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Sevoflurane in COVID19 patients: a prospective observational pilot study

B.C. Vinckier (*), A.C. Dumoulin (**), Y.E. Devriendt (**), M. Van de Velde (*), P.M. Lormans (**)

Abstract: *Background:* The SARS-cOV-2 virus has led to a global pandemic with acute respiratory failure as a major cause of admission to the ICU−with many severely affected patients requiring invasive ventilation. High sedation requirements and high airway reactivity, in combination with drug shortages inspired us to seek alternative options for sedation.
Methods: A single center, prospective observational pilot study with the inclusion of 7 COVID-19 patients. All mechanically ventilated patients received a standardized sedation protocol which was upscaled when signs of asynchrony with the ventilator were observed. This was quantified by high ventilatory peak airway pressures (> 35 cmH20) and the necessity of paralytics. Data retrieval started as soon as sevoflurane was introduced using a self-controlled case series methodology.
Results: Once sevoflurane was added to the sedation protocol, other intravenous sedatives were stopped until patients were sedated only by inhaled anaesthetic in combination with an opiate and/or clonidine. The mean time from starting sevoflurane to achieving dual sedation was 47h. The daily number of high peak airway pressure alarms were significantly lower once sevoflurane was initiated. ($p<0,01$) Additionally, there was a significant reduction in the daily use of neuromuscular blockers ($p<0,01$). Initiation of sevoflurane did not show significantly improved oxygenation measured by P/F ratio in this limited sample of patients ($p=0,67$).
Conclusions: Sevoflurane may be a good sedative and alternative in intubated patients with COVID-19 ARDS, improving synchrony with the ventilator. Larger, randomized trials are necessary.

Keywords: Covid-19; coronavirus infection Pneumonia; viral respiratory insufficiency; respiratory distress syndrome SARS-CoV-2 anaesthetics; inhalation Sevoflurane / administration & dosage.

Introduction

The rapid spread of the severe respiratory syndrome coronavirus-2 (SARS CoV-2) has led to a global pandemic with acute respiratory distress as a major complication (1). Severely affected patients demand respiratory support, with a high percentage requiring invasive ventilation (2, 3). In our experience, these patients exhibit a high airway reactivity with ventilator dyssynchrony, leading to profound desaturation and dangerously high airway pressures. This phenomenon seems difficult to control with classic intravenous sedatives and results in multidrug and high dose sedation (4, 5). This has led to recent discussion and interest concerning the potential benefits of volatile anesthetics in the context of COVID-19 induced acute respiratory distress syndrome (6, 7). Secondary, the high number of mechanically ventilated patients has created a public health challenge including a high demand for sedatives, analgesics and neuromuscular blocking agents, leading to shortages of many of these essential medications (8-10). In this prospective observational pilot study, we want to evaluate if inhaled sevoflurane might be of added value in this context. The results may lead to new insights in sedation and stabilization of these challenging patients. In addition, this study may contribute to medication saving techniques and help in the scarcity of intravenous anesthetics.

Materials and Methods

Study design

This single center, prospective observational pilot study was conducted in AZ Delta hospital in Roeselare, Belgium. All patients with confirmed SARS-coV-2 infection who were intubated and ventilated were eligible for inclusion and received

B.C. Vinckier, MD; A.C. Dumoulin, MD; Y.E. Devriendt, MD; M. Van de Velde, MD; P.M. Lormans, MD.
(*) Department of Anesthesiology, UZ Leuven, B-3000 Leuven
(**) Department of Anesthesiology, AZ Delta, B-8800 Roeselare
Corresponding author: B. Vinckier, F. Timmermanslaan 8, B-8670 Koksijde
Email: benedicte_vinckier@hotmail.com

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Conflict of interest: None.

Table 1

Sedation protocol

1. Propofol (max 1,5 mg/kg/h) and remifentanil (max 0,15 µg/kg/min)
2. Clonidine (max 900 µg/24h)
3. Ketamine (max 200 mg/24h)
4. Midazolam (max 0,05 mg/kg/h)
5. Sevoflurane (max MAC 1)

a standardized sedation protocol (Table 1).Sedation was upscaled when signs of asynchrony with the mechanical ventilator were observed, judged by the treating physician or ICU nurse. To evaluate and objectively quantify, we calculated the frequency of high ventilatory peak airway pressure alarms (> 35 cmH20). In the case of ventilator dyssynchrony in combination with dangerous desaturation, neuromuscular blockers in bolus were allowed. Once sevoflurane was introduced, sedation was downscaled the opposite way until dual sedation (sevoflurane + remifentanil +- clonidine) was achieved. Sevoflurane was administered using servo-u (Maquet) combined with AnaConDa (Sedana) or flow-I (Maquet) with intermediate fresh gas flow (2-4l) to achieve detailed logging and uniformity of data registration. Data retrieval started as soon as sevoflurane was introduced using a self-controlled case series methodology. Exclusion criteria were; non-necessity of an extensive high dose sedation protocol including sevoflurane, unavailability of servo-u or flow-I ventilator, treatment with ECMO and family history of malignant hyperthermia. 7 patients who received the total sedation protocol were included, from May until November 2020. Informed consent was obtained from all patients. (medical ethics board Roeselare, April 26th 2020, protocol number B1172020000005)

The same ventilatory strategy was applied in all patients, including lung protective ventilation (pressure-controlled ventilation Vt= 6-8 ml/kg IBW, driving pressures 15 cmH2O, Titrated positive end-expiratory pressure > 5 cmH20 according to ARDS low peep table, inspiratory plateau pressure < 30 cmH20) whenever possible. Respiratory goals included a peripheral oxygen saturation of 88-92% and/or PaO2 of 55-80 mmHg, with arterial pH greater than 7.2.

Outcomes

The primary outcome was ventilatory stabilization, measured by daily peak airway pressure alarms and paralytic free days which were used as a surrogate for synchrony with the ventilator. Additionally, the effects of sevoflurane on

Table II

Baseline Characterestics

	Patient no 1	Patient no 2	Patient no 3	Patient no 4	Patient no 5	Patient no 6	Patient no 7
Age (years)	79	62	62	78	68	72	65
sex	Female	Male	Male	Female	Male	Female	Female
BMI (kg/m2)	22,8	24,4	27,7	30,1	31,6	33,2	41,3
SOFA score on admission ICU	3	4	3	4	7	4	8
Coexisting conditions	COPD	GERD	GERD	obesity	obesity	obesity	obesity
	Diabetes mellitus		Tobacco abuse	AHT	AHT	Bulbar ulceration	CHD
				Diabetes mellitus	Diabetes mellitus	CLL	OSA
							TIA
							Diabetes mellitus
Time to volatile sedation since intubation (days)	4	4	3	5	8	2	3
Duration of volatile sedation (days)	6	2	7	14	9	10	4
outcome	Dead	Survived	Dead	dead	Survived	Survived	dead

COPD=chronic obstructive pulmonary disease. GERD= gastroesophgeal reflux disease. AHT= arterial hypertension. CLL=chronic lymphocytic leukemia. OSA=obstructive sleep apnea. TIA=transient ischemic attack

oxygenation were analyzed by comparison of P/F ratio the day before and after initiation of sevoflurane.

Statistical analysis

Data concerning neuromuscular blocking drugs (NMBD) and peak airway pressures were not normally distributed and therefore compared by the Mann-Whitney U-test. Analysis of P/F ratio the day before and day after initiation of sevoflurane was compared by the Wilcoxon rank tests. Analysis was performed using SPSS statistics version 27.

Results

Baseline characteristics

7 patients were included with a median age of 68 years old (Table 2). Three patients were excluded because of need for extracorporeal membrane oxygenation (difficult anesthetic gas delivery). Four patients died during the study. Median SOFA score of included patients on day of admission was 4.

Effects of inhaled sevoflurane on ventilator synchrony

Once sevoflurane was added to the sedation protocol, other intravenous sedatives were stopped until patients were sedated with only inhaled anaesthetic in combination with an opiate and/or clonidine. The mean time from starting sevoflurane to achieving dual sedation was 47h. Statistical analysis was performed on a total of 71 ventilation days, including 49 days of sevoflurane administration. The daily number of high peak airway pressure alarms were significantly lower once sevoflurane was initiated, with a reduction in the number of alarms from a median of 3,5 to 1 per day, suggesting improved synchrony with mechanical ventilation ($p< 0,01$). (figure 1) Additionally, there was a significant increase in neuromuscular blocker free days, with a mean from 0,82 boli/day to 0,26 boli/day ($p<0,01$).

Effects of inhaled sevoflurane on oxygenation

Initiation of sevoflurane did not show significantly improved oxygenation measured by P/F ratio in this limited sample of patients ($p=0,67$).

Discussion

This observational pilot study demonstrates the potential of sevoflurane in mechanically ventilated

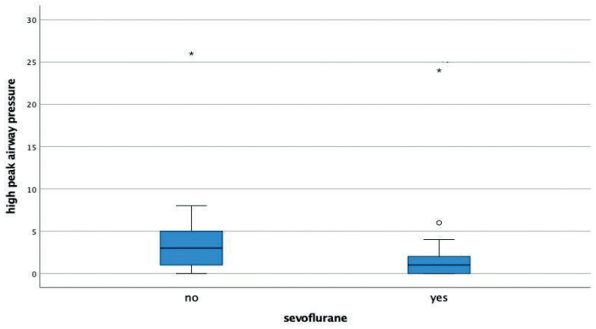

Fig. 1. — Daily high peak airway pressures. Significant reduction in daily high peak airway pressure alarms after initiation of sevoflurane.

COVID-19 patients with clear improvements in ventilatory synchrony, namely a reduction in peak airway pressures as well as the requirement of neuromuscular blockers.

To our knowledge, only one case series was published on inhaled anaesthetics in the sedation of this complex population using isoflurane and came to similar conclusions (11).

In contrast to ARDS not induced by COVID-19, unusually high sedation requirements are needed however the underlying reasons are not yet understood. Some suggest that this may be due to the younger age and good health of the population group. Our patient data did not support this theory however, as the mean age was 69 years (5). Other reasons that may contribute to more ventilator dyssynchrony are high fevers and an increased ventilatory drive which necessitate additional sedation (12).

Literature has shown that inhaled anaesthetics like sevoflurane are equally as safe as intravenous sedatives for long-term sedation in the ICU, with equivalent hemodynamic stability, no hepatorenal toxicity and that they can offer more than just sedation in ARDS (13, 14.) These benefits include immunomodulatory effects with neutrophil function modulation, and anti-inflammatory effects leading to a reduction in lung injury as well as a lower airway resistance due to dose dependent bronchodilatation (15). These effects may be similar in COVID-19 ARDS.

Alongside the possible sedation and stabilization advantages, inhaled anaesthetics may contribute to medication saving techniques as there are shortages of intravenous sedatives and paralytics reported all over the globe (8, 9). This might indicate the importance and need for the introduction of other options for sedation such as sevoflurane. Mortality during this self-controlled case series was

57% which is in line with large epidemiological reports (3, 16).

Technical delivery of sevoflurane was convenient using AnConDa system with servo-U ventilator, as well as administration via a conventional ventilator (flow-i) in combination with scavenging. Limited studies in the past have shown low occupational exposure limit values when using AnaConDa system (< 10 ppm) without the use of scavenging systems suggesting no health and safety risks for exposed personnel (17).

Although this study represents a limited sample size at a single center, it indicates that sevoflurane is likely an excellent sedative in COVID 19 ARDS showing a better compliance with mechanical ventilation.

Further research and long-term observational studies of ventilated COVID19 patients who receive sevoflurane are necessary to clarify the pharmacodynamic mechanisms and clinical effects in order to establish a sedation protocol for this challenging population.

Conclusions

Sevoflurane may be a good sedative and alternative in intubated patients with COVID 19 ARDS, improving synchrony with the ventilator. Larger, randomized trials are necessary.

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