IV sedation, the mean dose was 0.73 ± 0.29 (µg/kg/h) (difference from baseline of -0.08 ± 0.50, p=0.564).	Opioids could be reduced under isoflurane, reflecting its partial analgesic component.
Sevoflurane				
Randomized Controlled Trials	**Mesnil M et al., 2011**. Long-term sedation in intensive care unit: A randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. Intensive Care Med., Jun;37(6):933-941.	Randomized controlled trial with 60 ICU patients, either sedated with sevoflurane (n=19, delivered via AnaConDa ET 0.5%, age: 52 (33–64) years), propofol (n=14, 2 mg/kg/h; age: 54 (45–63) years), or midazolam (n=14, 0.1 mg/kg/h; 55 (31–61) years) for over 24 h.	Morphine consumption after extubation was reduced in patients sedated with sevoflurane: 20 (4.5–30) mg/24 h under sevoflurane vs 40 (30–60) mg/24 h for patients under propofol and 76 (55–111) mg/24 h for patients under midazolam, p<0.001.	Morphine consumption during the 24 h following extubation was lower in sevoflurane patients than in propofol or midazolam patients. Sevoflurane decreased wake-up and extubation times and increased awakening quality.
Prospective study	**Jung S et al., 2020.** Inhalation sedation for postoperative patients in the intensive care unit: initial sevoflurane concentration and comparison of opioid use with propofol sedation. Acute Crit Care. Aug;35(3):197-204.	Prospective study in patients in ICU after head and neck surgery (age: 62 (54.5–70.5) years to determine the proper initial sevoflurane concentration (0.6% MAC) and a retrospective analysis to compare postoperative opioid consumption between sevoflurane (n=24) and propofol (n=24) sedation.	Remifentanil consumption was significantly lower in the sevoflurane group (2.52 ± 1.00 µg/kg/h) than it was in the propofol group (3.66 ± 1.30 µg/kg/h), p=0.001.	There was a lower opioid requirement during mechanical ventilation in the sevoflurane group than in the propofol group.

ARDS – Acute respiratory distress syndrome, **ACD** – Anaesthetic conserving device, **ECMO** – Extracorporeal membrane oxygenation, **RASS** - Richmond agitation-sedation scale