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► To cite this version:

Léo Berger, Yohan Soreze, Jérôme Rambaud, Julie Starck, Yael Levy, et al.. Halogenated volatile anaesthetics for prolonged sedation in pediatric intensive care unit: first experience in two French pediatric intensive care units. *Intensive Care Medicine – Paediatric and Neonatal*, 2023, 1 (11), 10.1007/s44253-023-00009-y . inserm-04225821

HAL Id: inserm-04225821

<https://inserm.hal.science/inserm-04225821>

Submitted on 3 Oct 2023

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Halogenated volatile anaesthetics for prolonged sedation in pediatric intensive care unit: first experience in two French pediatric intensive care units

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Abstract

Objective Sedation is necessary for patients to achieve comfort and safety, but prolonged sedation can lead to the need for increased doses, resulting in withdrawal syndrome and delayed extubation. Inhaled anaesthetics (IAs) may cause less withdrawal syndrome while providing similar sedative effects to intravenous agents. This study aims to describe the efficacy of halogenated IAs during prolonged sedation and identify any adverse effects on the PICU.

Design This is a retrospective, bicentric cohort study.

Setting The study was conducted at two PICUs in university hospitals in Paris between January 2018 and December 2020.

Patients The study included 50 children (aged 2.2 years, [0.8–7.2]) who received prolonged sedation (> 72 h) and were sedated with volatile anaesthetics for at least 24 h.

Interventions No interventions were performed.

Measurements and main results The study found a statistically significant reduction in benzodiazepine dosages ($\mu\text{g}/\text{kg}/\text{h}$) (118 [62.5; 200] vs 80.0 [32.5; 120], $p < 0.01$). Similar results were observed for other hypnotics (ketamine 2.00 [1.00; 2.00] vs 1.50 [1.00; 2.00], $p = 0.036$, mg/kg/h; clonidine: 0.55 [0.35; 1.27] vs 0.20 [0.12; 0.43], $p = 0.036$, $\mu\text{g}/\text{kg}/\text{h}$). For opioids ($\mu\text{g}/\text{kg}/\text{h}$), no significant reduction in doses was observed 24 h after IA introduction (4 [1.00; 8.00] vs 4.00 [1.00; 6.70], $p = 0.7$). No major adverse effects were reported, although 26% of patients developed withdrawal syndrome.

Conclusions Halogenated IAs appear to be a promising therapy to reduce the dosages of hypnotics and opioids used during prolonged sedations.

Keywords Inhaled anaesthetics, Halogenated, Isoflurane, Prolonged sedation, Sevoflurane, Withdrawal syndrome

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Introduction

Sedation analgesia is a crucial aspect of the pediatric intensive care unit (PICU) and can pose challenges in critically ill patients. Its primary objectives are to enhance patient comfort, optimize ventilator synchronization, and facilitate invasive therapeutics or nursing care. Sometimes, it may also have more specific roles, such as neuroprotection or palliative care for end-of-life patients [1, 2]. However, the selection of sedatives for children is limited. The most commonly used hypnotic is midazolam, often combined with an opioid such as morphine or sufentanil. Propofol is contraindicated in children under the age of 15 years due to an increased risk of propofol-related infusion syndrome (PRIS). Although alpha-2-adrenergic agonists have been increasingly used in recent years, they do not provide deep sedation [3, 4]. Prolonged sedation in critically ill patients is associated with adverse events such as withdrawal syndrome or delirium, resulting in an extended duration of mechanical ventilation and PICU length of stay [5, 6]. Furthermore, during prolonged sedation, patients may develop a tolerance to the intravenous agents used, resulting in an increase in dosage and a loss of sedative effectiveness. These scenarios of sedation difficulty can be harmful to the patient.

Inhaled anaesthetics (IAs) are commonly used in the operating room during surgical procedures. Since the beginning of the twenty-first century, IAs have also been used in the ICU for prolonged sedation due to the development of a specific device that can be attached to modern critical care ventilators, such as the AnaConDa® humidifier filter. IA appears to be an appealing alternative for deep sedation of critically ill patients who require prolonged sedation due to their pharmacokinetics and ease of application. IA are minimally metabolized, leading to low tissue accumulation and a rapid wake-up time after discontinuation of IA [7]. The RESPIRE (Etude Rétrospective sur l'Effet d'une Sédation Prolongée par Agents Inhalés chez l'enfant en Réanimation) study aims to describe the effectiveness of IA during prolonged sedation in the PICU and report any adverse effects associated with IA introduction.

Materials and methods

Study design and data collection

We conducted a retrospective observational study in two PICUs. The inclusion criteria were children over 1-month-old (and over 36 weeks corrected age) but under 18 years old who had undergone invasive mechanical ventilation and sedation for more than 72 h. Additionally, they must have received continuous IA for at least 24 h to be eligible for inclusion in the study.

Patient data were extracted from our electronic patient data management system (ORBIS, France), while the

remaining medical data were obtained from the nurses' monitoring sheets. The RESPIRE study was reviewed and approved by the Ethics Committee of the SRLF (Société de Réanimation de Langue Française) with approval number CE SRLF 21–77. Procedures were conducted following the ethical standards of the committee responsible for human experimentation and in accordance with the Helsinki Declaration of 1975. The authors declare that they have no conflicts of interest to disclose for this study.

Clinical setting

All patients received mechanical ventilation and sedation with midazolam and opioids (morphine, sufentanil, or fentanyl). Some patients also received co-analgesic treatment (ketamine, clonidine, or dexmedetomidine). The data collected included ventilatory parameters such as respiratory rate, FiO_2 , PaO_2 , PaCO_2 , and $\text{PaO}_2/\text{FiO}_2$, hemodynamic parameters (heart rate, blood pressure, vascular filling, vasopressors), liver and kidney function blood samples (ASAT, ALAT, urea, creatinine), severity scores at PICU admission (PELOD II and PIM III), and sedation quality scores (COMFORT-B).

The optimal sedation score was defined as a score between 11 and 17 on the COMFORT-B scale. IA was prescribed as an alternative sedative when the clinician had difficulty achieving adequate sedation. Sedation was considered difficult in any patient with a COMFORT-B score above 17. Additionally, the decision to introduce IA rather than increase or start another IV drug was at the discretion of the clinician. IA (isoflurane or sevoflurane) was delivered using an Anaesthetic Conserving Device (AnaConDa®) from Sedana Medical, Danderyd, Sweden. The AnaConDa® (ACD) device was placed between the Y-piece and the endotracheal tube of the patient or directly on the inspiratory limb if the child weighed less than 30 kg. IA was administered in liquid form from specific syringes. A bolus of 1.5 ml was systematically given to purge the extender. An initial flow rate of 3 ml/h was set up, which was adapted secondarily according to the clinic (COMFORT-B) and the exhaled fraction (EF) gas, measured by a specific sensor. IA was stopped directly without any decrease due to their “on–off” effect.

Statistical analysis

We first conducted a descriptive analysis by calculating frequencies for qualitative data and medians (25th–75th percentiles) for quantitative data. To detect longitudinal changes between measurements at different time points, we used Mann–Whitney's *U* test for paired samples. Statistical significance was set at $p < 0.05$.

Results

Fifty critically ill children from two PICUs of a tertiary-care academic medical center were included in the study. Forty-five children were from Armand-Trousseau Hospital, and 5 patients were from Kremlin-Bicêtre Hospital, all of whom were treated with IA during the study period. The baseline characteristics of the study population are reported in Table 1.

During this study, we compared hemodynamic, respiratory, and sedative parameters during IA induction and then monitored them over the next 24 h. Table 2 lists the various settings that were measured during the first 24 h after the start of IA sedation. With regard to ventilatory settings, we divided patients into two groups: extracorporeal membrane oxygenation (ECMO) (21 patients) and non-ECMO (29 patients).

Table 1 Baseline characteristics

Patients,	n 50
Age (year), median [Q1-Q3]	2.6 [0.8;7.2]
Male, n (%)	33 (66%)
Comorbidity, n (%)	
Pneumological	9 (18%)
Oncological	9 (18%)
Neurological	5 (10%)
Hematological	5 (10%)
Prematurity	5 (10%)
Gastrologic	5 (10%)
Cardiological	1 (2%)
Other	11 (22%)
Reason for admission, n (%):	
Respiratory distress	22 (44%)
Surgical	7 (14%)
Hematological	9 (18%)
Septic shock	6 (12%)
Neurological	5 (10%)
Others	3 (6%)
Severity scores, median [Q1-Q3]	
PELOD predicted mortality (%)	9.6% [1;16]
PIM II predicted mortality (%)	3.9% [2.8; 5.3]
Duration (days), median [Q1-Q3]:	
ECMO, n (%)	21 (42%)
Survivors, n (%)	38 (76%)
Duration of intravenous sedation before IA, days [Q1; Q3]	8.4 [1; 7.8]
Duration IA dispensed, days [Q1-Q3]	4.5 [3; 9]
IA patients treated, n (%)	
- Isoflurane	45 (90%)
- Sevoflurane	5 (10%)

Data are median [interquartile range]

NMBA Neuromuscular blocking agents

Table 2 Respiratory, hemodynamic, and sedative parameters during 24 h after IA introduction (isoflurane of sevoflurane)

Parameters	Before IA introduction (H0)	After IA introduction (H24)	p
Respiratory, group without ECMO (n=29), median [Q1-Q3]:			
FiO2 (%)	40.0 [35.0; 60.0]	40.0 [30.0; 45.0]	0.02*
PaO2/FiO2	176 [120; 233]	240 [172; 285]	<0.001*
PEEP (cmH2O)	7.00 [5.00; 10.0]	7.00 [5.00; 10.0]	0.09
PaCO2 (mmHg)	51.0 [43.0; 60.0]	46.0 [39.0; 55.0]	0.097
pH	7.41 [7.28; 7.44]	7.43 [7.38; 7.46]	0.144
Group with ECMO (n=21), median [Q1-Q3]:			
FiO2 (%)	100 [50.0; 100]	50.0 [40.0; 100]	<0.001*
PaO2/FiO2	90 [60.0; 110]	145 [78.0; 180]	0.014*
PEEP (cmH2O)	10.0 [7.00; 10.0]	10.0 [8.00; 12.0]	0.26
PaCO2 (mmHg)	51.0 [44.0; 61.0]	46.0 [39.0; 55.0]	<0.01*
pH	7.44 [7.39; 7.47]	7.41 [7.30; 7.44]	0.1
Hemodynamic settings, median [Q1-Q3]:			
HR (per min)	124 [109; 142]	118 [95.0; 130]	<0.01*
MAP (mmHg)	66.5 [58.2; 77.8]	64.0 [60.0; 71.0]	0.44
Hepatic and renal assessments [Q1-Q3]:			
ASAT (U/l)	41 [29.0;80.2]	41 [29.0; 68.5]	0.44
ALAT (U/l)	23.0 [16.0; 45.5]	25.0 [17.0; 46.0]	0.66
Urea (mmol/l)	3.05 [2.10;4.80]	3.10 [2.40; 5.25]	0.12
Creatinine (µmol/l)	23.0 [18.5; 29.8]	25.5 [18.2; 31.8]	0.24

Data are median [interquartile range]

ASAT Aspartate aminotransferase, ALAT Alanine aminotransferase

*p < 0,05

In the non-ECMO group, we observed a significant decrease in the PaO2/FiO2 ratio 24 h after IA introduction. In the ECMO group, we also observed a significant decrease in the PaO2/FiO2 ratio and a significant reduction in the PaCO2 value (supplementary data).

Regarding hemodynamic parameters, during the first 24 h after IA application, 14 patients (28%) required fluid replacement. Nine patients (18%) were already receiving norepinephrine replacement, and only three additional patients (6%) required vasoactive support during this period. Norepinephrine was discontinued in three other patients 24 h after IA was introduced. We found no difference in blood pressure, but the heart rate decreased significantly. At 24 h after the introduction of IA, levels of aspartate aminotransferase and alanine aminotransferase were not statistically different. No renal insufficiency was found, and variations in urea level and creatinine were not significant. No specific serious adverse events related to IA were observed in this study.

We did not observe any differences in IA administration between the ECMO and non-ECMO groups, either in terms of IA rate (ml/h) (5.00 [4.00; 7.00] vs 6.00 [4.00;

Table 3 Inhaled anesthetic characteristics and withdrawal syndrome

Parameters	Before IA introduction (H0)	After IA introduction (H24)	p
COMFORT-B scale	10 [6.00; 10.0]	6 [6.00; 9.50]	0.2
Withdrawal symptoms after IA (H24), n (%)			
- Agitation		20 (40%)	
- Tachycardia		20 (40%)	
- Excessive sweating		9 (28%)	
- Hallucination		8 (16%)	
- High blood pressure		8 (16%)	
- Tremor		6 (12%)	

8.00], $p=0.72$) or in terms of EF (%) (0.50 [0.40; 0.60] vs 0.40 [0.40; 0.63], $p=0.9$).

Table 3 presents the occurrence of withdrawal symptoms. Thirteen patients (26%) developed withdrawal symptoms when sedation was discontinued or tapered. Additionally, we did not observe any significant changes in sedation quality after IA introduction. For evaluate sedation quality we used the COMFORT-B score. However, these results should be interpreted cautiously, as data for quality and depth sedation 38% of the patients were missing.

Sedation analgesia efficacy

All patients were sedated with midazolam, 22 children (44%) required ketamine, and six (12%) required clonidine before IA administration. We observed a significant reduction of 33% in midazolam dosage ($\mu\text{g}/\text{kg}/\text{h}$) 24 h

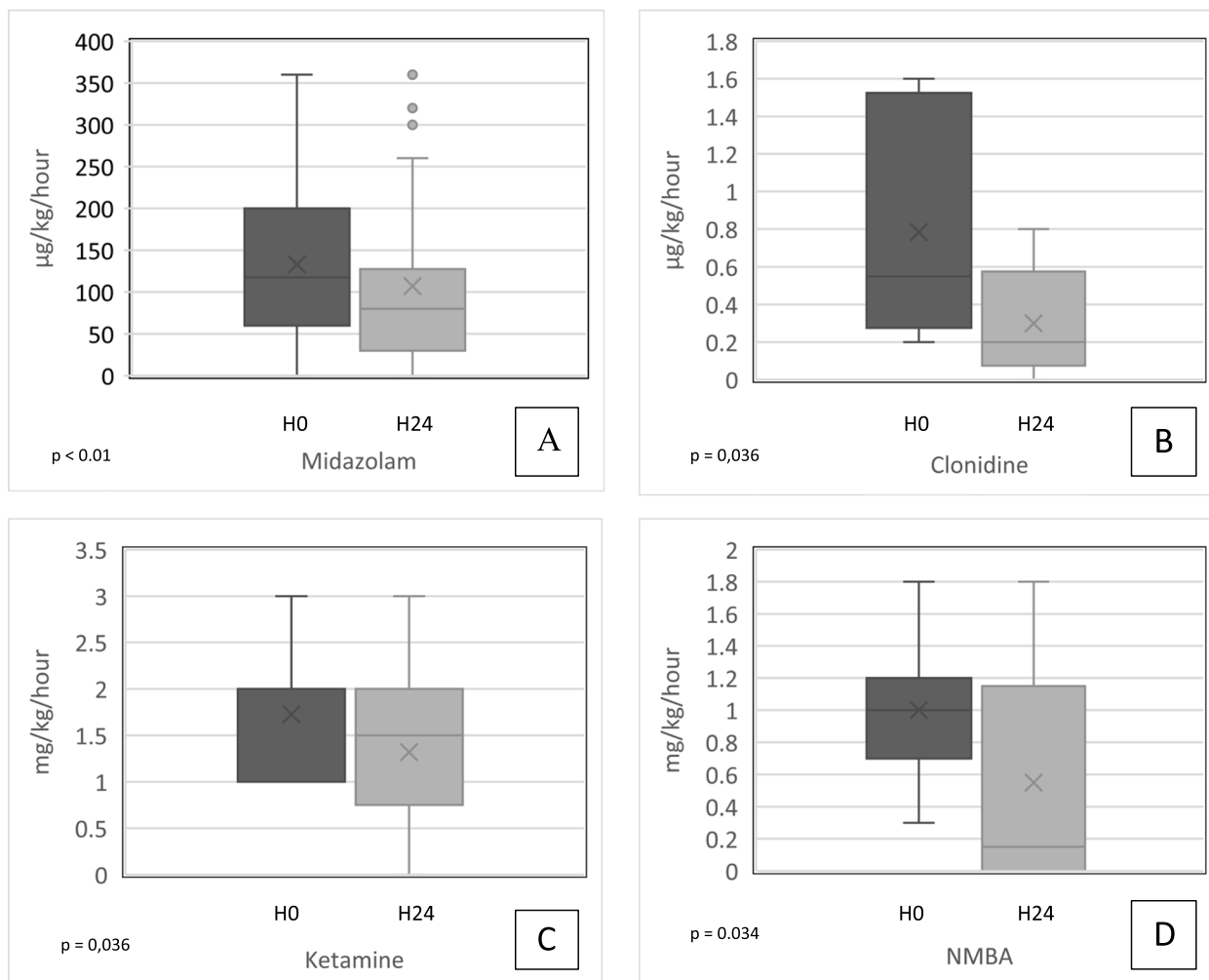


Fig. 1 Sedatives drugs and neuromuscular blockers drugs after introduction of inhaled anesthetics. Box plots several sedatives and NMBA before and 24 h after starting the inhaled. Median, 25th and 75th percentiles, 10th and 90th percentiles. Open circles represent values outside percentiles. NMBA neuromuscular blocking agents

after IA introduction (118 [62.5; 200] vs 80.0 [32.5; 120], $p < 0.01$) (Fig. 1a). We also found a significant decrease of 25% in ketamine consumption (mg/kg/h) (2.00 [1.00; 2.00] vs 1.50 [1.00; 2.00], $p = 0.036$) and a 66% decrease in clonidine consumption ($\mu\text{g}/\text{kg}/\text{h}$) (0.55 [0.35; 1.27] vs 0.20 [0.12; 0.43], $p = 0.036$) (Fig. 1b, c). Twelve patients (24%) required a neuromuscular blockade agent (NMBA) prior to IA, of which 24% required atracurium due to ARDS. We also found a significant decrease in NMBA dosage (mg/kg/h) 24 h after IA introduction (1.00 [0.90; 1.20] vs 0.15 mg/kg/h [0; 1.05]; $p = 0.034$) (Fig. 1d).

For analgesia, three different opioids were used ($\mu\text{g}/\text{kg}/\text{h}$). Fentanyl was used in 26 patients (52%), Sufentanil in 17 (34%), and morphine in seven (14%). We did not observe a significant reduction in opioid consumption 24 h after IA introduction (4 [1.00; 8.00] vs 4.00 [1.00; 6.70], $p = 0.7$).

Discussion

The RESPIRE study is currently the largest cohort reported in the literature involving the pediatric population. In this study, 50 patients required prolonged sedation (>72 h) to achieve adequate mechanical ventilation. Of these patients, 25 (50%) received multimodal sedation, which involved combining several hypnotics. All of the patients received midazolam, while ketamine was administered in 22 patients (44%) and clonidine in six patients (12%). IAs were only used when the clinician encountered difficulty in achieving adequate sedation. A significant decrease in the dosage of all hypnotics 24 h after the introduction of IA was observed. Additionally, a significant reduction in the dosage of neuromuscular blocking agents (NMBA) was also observed.

In the PICU, long-term sedation can be challenging for patients who require mechanical ventilation and invasive care. Optimal sedation should provide patient comfort and calm during nursing while allowing for easy arousal. During prolonged sedation, accumulating sedative drugs and their metabolites can lead to withdrawal syndrome and delirium. There is also a phenomenon of tolerance, which results in a gradual increase in doses and secondary to oversedation. Inadequate awakening can prolong invasive mechanical ventilation, leading to longer PICU stays. To avoid oversedation and withdrawal syndrome, a few strategies have been suggested, such as daily interruption of sedation or using nurse-implemented sedation protocols [5].

The ideal hypnotic is still unknown, but it should ideally provide a rapid and easily reversible sedative effect without major side effects. Therefore, IAs are of interest in the context of prolonged sedation. IA has several advantages. Initially used for anesthesia, they provide a faster induction with low solubility and limited tissue accumulation.

They can also provide deep sedation without major side effects other than moderate cardiac depression [8–11].

In 2016, Jerath et al. conducted a meta-analysis of 15 randomized prospective trials in adult ICU, comparing IA sedation (desflurane, isoflurane, or sevoflurane) with IV sedation (midazolam or propofol). The primary outcome was the time from cessation of sedation to awakening. Secondary outcomes were time to respond to verbal commands, ICU length of stay, and mortality. Overall, 8 studies involving 523 patients found a significant reduction in extubation time after weaning from sedation in favor of the IA group (–52.7 min; 95% CI [–75.1; –30.3], $p < 0.001$). The results were more pronounced when comparing IA with midazolam (–292.2 min; 95% CI [–384.4; –200.1], $p < 0.001$) than IA with propofol (–29.1 min; 95% CI [–46.7; –11.4], $p < 0.001$). There were no significant differences in secondary endpoints [12].

In the pediatric population, data regarding the use of IA during prolonged sedation are rare. In 2018, Mencia et al. conducted a prospective, multicenter cohort study to assess the interest in sevoflurane for prolonged sedation in pediatric resuscitation. A total of 23 patients were included, and sevoflurane was introduced when clinicians encountered sedation difficulties despite the combination of multiple therapies (hypnotics and morphine). Forty-eight hours after the introduction of sevoflurane, they reported a significant reduction in some hypnotic therapies (Midazolam and Fentanyl) in 78% of patients. The average duration of sedation with sevoflurane was 5 days. Interestingly, withdrawal syndrome occurred only in patients who received sevoflurane for more than 6 days [13].

More recently, a German study suggested that using isoflurane for prolonged sedation in the PICU for patients with severe lung disease is feasible and safe compared to children with “healthy” lungs. Twenty-nine patients were included, and no significant difference was found between the two groups. They also reported no major side effects except for moderate hypotension [14]. There are also some reported cases of prolonged use of IA in children with severe ARDS, sometimes supplemented by ECMO, showing reduced sedative doses after IA introduction [15–21].

Regarding opioid use, we observed a significant reduction in fentanyl and sufentanil doses. However, there was no statistical difference in morphine consumption. IA does not have an analgesic effect of their own. However, using PET-CT, Alkire et al. found that the neurological action target of IA would be the thalamus and the cross-linked substance. This site of action would allow modification of nociceptive integration and could potentially potentiate the analgesic effect of morphine [22].

In 2021, a randomized controlled non-inferiority trial was published to assess whether using isoflurane for prolonged sedation was as effective as propofol. A total of 301 adult patients were randomized (150 in the isoflurane group and 151 in the propofol group) and followed for 24 h. The quality of sedation, assessed by the RASS scale with predefined targets, was similar in both groups (isoflurane 90.7%, 95% CI [8–94]; propofol: 91.1%, 95% CI [2–95]). Regarding opioid consumption, they reported a significant reduction of 29% in the isoflurane group. Furthermore, the time to wake up after cessation of sedation was significantly shorter in the isoflurane group (20 min [10–30] vs 30 min [10–120], $p < 0.001$). No serious adverse events were reported. However, delirium was reported in 5% of patients in each group [23].

We also observed a significant decrease in NMBA doses 24 h after introducing halogenated agents. Several studies have reported similar findings, reinforcing the idea that halogenated agents have potentiating effects with NMBA. In 2015, Ye et al. showed that sevoflurane enhances the neuromuscular blocking effect of curare by indirectly increasing skeletal muscle sensitivity to neuromuscular blockers [24]. IA have several effects on the respiratory tract and especially a bronchodilator effect, making their use interesting in context of asthma [25–32]. We observed an improvement in oxygenation ratios within 24 h after IA introduction. Recent studies have investigated ARDS. Jabaudon et al. conducted a randomized study of 50 patients and compared patients sedated with sevoflurane versus midazolam. They found a significant improvement in the $\text{PaO}_2/\text{FiO}_2$ ratio 48 h after the introduction of sedation in the sevoflurane group (205 ± 56 vs 166 ± 59 , $p = 0.04$). Alveolar and plasma cytokines were also significantly lower in the sevoflurane group. The authors found no difference in sedation efficacy, opioid, and NMBA doses, or incidence of adverse events such as hypotension or renal failure [33].

No serious adverse effects of IA sedation were reported during the study period. We did not report significant hypotension but 14 patients (28%) required fluid replacement, and only three (6%) requiring vasopressor support. Each patient received repeated blood tests during the study period, and no renal failure or hepatic cytolysis was observed. Renal tubulopathy secondary to prolonged isoflurane sedation has been described in the literature but only in rat models. No human toxicity has been demonstrated for isoflurane or sevoflurane but they could have a neurotoxic effect, especially on new born brain [34–38]. However, questions have been raised regarding an association between prolonged administration of IA and the occurrence of insipid nephrogenic diabetes (DIN). A retrospective study included 35 patients who received prolonged sedation with sevoflurane (92 h [22–135]).

Seven patients (20%) met the DIN criteria, and in these seven patients, the duration of exposure was significantly longer. Additionally, the EF of sevoflurane was significantly higher in these seven patients. No difference in mortality was found between the two groups. However, withdrawal syndrome occurred in 26% of patients after discontinuing IA sedation [39].

A limited amount of data is available in the literature regarding withdrawal syndrome associated with IA. Mencia et al. reported withdrawal syndrome in 26% of patients following the discontinuation of sevoflurane. However, since their study discontinued only sevoflurane, the withdrawal syndrome was attributed solely to halogenated. In our study, several drugs were stopped simultaneously, which poses a significant source of bias when attributing the syndrome to only one agent. Based on our findings, halogenated could be a promising approach to reduce IV sedatives, opioids, and NMBA drugs in PICU and shorten the length of stay.

There are several limitations to this study that need to be acknowledged. Firstly, it is a retrospective study, which introduces the potential for selection bias. A prospective, randomized study would be less susceptible to bias. Furthermore, some of the data collected was from handwritten nursing records, which could introduce additional biases. For instance, sedation scores on the COMFORT-B scale were not available for 36% of patients, which increases the risk of over or underestimating the data.

Additionally, there was no predefined sedation protocol. All patients received midazolam, and the decision to increase doses or introduce a new IV drug was at the clinician's discretion. The choice of using IA rather than an IV drug was also up to the clinician, partly due to the newness of IA in our services and the absence of a clearly established protocol. The assessment of withdrawal syndrome was left to the clinician's judgment, and there was no predetermined scoring system, which could introduce bias. Furthermore, the study population included patients with a poor prognosis (34% mortality, 42% on ECMO), so these findings must be cautiously applied to a larger pediatric population. Additional prospective studies are required to better evaluate the tolerability and feasibility of prolonged halogenated sedation in the PICU.

Conclusion

Prolonged sedation with IAs appears to be a straightforward approach to maintaining long-term sedation in the PICU and may be a promising strategy. The use of IA has the potential to decrease the dosage of other hypnotics. This study did not report any significant side effects

associated with IA sedation. Using a specialized device on the respiratory circuitry, IA sedation could serve as an alternative method to the typical midazolam-based intravenous regimen. However, further prospective studies are necessary to assess the safety and efficacy of IA sedation in the PICU.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Berger Léo, and Léger Pierre-Louis. The first draft of the manuscript was written by Berger Léo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate

The RESPIRE study was reviewed and approved by the Ethics Committee of the SRLF (Société de Réanimation de Langue Française) with approval number CE SRLF 21–77. Procedures were conducted following the ethical standards of the committee responsible for human experimentation and in accordance with the Helsinki Declaration of 1975.

Competing interests

The authors declare that they have no conflicts of interest to disclose for this study.

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Received: 15 February 2023 Accepted: 12 June 2023

Published online: 14 July 2023

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