Journal of Intensive Care Medicine
2021, Vol. 36(11) 1305–1312

DOI: 10.1177/0885066620953395
journals.sagepub.com/home/jic
SAGE

Long-Term Inhalative Sedation in Children With Pulmonary Diseases

Jochen Meyburg, MD[1], David Frommhold, MD[2,3], Johann Motsch, MD[4], and Navina Kuss, MD[2]

Abstract

Objectives: To describe safety and feasibility of long-term inhalative sedation (LTIS) in children with severe respiratory diseases compared to patients with normal lung function with respect to recent studies that showed beneficial effects in adult patients with acute respiratory distress syndrome (ARDS). **Design:** Single-center retrospective study. **Setting:** 12-bed pediatric intensive care unit (PICU) in a tertiary-care academic medical center in Germany. **Patients:** All patients treated in our PICU with LTIS using the AnaConDa® device between July 2011 and July 2019. **Measurements and Main Results:** Thirty-seven courses of LTIS in 29 patients were analyzed. LTIS was feasible in both groups, but concomitant intravenous sedatives could be reduced more rapidly in children with lung diseases. Cardiocirculatory depression requiring vasopressors was observed in all patients. However, severe side effects only rarely occured. **Conclusions:** In this largest cohort of children treated with LTIS reported so far, LTIS was feasible even in children with severely impaired lung function. From our data, a prospective trial on the use of LTIS in children with ARDS seems justified. However, a thorough monitoring of cardiocirculatory side effects is mandatory.

Keywords

inhalative sedation, anesthetics, AnaConDa®, isoflurane, ARDS, PICU

Introduction

Despite recent therapeutic advances, acute respiratory distress syndrome (ARDS) in children remains a serious condition with mortality rates of 22-40%.[1] As in adults, lung-protective ventilation is the key to improve the outcome in severely affected children, hence the Pediatric Acute Lung Injury Consensus Group promotes the use of low tidal volumes and adequate positive endexspiratory pressure (PEEP) to prevent both volo- and atelectrauma.[2] Beyond these widely adopted ventilation strategies, there might be an additional way of lung protection in ARDS. A growing amount of data suggest that volatile anesthetics have beneficial effects in animal models of ARDS.[3,4] Besides reduction of inflammatory mediators, preservation of alveolar-epithelial integrity has been observed.[5] These effects might be substance-specific with better results for isoflurane and sevoflurane as compared to desflurane.[6]

Following a meta-analysis which showed that adult patients had better outcomes after cardiac surgery when they received inhalative as compared to intravenous anesthesia,[7] Bellgardt at al. retrospectively analyzed their patient cohort of critically ill surgical patients in the intensive care unit (ICU). They could show that long-term inhalative sedation (LTIS) with isoflurane reduced the risk of death during the hospital stay and within the first 365 days compared to intravenous sedation with midazolam and propofol.[8] Recently, several clinical trials have shown that LTIS using either isoflurane or sevoflurane in adult patients with ARDS is feasible, and decreases markers of alveolar epithelial injury and inflammatory biomarkers.[9-11] However, the use of volatile anesthetics in patients with lung injury remains controversial, as older studies suggest they may have deleterious effects on the alveolar epithelia[12,13] and impair ventilation/perfusion mismatch in injured lungs.[14]

Experience with LTIS in children is limited. The anesthetic conserving device AnaConDa® which is used in the treatment of adult patients, has a relatively large dead space which restricts its use in the pediatric intensive care unit (PICU) to adolescents. However, the system may be modified to deliver volatile anesthetics to the breathing circuit of smaller children and even infants, but this modification implies the loss of the

[1] Department of General Pediatrics, University Children's Hospital, Heidelberg, Germany
[2] Department of Neonatology, University Children's Hospital, Heidelberg, Germany
[3] Department of Pediatrics, Klinikum Memmingen, Germany
[4] Department of Anesthesiology. University Hospital Heidelberg, Germany

Received December 10, 2019. Received revised April 20, 2020. Accepted August 7, 2020.

Corresponding Author:
Jochen Meyburg, University Children's Hospital, Im Neuenheimer Feld 430, D-69120 Heidelberg, Germany.
Email: jochen.meyburg@med.uni-heidelberg.de

conservation of anesthetics and the need for a special scavenging system. While some patients in the few pediatric studies on LTIS had pulmonary diseases, it is not clear whether they responded to LTIS to the same extent, and had the same rate of side effects as compared to children with healthy lungs.

To this end we retrospectively analyzed our data on LTIS in pediatric patients with and without respiratory diseases using the AnaConDa® system. We hypothesized that patients with lung disease would need more concomitant intravenous sedation due to impaired isoflurane uptake, because it would be more difficult to provide stable MAC, resulting in a higher rate of side effects.

Methods and Materials

Study Design and Data Collection

This study was a retrospective chart review of all patients treated in our PICU with LTIS using the AnaConDa® device between July 2011 and July 2019. The study was reviewed and approved by the Institutional Review Board of the University Hospital Heidelberg (S-201/2019). Patient data were extracted from our electronic patient data management system (ISH-MED, SAP SE, Walldorf, Germany) which includes digital scans of all paper-based documentation (HYDMedia G5, Agfa Healthcare, Greenville, SC, USA). To assess neurological outcome, discharge reports and documentation from ambulatory follow-up visits or subsequent hospital admissions were analyzed likewise.

Clinical Setting

All patients were treated on a 12-bed general PICU in a tertiary-care academic medical center. During the study period, all patients who received mechanical ventilation in our institution were sedated with midazolam at a dosage of 0.2-0.4 mg/kd x h and sufentanil 0.5-1.0 µg/kg x h. When adequate sedation could not be achieved by this combination, esketamine was added at a dosage of 0.5-1.0 mg/kg x h. Children were eligible for LTIS if they met the following conditions: (1) Long-term mechanical ventilation requiring sedation of at least 5 days, (2) difficult intravenous sedation, i.e. increasing demand of sedatives defined as midazolam doses $\geq$ 0.4 mg/kg x h and/or sufentanil $\geq$ 1.0 µg/kg x h, and/or esketamine $\geq$ 1.0 mg/kg x h, and (3) absence of contraindications to inhalative sedation (cardiocirculatory instability or renal failure).

Isoflurane was administered using the anesthetic conserving device AnaConDa® (Sedana Medical, Danderyd, Sweden) with 1 of 3 different ventilators: Servo-I (Maquet, Solna, Sweden), Evita V500, or Babylog VN500 (both Dräger, Lübeck, Germany). To avoid excessive deadspace in our pediatric patients, the AnaConDa® was connected between the respirator and the inspiratory limb of the respiratory circuit as previously described.[15] Isoflurane was administered into the breathing circuit via a syringe pump (Perfusor® Space, Braun, Melsungen, Germany), and a scavenging system (Contrafluran, Zeosys, Berlin, Germany) was attached to the expiratory port of the ventilator. Endtidal isoflurane concentrations were measured with an anesthesia gas analyzer monitor (MAX Multigas Analyzer, Phasein, Danderyd, Sweden).

Appropriate sedation (both intravenous and inhalative) was assessed with the COMFORT B scale, aiming at scores of 12-15,[16] at the following time points: start of LTIS, 6/12/24/48 hours thereafter, and 2 hours before discontinuation. Doses of intravenous sedatives were adapted to reach adequate sedation, whereas isoflurane rates were adjusted to maintain expiratory concentrations of 0.5 MAC according to the initial study by Sackey et al.[17] If a patient was still deeply sedated after all intravenous sedatives had been discontinued, isoflurane rates were also decreased and expiratory concentrations < 0.5 MAC were accepted. However, because of insufficient data on potential neuro- and nephrotoxicity, isoflurane rates were not increased beyond 0.7 MAC in phases of insufficient sedation. Blood gas analyses, vital parameters, and ventilator settings were documented every 2 hours. For the retrospective analysis, these parameters were taken from the PDMS at the following time points: start of LTIS, 2/4/6/12/24/48 hours thereafter, and 2 hours before discontinuation. The following laboratory parameters, taken prior to inhalative sedation, during LTIS, and afterward, were analyzed: red blood cell count, white blood cell count, platelet count, hemoglobin, creatinine, blood urea nitrogen, aspartate aminotransferase, alanin aminotransferase, and gamma glutamyl transferase. Fluctuations of MAC and isoflurane delivery rates were calculated as percentual changes between 2 consecutive time points. Plasma fluoride concentrations were measured in children at risk for renal insufficency.

Statistical Analysis

Differences between the 2 groups were analyzed by Student's t-test for continuous and Chi-Square test for categorial variables. To detect longitudinal changes between measurements at different time points, Student's t-test for related samples was used. P values of less than 0.05 were regarded as statistically significant. All analyses were performed in SPSS 20 (IBM Corporations, Armonk, New York).

Results

Patient Characteristics, Inhalative Sedation, and Outcome

Patient characteristics are shown in Table 1, underlying diseases are given in Table 2. The 2 groups had similar sizes. Multiple courses of LTIS were administered to 2 patients with pulmonary diseases and 3 with extrapulmonary diseases, respectively. Taken together, 37 courses of inhalative sedation were analyzed. Patients with extrapulmonary diseases were older and heavier. No significant differences were found regarding time of intravenous sedation prior to LTIS or the duration of inhalative sedation.

Fraction of inspired oxygen, arterial partial pressure of carbon dioxide, peak inspiratory pressure, PEEP, and minute

Table 1. Patient Characteristics.

Parameter	Patients with pulmonary disease	Patients with extrapulmonary disease	p
Number of patients	15	14	
Male: female patients	6: 9	9: 5	n. s.
Age [years]	4.0 ± 3.5	5.8 ± 5.2	n. s.
Body weight [kg]	11.0 ± 5.7	20.8 ± 16.7	0.041
Courses of inhalative sedation	19	18	
Duration of intravenous sedation [days]	11.7 ± 8.5	12.5 ± 9.8	n. s.
Duration of inhalative sedation [days]	9.3 ± 8.7	5.8 ± 4.6	n. s.
FiO_2 [%]	58.2 ± 11.0	30.5 ± 5.4	0.001
pCO_2 [mm Hg]	54.9 ± 7.8	45.7 ± 5.9	<0.001
Minute ventilation [ml/min x kg bodyweight]	231 ± 49	146 ± 66	<0.001
Tidal volume [ml/kg bodyweight]	7.8 ± 1.4	7.1 ± 1.2	n. s.
Peak Inspiratory Pressure	21.6 ± 4.1	17.6 ± 3.6	0.004
PEEP [mbar]	6.5 ± 1.9	5.3 ± 1.0	0.023
Endtidal isoflurane concentration [MAC]	0.53 ± 0.06	0.52 ± 0.09	n. s.
Isoflurane delivery rate [ml/h]	9.1 ± 2.8	9.2 ± 4.8	n. s.
Fluctuation of endtidal isoflurane concentration [%]	18.4 ± 8.4	15.5 ± 9.8	n. s.
Fluctuation of Isoflurane delivery rate [%]	18.3 ± 11.0	23.5 ± 35.5	n. s.

Values are expressed as mean and standard deviation. n.s.: not significant.

Table 2. Causes of Long-Term Mechanical Ventilation.

Patiens with pulmonary diseases (n = 15)	Patients with extrapulmonary diseases (n = 14)
Pneumonia (n = 10)	Liver transplantation (n = 3)
ARDS (n = 3)	Shock / multi organ failure (n = 2)
Alveolar proteinosis (n = 1)	Gastrointestinal bleeding (n = 1)
Recurrent pleural effusions (n = 1)	Dystonic crisis (n = 1)
	Intractable pain (n = 1)
	Midface reconstruction (n = 1)
	Bacterial laryngotracheitis (n = 1)
	Spinal muscle atrophy (n = 1)
	Intraabdominal abscess (n = 1)
	Nasal encephalocele (n = 1)
	Gastroschisis (n = 1)

ventilation were significantly higher in the patients with pulmonary diseases (Table 1, Figure 1). Mean alveolar isoflurane concentration, isoflurane delivery rates, and fluctuation of these 2 parameters were similar in both patient groups.

One patient of the extrapulmonary group died 2 weeks after the discontinuation of isoflurane from complications of liver transplantion that were unrelated to LTIS. Of the 15 patients with pulmonary disease, 8 could be extubated, and 3 required tracheostomy. In 1 patient, LTIS was terminated before transfer to a different hospital. Extubation was successful in 9 of the 14 patients with extrapulmonary disease, 3 children could be extubated after switching to intravenous sedation, and 2 patients required tracheostomy.

Ten of the children with pulmonary diseases were neurologically impaired (defined as developmental problems that affected the child's behavior or ability to communicate diagnosed by clinical assessment and/or parental report[18]) before admission to the PICU. No neurological consequences were found in the remaining 5 patients. Of the children with extrapulmonary disease, 3 (including the patient who eventually died) had neurological impairment prior to LTIS. Of the 11 neurologically healthy children, 8 did not have neurological sequelae, 1 developed severe neurological impairment (after an eventful liver transplant), and no further information about the neurological outcome were available in the remaining 2 children.

Sedatives

Adequate sedation could be obtained in all patients with expiratory isoflurane concentrations of about 0.5 MAC. Doses of intravenous sedatives were adapted accordingly to reach adequate COMFORT-B scores (baseline: 16.3 ± 3.1; 6 hours: 11.7 ± 3.9; 12 hours: 13.0 ± 4.1; 24 hours: 11.8 ± 2.5; 48 hours: 12.3 ± 2.6; before discontinuation: 13.5 ± 2.3). Midazolam could be discontinued in 25% of the LTIS courses in children with pulmonary diseases, and in 35% of the patients with healthy lungs, but this difference was not statistically significant. Neither did we find significant differences between the 2 groups regarding the discontinuation of sufentanil (25% vs. 31%) or esketamine (85% vs. 55%). However, these concomitant intravenous sedatives could be reduced significantly faster in children with pulmonary compared to extrapulmonary diseases (Figure 2). In both groups, the use of clonidine toward the end of LTIS was favored to have a positive impact on the development of delirium.

Additional sedatives (fentanyl, dexmedetomidine, and propofol, respectively) were used in 4 children prior to LTIS and were discontinued shortly after commencing LTIS. One child, a 15 year old girl with intractable pain, additionally received methadone and hydromorphone which was not changed during LTIS. Vecuronium for muscle relaxation was used in 4 children, and could be discontinued in all but 1 patient during the first 48 hours of LTIS.

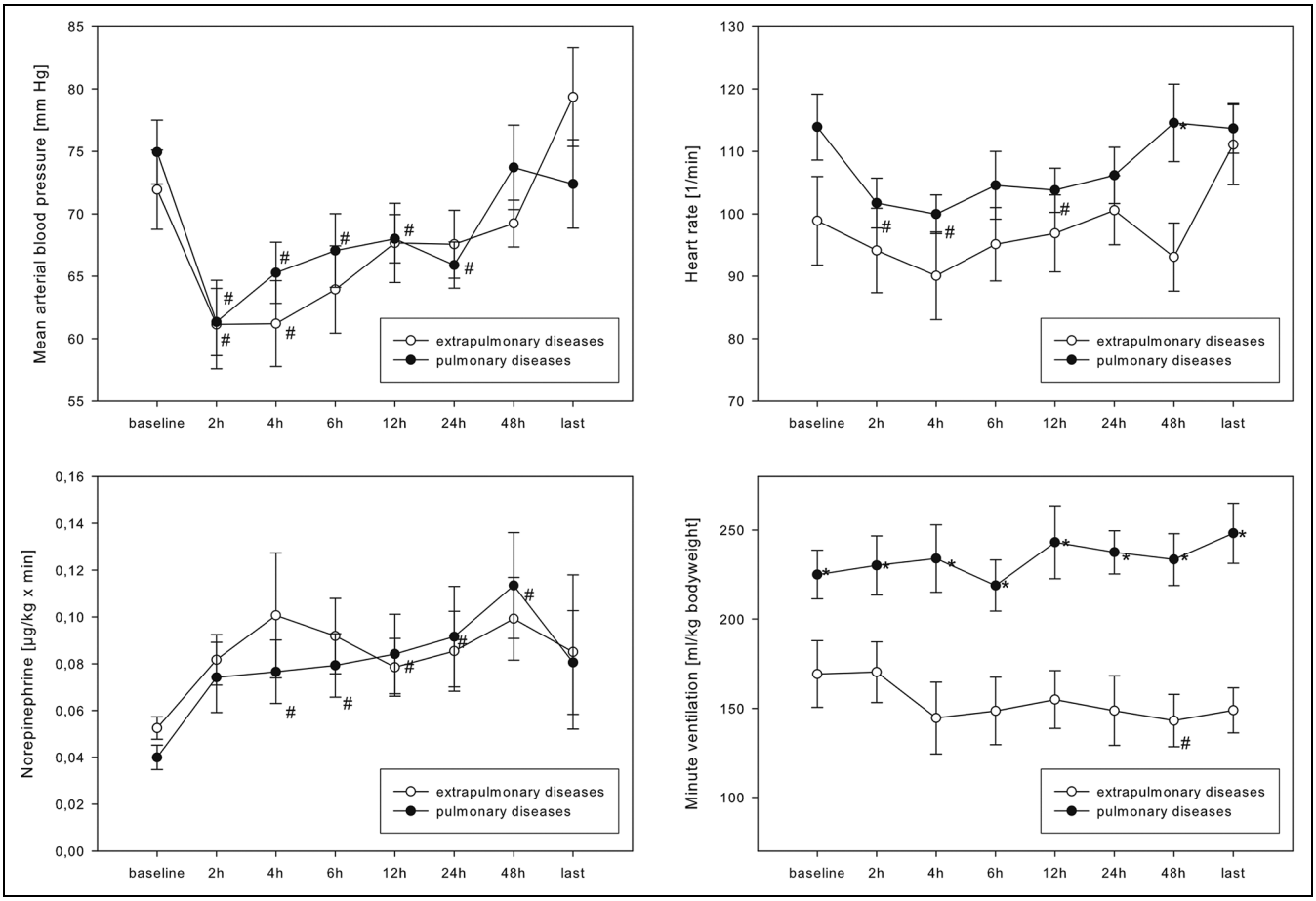

Figure 1. Mean arterial blood pressure, heart rate, norepinephrine doses, and minute ventilation in children with (black circles) or without (white circles) pulmonary diseases. Values are shown as mean and standard errors. # $p < 0.05$ compared to baseline, * $p < 0.05$ comparing the 2 patient groups.

Effects on Circulation

Mean arterial blood pressure as well as heart rate significantly decreased in the first 2-4 hours after commencing LTIS (Figure 1). Values returned to pre-LTIS levels within 48 hours using increased doses of norepinephrine. These observations were made in both patient groups, however, the circulatory effects were more pronounced (and statistically significant to a greater extent) in the children with pulmonary disease. In all 29 patients, mean arterial blood pressure decreased within the first 24 hours after initiating LTIS, and vasopressors were started or increased in all but 2 children.

Of note, clinically relevant decreases in blood pressure were noted in 2 patients (both with extrapulmonary disease). While 1 patient, who had accidentally received isofluran at 1.2 MAC, recovered quickly after temporary cessation of the anesthetic, one 16 year old patient with septic shock did not and the AnaConDa® system had to be withdrawn subsequently.

Laboratory Parameters

In 1 child with recurrent pleural effusions due to tuberculosis, liver enzymes and blood urea nitrogen significantly increased under LTIS, and returned to pre-treatment levels within a few days after discontinuation of isoflurane. Of note, major changes to the tuberculostatic therapy were made on the same day that LTIS had been started, and the aspartate aminotransferase levels were already high at baseline. In all other children, laboratory parameters were unaffected by LTIS, albeit not normal in some patients due to their underlying diseases. In children at risk for renal insufficiency, plasma fluoride levels were measured. However, due to the retrospective study design, number and the timing of fluoride measurement widely varied between the individual patients (Figure 3). While all measured fluoride levels were below the toxic threshold of 50 µg/l,[19] at least in 1 patient it has to be suspected that toxic concentrations would have been reached in case isoflurane had not been discontinued (Figure 3, lower panel). There was no correlation between duration of LTIS and fluoride levels.

Discussion

Prolonged inhalative sedation on the PICU using a conventional vaporizer was first described 25 years ago by Arnold et al. In this study on 10 patients, relatively high endtidal

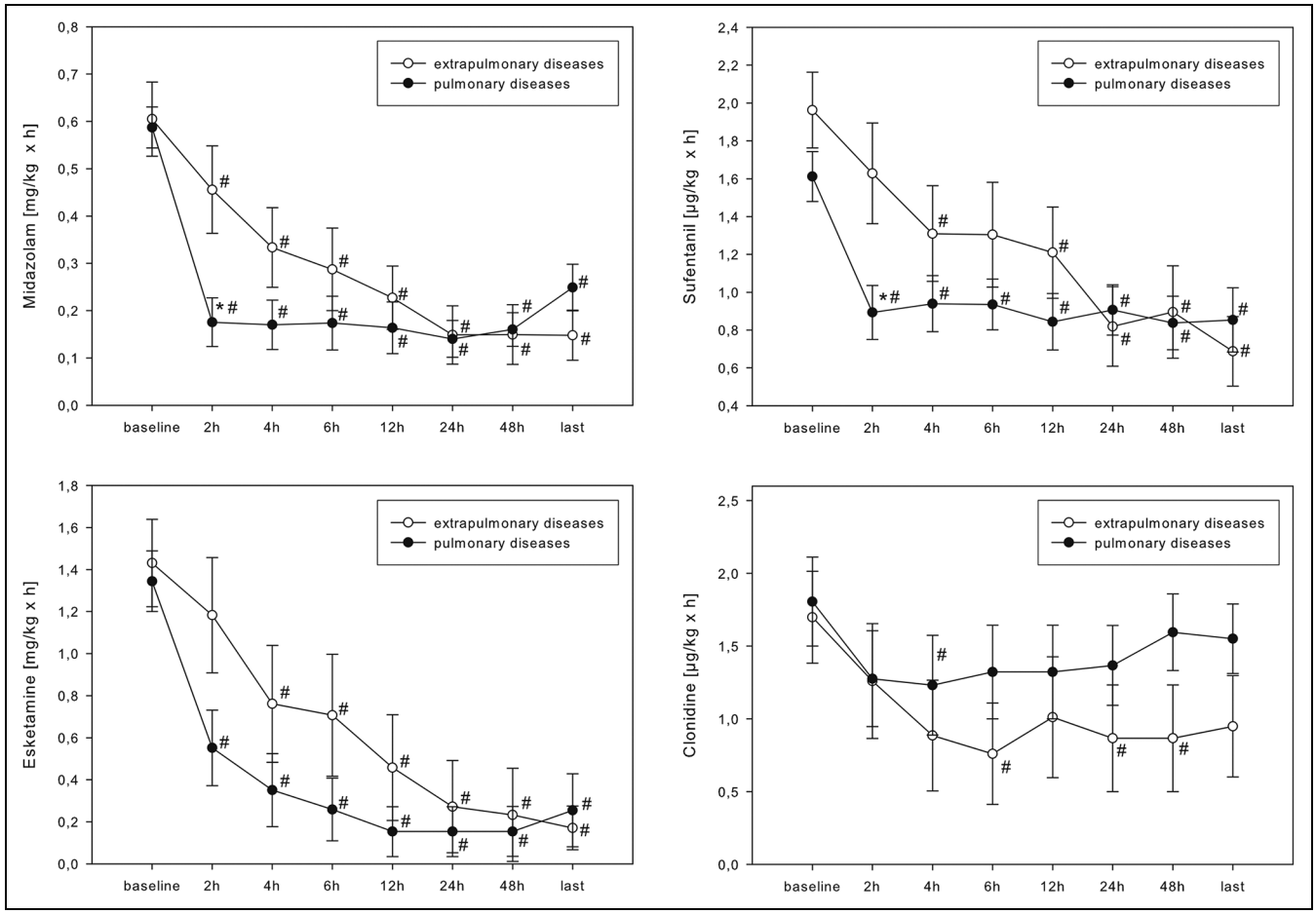

Figure 2. Doses of concomitant intravenous sedatives prior to the start of the inhalative sedation (baseline), after 2/4/6/12/24/48 hours, and 2 hours before termination of isoflurane (last). Black circles: patients with pulmonary diseases, white circles: patients with extrapulmonary diseases. Values are shown as mean and standard errors. # $p < 0.05$ compared to baseline, * $p < 0.05$ comparing the 2 patient groups.

isoflurane concentrations of 2.0% were reached using a conventional vaporizer, a fact that possibly explains decreases in blood pressures and transient hepatotoxicity.[20] Sackey et al. introduced the concept of a modified AnaConDa® device in the inspiratory limb of the ventilator for LTIS in children.[17] More recently, 2 studies with larger pediatric cohorts showed that this approach is feasible in the PICU.[15,21] However, the vast majority of these patients had extrapulmonary rather than pulmonary diseases requiring long-term mechanical ventilation. One of 3 patients in Sackey's 2005 study had "significant respiratory distress" and responded well to isoflurane sedation.[17] None of the 15 patients in the study by Eifinger et al. had primary pulmonary pathology, and only a small subset of patients (4/23) in the study by Mencia et al. were ventilated due to respiratory disease.[15,21] Another 5 infants with severe bronchiolitis due to infection with respiratory syncitial virus (RSV) received LTIS with sevoflurane in the case report series by Nacoti et al.[22] Although the period of inhalative sedation was rather short (mean Sevoflurane MAC-hours: 41.2), increased respiratory mechanics and gas exchange could be demonstrated in all 5 patients. Despite of the low patient number, this study is remarkable because bronchial obstruction plays a major role in the pathogenesis of RSV bronchiolitis, and sevoflurane as well as isoflurane are potent bronchodilators.

Based on the positive results of the recent adult studies on inhalative sedation in ARDS[23] it is tempting to promote its use also in children with severe lung diseases. However, such recommendation cannot be justified by the existing literature. Only small patient numbers have been reported so far (10 patients from 4 studies), and a comparison to children without pulmonary diseases is lacking. Our retrospective study aimed to shed some light on this question.

Our patient series is the largest reported so far with 29 patients that received a total of 37 courses of LTIS. It has an almost equal distribution of children with pulmonary and extrapulmonary diseases thus allowing a comparison between these 2 groups. In both patient groups, adequate sedation could be achieved with LTIS. The rate of successful extubation as the primary goal of LTIS did not significantly differ between the 2 groups. The targeted endexpiratory MAC could be reached in both groups without significant fluctuations over time. In

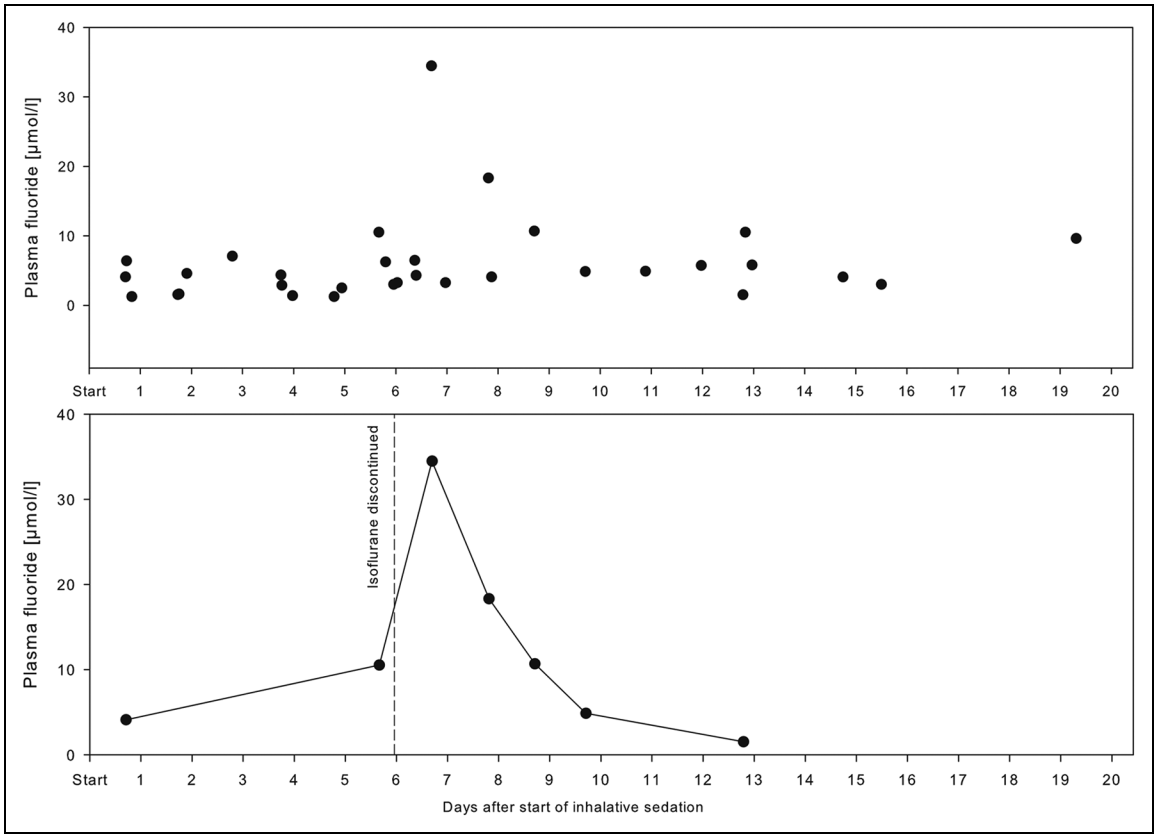

Figure 3. Plasma fluoride concentrations at different time points during inhalative sedation (upper panel, pooled from 11 patients), and in one individual patient (lower panel).

contrast to our initial hypothesis, patients with pulmonary diseases did not need higher doses of concomitant intravenous sedatives. More surprisingly, these sedatives could be reduced much faster in children with lung diseases after the initiation of LTIS than in the patients with healthy lungs. Although we did not measure plasma isoflurane levels, we speculate that a lower demand of intravenous sedatives reflects a higher isoflurane concentration in the blood. This could be explained by the significantly higher minute ventilation in this patient group, one of the main determinants of isoflurane uptake. Whether increased cardiac output in the patients with pulmonary diseases additionally facilitated isoflurane uptake cannot be derived from our data.

While isoflurane sedation was effective in our patients, adverse events of LTIS are considerable. Isoflurane and sevoflurane are potent vasodilators, and 11 of 41 (27%) patients from the literature developed at least mild arterial hypotension.[15,17,20,22] However, Eifinger et al. did not report hypotension in their 15 patients.[21] We recorded hemodynamic parameters very thoroughly in our patients, and found that mean arterial blood pressure decreased in all patients within 24 hours after the start of isoflurane sedation. This decrease was most significant during the first 4 hours after initiation of LTIS. Due to the retrospective nature of the study, depth of sedation was not routinely assessed with COMFORT B scores during that period. Hence, we cannot exclude that the early decrease in blood pressure was the result of a potential oversedation caused by the combination of isoflurane and the intravenous sedatives which had not yet been reduced sufficiently or had long half-lifes. Vasopressors had to be started or increased in 93% of the children, a fact that is in line with Nacoti et al.[22] Moreover, we observed 2 clinically relevant episodes of hypotension that were clearly related to isoflurane and required immediate therapy and discontinuation of LTIS in 1 patient. Heart rate also decreased regularly, but to a lesser extent. Based on our findings we think that cardiocirculatory depression can be expected in almost every patient after the initiation of LTIS, but dangerous hypotension only rarely occurs. Nevertheless, every PICU team using AnaConDa® or similar devices should be aware of this fact.

Adverse events other than cardiocirculatory depression have been reported very rarely so far. Transient elevation of liver enzymes were found in 3 of 10 patients in the study by Arnold et al., one of which also had a temporary rise in blood urea nitrogen.[20] We found the same pattern in one of our patients, although potential toxic effects of isoflurane could not be clearly distinguished from side effects of a quadruple tuberculostatic therapy that had been converted to intravenous medications at the same time. However, the laboratory changes dissolved after discontinuation of LTIS while the tuberculostatic medications remained unchanged. In all other patients, laboratory parameters remained unchanged. Bronchospasm

requiring specific medication was observed in 2 of 23 children by Mencia et al.,[15] and 2 patients had seizures related to the inhalative sedation.[17,22] Neither bronchospasm nor seizures were observed in our study cohort. Based on the time-dependent increase of fluoride in the blood reported by Arnold et al.,[20] we also analyzed plasma fluoride levels in some of our patients. Although it was measured inconsistently due to the lack of a specific protocol in this retrospective analysis, it became clear that toxic plasma levels were not reached in our patients at the desired endexpiratory MAC of 0.5. However, because 1 patient unexpectedly had a more pronounced increase of plasma fluoride 6 days after the start of LTIS, we would recommend to implement a respective protocol in future clinical trials.

A limitation of this study is that it was performed in a single center, which may limit its generalizability. In addition, due to the retrospective analysis, both patient groups were quite heterogeneous with respect to underlying diseases and concomitant medications. Furthermore, neurological outcome was not assessed using a standardized investigation. Lastly, children were not screened for delirium on a regular basis, which might have influenced the assessment of sedation levels and subsequent dose adaption of intravenous sedatives.

Taken these limitations into account, from our observations LTIS still seems to be feasible and safe in children with severe respiratory diseases. In contrast to our initial hypothesis, concomitant intravenous sedatives could be reduced more rapidly in patients with pulmonary diseases and adverse events were similar in both groups. Of note, the majority of our patients with pulmonary diseases was ventilated because of severe pneumonia, and only 3 of 15 children had a full-blown ARDS. Nevertheless, from our data a prospective trial on the use of LTIS in children to evaluate potential beneficial effects in ARDS seems justified. However, a thorough monitoring of side effects is mandatory.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Jochen Meyburg https://orcid.org/0000-0002-8491-5819

References

1. Cheifetz IM. Pediatric ARDS. *Respir Care*. 2017;62(6):718-731.
2. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439.
3. Tang QF, Fang ZY, Shi CH. The protective effect and mechanism of sevoflurane on LPS-induced acute lung injury in mice. *Am J Transl Res*. 2017;9(4):1732-1742.
4. Kellner P, Muller M, Piegeler T, et al. Sevoflurane abolishes oxygenation impairment in a long-term rat model of acute lung injury. *Anesth Analg*. 2017;124(1):194-203.
5. O'Gara B, Talmor D. Lung protective properties of the volatile anesthetics. *Intensive Care Med*. 2016;42(9):1487-1489.
6. Strosing KM, Faller S, Gyllenram V, et al. Inhaled anesthetics exert different protective properties in a mouse model of ventilator-induced lung injury. *Anesth Analg*. 2016;123(1):143-151.
7. Uhlig C, Bluth T, Schwarz K, et al. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and meta-analysis. *Anesthesiology*. 2016;124(6):1230-1245.
8. Bellgardt M, Bomberg H, Herzog-Niescery J, et al. Survival after long-term isoflurane sedation as opposed to intravenous sedation in critically ill surgical patients: retrospective analysis. *Eur J Anaesthesiol*. 2016;33(1):6-13.
9. Meiser A, Groesdonk HV, Bonnekessel S, Volk T, Bomberg H. Inhalation sedation in subjects with ARDS undergoing continuous lateral rotational therapy. *Respir Care*. 2018;63(4):441-447.
10. Rand A, Zahn PK, Schildhauer TA, Waydhas C, Hamsen U. Inhalative sedation with small tidal volumes under venovenous ECMO. *J Artif Organs*. 2018;21(2):201-205.
11. Jabaudon M, Boucher P, Imhoff E, et al. Sevoflurane for sedation in acute respiratory distress syndrome. A randomized controlled pilot study. *Am J Respir Crit Care Med*. 2017;195(6):792-800.
12. ChangLai SP, Hung WT, Liao KK. Detecting alveolar epithelial injury following volatile anesthetics by (99 m)Tc DTPA Radioaerosol inhalation lung scan. *Respiration*. 1999;66(6):506-510.
13. Hung CJ, Liu FY, Shaiu YC, Kao A, Lin CC, Lee CC. Assessing transient pulmonary injury induced by volatile anesthetics by increased lung uptake of technetium-99 m hexamethylpropylene amine oxime. *Lung*. 2003;181(1):1-7.
14. Putensen C, Rasanen J, Putensen-Himmer G, Downs JB. Effect of low isoflurane concentrations on the ventilation-perfusion distribution in injured canine lungs. *Anesthesiology*. 2002;97(3):652-659.
15. Mencia S, Palacios A, Garcia M, et al. An exploratory study of sevoflurane as an alternative for difficult sedation in critically Ill children. *Pediatr Crit Care Med*. 2018;19(7):e335-e341.
16. Ista E, van Dijk M, Tibboel D, de Hoog M. Assessment of sedation levels in pediatric intensive care patients can be improved by using the COMFORT "behavior" scale. *Pediatr Crit Care Med*. 2005;6(1):58-63.
17. Sackey PV, Martling CR, Radell PJ. Three cases of PICU sedation with isoflurane delivered by the 'AnaConDa'. *Paediatr Anaesth*. 2005;15(10):879-885.

18. Traube C, Silver G, Kearney J, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. *Crit Care Med*. 2014;42(3):656-663.
19. Gentz BA, Malan TP Jr. Renal toxicity with sevoflurane: a storm in a teacup? *Drugs*. 2001;61(15):2155-2162.
20. Arnold JH, Truog RD, Rice SA. Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. *Anesth Analg*. 1993;76(3):520-526.
21. Eifinger F, Hunseler C, Roth B, et al. Observations on the effects of inhaled isoflurane in long-term sedation of critically ill children using a modified AnaConDa(c)-system. *Klin Padiatr*. 2013; 225(4):206-211.
22. Nacoti M, Colombo J, Fochi O, et al. Sevoflurane improves respiratory mechanics and gas exchange in a case series of infants with severe bronchiolitis-induced acute respiratory distress syndrome. *Clin Case Rep*. 2018;6(5): 920-925.
23. Koutsogiannaki S, Shimaoka M, Yuki K. The use of volatile anesthetics as sedatives for acute respiratory distress syndrome. *Transl Perioper Pain Med*. 2019;6(2):27-38.