Short-Acting Sedative-Analgesic Drugs Protect Against Development of Ventilator-Associated Events in Children: Secondary Analysis of the EUVAE Study

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BACKGROUND: The U.S. Centers for Disease Control and Prevention proposed a shift in its surveillance paradigm from ventilator-associated pneumonia to ventilator-associated events (VAE) to broaden the focus of prevention and achieve a greater impact on outcomes. The main objective of the present study was to identify factors associated with pediatric VAEs in children undergoing mechanical ventilation ≥ 48 h. METHODS: This was a secondary analysis of a pediatric cohort of a multicenter prospective study. Children who underwent mechanical ventilation ≥ 48 h were included. Exclusion criteria were previous ventilation, extracorporeal life support, and right-to-left shunt or pulmonary hypertension. In the subjects with multiple episodes of mechanical ventilation, only the first episode was considered. Remifentanil and propofol are classified as short-acting sedative and analgesic agents. Pediatric VAE is defined as an "increase in PEEP ≥ 2 cm of H_2O, an increase in F_{IO_2} of 0.20, or an increase in F_{IO_2} of 0.15 plus an increase in PEEP ≥ 1 cm of H_2O sustained for ≥1 d. Associations with pediatric VAE were estimated through multivariate Cox proportional hazards analysis. Hazard ratios and 95% CI were computed. RESULTS: In a cohort of 90 children, 24 pediatric VAEs were documented in 906 ventilator-days. Pediatric VAEs developed after a median of 4.5 (interquartile range, 4–7.25) d. Surgical admissions, spontaneous breathing trials, early mobility, vasopressors, red blood cell units transfusion, type of sedation (continuous vs intermittent), benzodiazepine use for >3 d, and pharmacologic paralysis were not associated with pediatric VAE, whereas the use of continuous short-acting sedative-analgesic agents was identified as a strong protective factor against pediatric VAE (hazard ratio 0.06 [95% CI 0.007–0.5]). CONCLUSIONS: Treatment with short-acting sedative-analgesic agents should be preferred for sedation of mechanically ventilated children in intensive care. *Key words: ventilator-associated event; ventilator-associated pneumonia; midazolam; prevention bundles; mechanical ventilation; safety.* [Respir Care 2021;66(5):798–805. © 2021 Daedalus Enterprises]

Introduction

In 2013, the U.S. Centers for Disease Control and Prevention replaced their surveillance definition of ventilator-associated pneumonia with a broader concept of preventable conditions related to mechanical ventilation, termed ventilator-associated events (VAE).[1,2] The aim of the VAE algorithm was to create a practical tool for surveillance in patients on mechanical ventilation and admitted

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to ICUs in the United States to expand the focus of prevention and improve outcomes.[3] Few studies have identified potential risk factors for VAEs or how best to prevent these events in adults.[4,5] Information is even more scarce in children.[6,7] Recently, 2 prospective studies with a similar design assessed VAEs in adults and children undergoing mechanical ventilation.[8,9] The findings in the adult cohort were consistent with the meta-analysis conducted by Fan et al,[10] who reported that VAE was associated with increased mortality, more days of mechanical ventilation, and greater hospital length of stay than traditional ventilator-associated pneumonia criteria. A secondary analysis of this study found that restricting prescriptions of long-acting sedative-analgesic agents may prevent VAE in adults.[5]

In the pediatric cohort, the standard VAE definition only identified very severe events, with a much lower incidence versus adults (2.74 per 1,000 ventilator-days vs 40.8 per 1,000 ventilator-days). VAEs were associated with a significant increase in the ventilation period and pediatric ICU length of stay, and a 7-fold increase in mortality. These findings confirmed that the application of VAE criteria in children selects only the most severe cases. Therefore, Iosifidis et al[7] stressed the need for a specific pediatric definition.

In an attempt to adapt adult criteria to pediatric patients, the U.S. Centers for Disease Control and Prevention proposed a pediatric definition that contemplates a F_{IO_2} increase of 0.25 and increases in mean airway pressure values instead of PEEP.[11] Although this definition may be useful for neonates who underwent high-frequency oscillatory ventilation, it may be suboptimal in pediatric patients who use higher tidal volumes and PEEP, which is the standard ventilation method in this population. In Europe, on the other hand, a modified VAE definition for children (pediatric VAE) based on smaller PEEP increase has been validated. This definition is less restrictive and has a greater predictive accuracy for outcomes than the adult VAE definitions.[9] The present study is a secondary analysis of a pediatric cohort to test the hypothesis that modifying the sedation strategy[12] may have an impact on pediatric VAE incidence in children. The main objective was to identify factors associated with pediatric VAEs in children undergoing mechanical ventilation for ≥ 48 h.

QUICK LOOK

Current knowledge

Ventilator-associated events have a great impact on outcomes in patients on mechanical ventilation, including children who are critically ill. Identifying risk factors for pediatric ventilator-associated events in children can help their prevention and improve outcomes in pediatric critical care settings.

What does this paper contribute to our knowledge?

This study found that the use of continuous short-acting drugs for sedation and analgesia in children on mechanical ventilation is a strong protector against the development of pediatric ventilator-associated event.

Methods

Study Design, Setting, and Participants

The study was a secondary analysis of the pediatric cohort of a prospective study conducted at a group of European ICUs from February 2015 to February 2016,[8] sponsored by the European Society of Clinical Microbiology and Infectious Diseases. Subjects ages < 18 y were classified as children, and those who had undergone mechanical ventilation for ≥ 48 h were included. Exclusion criteria were previous ventilation, extracorporeal life support, and right-to-left shunt or pulmonary hypertension. Daily follow-up was implemented for 30 d. Patients with ICU-acquired respiratory viral infections or missing data were excluded. The duration of ventilation was considered until extubation or ICU death. Each individual admission was assessed and used in the evaluation. In the subjects with more than one episode of mechanical ventilation during the same ICU admission, only the first episode was considered. The study protocol was approved by the institutional review board on human research at Vall d'Hebron University Hospital (PR[AG]

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25/2014). The parents were asked to provide written consent before their children's participation in the study.

Definitions

An episode of mechanical ventilation was defined as one that occurs during the period between tracheal intubation (day 1) and 24 h after successful extubation. The current study uses a definition of pediatric VAE reported elsewhere[9]: an increase in the minimum PEEP value of ≥2 cm H_2O (instead of 3 cm H_2O, as in adults), and a change in the ventilator settings sustained for ≥ 1 d (instead of ≥ 2 d, as in adults), with an additional modification of an increase in F_{IO_2} of 0.15 plus an increase in PEEP of ≥1 H_2O sustained for ≥ 1 d.

Study Variables

The following subject characteristics were considered: sex, age, the presence of comorbidities, severity-of-illness index, and vasopressor use during the first 4 d of the mechanical ventilation episode. High severity was defined as a Pediatric Risk of Mortality III score above the 75th percentile.[13] Medical, trauma, and surgical subjects were included. The reason for intubation was classified as the following: respiratory failure, surgery, cardiogenic shock, altered level of consciousness, and sepsis/septic shock. Intubation could be performed in the ICU or elsewhere (operating room, pre-hospital, emergency department, or hospital ward). Other variables recorded were spontaneous breath trials, pharmacologic paralysis, early mobility, red blood cell units transfusion, type of sedation administration (continuous or intermittent), and the use of continuous sedation for ≥7 d. To analyze the time effect on pediatric VAE development, sedative-analgesic drugs were classified into groups: by pharmacologic family (benzodiazepines, opioids, propofol) or by length of action (long-acting: midazolam, fentanyl, and morphine)[8] and short-acting drugs: remifentanil or propofol as a simple continuous infusion). The following outcomes were considered as end points: length of stay (ICU and hospital) and ICU mortality.

Statistical Analysis

A descriptive analysis was performed of subjects' characteristics, reporting percentages and medians with their interquartile ranges (IQR) for quantitative variables. Two measures of pediatric VAE incidence were computed: (1) the number of pediatric VAEs divided by the total number of ventilator-days and (2) the number of pediatric VAEs divided by the total number of episodes of mechanical ventilation. As in subjects with more than one episode of mechanical ventilation, only the first episode was considered in our study; the total number of ventilator-days corresponded to the first ventilation episode, and the total number of episodes of mechanical ventilation was the same as the number of subjects. The Pearson chi-square test was used to compare proportions and the Mann-Whitney test (2 tailed) was used to compare medians of the quantitative variables, ICU and hospital stay. The association between these factors and pediatric VAEs was estimated by using Cox proportional hazard regression models.

Hazard ratios (HR) and 95% CI were computed. All risk factors with $P < .2$ in the univariate analysis were included in the initial multivariate Cox proportional hazard model by using the best-fitting univariate models. The final multivariate model was selected manually by backward selection by using the likelihood ratio test. At each iteration, the variables that were associated with the highest P value $> .05$ and had no impact on the concordance value were removed from the model. Statistical significance was considered if the P value was $< .05$. All statistical analyses were performed with R software version 1.2.1335 (R, Vienna, Austria).

Results

There were 92 eligible children. Two were excluded due to missing data, and so the study population included 90 children (median age, 1.2 [IQR, 0.3–5.0] y) who were undergoing mechanical ventilation (906 ventilator-days) for at least 48 h. None underwent a tracheostomy. Boys ($n = 60$ [66.7%]) were predominant. The median Pediatric Risk of Mortality III score was 8 (IQR, 5–13). The median duration of mechanical ventilation was 7 (IQR, 7–23) d. The median ICU and hospital length of stays were 11 (IQR, 8–18) d, and 22 (IQR, 15–35) d, respectively. Characteristics of the overall population and pediatric VAE and non-pediatric VAE groups are summarized in Table 1. The prevalence of pediatric VAE was 32.2% in the subjects age ≤ 3 y and 14.3% ($P = .13$) in those > 3 y. There were no statistically significant differences between the pediatric VAE and non-pediatric VAE groups. Acute respiratory failure was the cause of intubation in 31 children (34.4%), and 49 presented one or more comorbidities (54.4%).

Among 24 pediatric VAEs (26.5 per 1,000 ventilator-days, 26.7 per 100 episodes), 9 were pediatric ventilator-associated conditions, 6 were pediatric infection-related ventilator-associated complications, and 9 were pediatric possible ventilator-associated pneumonia. The median time of pediatric VAE onset was 4.5 (IQR, 4–7.25) d, with 15 (62.5%) presenting within the first 7 d of mechanical ventilation. Pediatric infection-related ventilator-associated complications and pediatric possible ventilator-associated pneumonia represented 10 of 15 pediatric VAEs (66.7%) within the first 7 d of ventilation compared with 5 of 9 pediatric VAEs (55.5%) that occurred after ≥ 7 d of mechanical ventilation, without statistical significance. The subjects with pediatric VAE had longer ICU length of stay (median,

Table 1. Characteristics of the Overall Population and Pediatric VAE and Non-Pediatric VAE Groups ($N = 90$)

Variable	All	Pediatric VAE	Non-Pediatric VAE	*P*
Subjects	90 (100)	24 (26.7)	66 (73.3)	
Sex				.68
Girls	30 (33.3)	14 (58.3)	16 (24.2)	
Boys	60 (66.7)	10 (41.7)	50 (75.8)	
Age				.18
≤3 y	62 (68.9)	20 (83.3)	42 (63.6)	
4-8 y	11 (12.2)	1 (4.2)	10 (15.2)	
8-6 y	17 (18.9)	3 (12.5)	14 (21.2)	
PRISM III score				.09
High severity (subjects with PRISM score >Q3)	25 (27.8)	3 (12.5)	22 (33.3)	
Low severity (subjects with PRISM score = or >Q3)	65 (72.2)	21 (87.5)	44 (66.7)	
Comorbidities				.68
No	41 (45.6)	10 (41.7)	31 (47)	
Yes	49 (54.4)	14 (58.3)	35 (53)	
Reason of intubation*				.08
Respiratory failure	31 (34.8)	12 (50)	19 (29.2)	
Other	58 (65.2)	12 (50)	46 (70.8)	
Surgery	26 (44.8)	8 (66.6)	18 (39.1)	
Cardiogenic shock	9 (15.5)	0 (0)	9 (19.6)	
Altered level of consciousness	18 (31.1)	2 (16.7)	16 (34.8)	
Sepsis and/or septic shock	5 (8.6)	2 (16.7)	3 (6.5)	
Place of intubation				.68
ICU	34 (37.8)	10 (41.7)	24 (36.4)	
Other	56 (62.2)	14 (58.3)	42 (63.6)	
Operating room, anesthesia	27 (48.2)	8 (57.1)	19 (45.2)	
Pre-hospital, hospital ward, ED	29 (51.8)	6 (42.9)	23 (54.8)	
Type of subject				.51
Medical	55 (61.1)	15 (62.5)	40 (60.6)	
Surgical	26 (28.9)	8 (33.3)	18 (27.3)	
Trauma	9 (1.0)	1 (4.2)	8 (12.1)	
Vasopressors first 4 d*				.39
Yes, almost 1 d	60 (67.4)	14 (58.3)	46 (70.8)	
No	29 (32.6)	10 (41.7)	19 (29.2)	

All data are *n* (%).
* $n = 89$.
VAE = ventilator-associated event
PRISM III = Pediatric Risk of Mortality III
Q3 = 75th percentile

14 vs 11 d; $P < .01$), although there was no difference in hospital length of stay (median, 22 vs 20.5 d; $P = .31$). Five of 90 subjects (5.5%) died (3 within the first 7 d of hospitalization). ICU mortality was nearly twice as high among children who developed pediatric VAE (8.33% vs 4.54%) but the difference was not statistically significant ($P = .42$).

Associations between variables and pediatric VAEs are displayed in Table 2 (univariate Cox proportional hazard analysis) and Figure 1 (multivariate Cox proportional hazard analysis). Surgical admission, spontaneous breath trials, early mobility, red blood cell units transfusion, type of sedation (continuous or intermittent), benzodiazepine use, and pharmacologic paralysis were not associated with pediatric VAE in the multivariate analysis, whereas the use of remifentanil or propofol as short-acting continuous sedative-analgesic agents was identified (Fig. 1) as a protective factor against pediatric VAE (HR 0.06 [95% CI 0.007–0.5]). These findings did not change after adjusting for age, sex, severity of illness at the first 24 h, and vasopressor use during the first 4 d.

Discussion

This study assesses variables potentially associated with VAEs in children by using a definition of VAE based on smaller variations of PEEP or F_{IO_2} than in adults but still maintaining an impact on ICU length of stay. Pediatric

Table 2. Factors Associated With Pediatric Ventilator-Associated Events: Univariate Cox Proportional Hazards Model ($N = 90$)

Variable	HR (95% CI)	*P*
Type of subject		
Medical	Reference	
Surgical	2.25 (0.90–5.70)	.08
Trauma	0.57 (0.07–4.50)	.60
Comorbidities		
No	Reference	
≥1 comorbidities	0.94 (0.40–2.20)	.88
Reason for intubation		
Other	Reference	
Respiratory failure	3.60 (0.45–29.0)	.23
Surgery	2.50 (0.30–2.0)	.39
Altered level of consciousness	0.60 (0.05–6.70)	.68
Place of intubation		
ICU	Reference	
Operating room, anesthesia	2.30 (0.86–6.40)	.09
Pre-hospital, hospital ward, ED	1.10 (0.37–3.30)	.86
Sedation, type administration		
Intermittent	1.00 (0.39–2.60)	.98
Continuous ≥7 d	2.12 (0.39–11.40)	.38
Sedative-analgesic drugs		
Benzodiazepines for >3 d	2.80 (0.64–12.00)	.17
Opioids for >3 d	0.89 (0.35–2.20)	.80
Propofol for > 3 d	0.70 (0.30–1.60)	.40
Only long-acting drugs*	1.00 (0.41–2.60)	.96
Only short-acting drugs†	0.22 (0.05–0.94)	.04
Other interventions		
RBC transfusion	0.65 (0.27–1.50)	.32
Spontaneous breathing trial	0.95 (0.41–2.20)	.90
Early mobility, first 4 d	3.10 (1.20–7.60)	.01
Pharmacologic paralysis	1.80 (0.75–4.10)	.18

* Midazolam, fentanyl, and morphine.
† Propofol and remifentanil.
HR = hazard ratio
RBC = red blood cell

VAEs were a common complication; most of them developed early and were associated with respiratory infections. In this cohort, respiratory failure was the most frequent cause of intubation in children, and this condition may have influenced our results. We observed that the use of continuous short-acting drugs, such as remifentanil or propofol, had a strong protective factor against pediatric VAE development, a finding that may have important clinical implications.

There is growing evidence that many VAEs in adults are preventable.[14] In our study in a pediatric population, surgical admission, spontaneous breath trials, early mobility, vasopressors, red blood cell units transfusion, type of sedation (continuous vs intermittent), benzodiazepine use for >3 d, and pharmacologic paralysis were not associated with pediatric VAE. Although age ≤ 3 y seemed to be associated with an increased prevalence of pediatric VAE, the age variable did not remain significant in the multivariate models. Positive fluid balance and mandatory modes of ventilation have been reported as important risk factors for VAE in adults.[6,15,16] Unfortunately, the role of preventive measures classically included in ventilator-associated pneumonia bundles (such as stress ulcer prophylaxis, head of bed elevation, or subglottic suction) remains unknown.[14,17,18] Moreover, recently, serious concerns have been raised about chlorhexidine oral care and the development of VAE.[19]

On the other hand, the use of minimal sedation strategies and daily spontaneous breathing trials have been proposed as possible strategies to reduce VAE due to their association with a reduction in ventilator-days.[4,17] In addition, the use of light sedation protocols was shown to be a safe strategy with better outcomes in subjects with ARDS.[12] In a recent international study conducted by our group that assessed variables that influence VAE in adults ventilated for ≥ 48 h, sedation with long-acting drugs (HR, 4.3), and surgical or trauma admission (HR, 2.3) were identified as risk factors for developing VAE, whereas the use of light sedation and selective digestive decontamination emerged as protective factors; moreover, there was an 8-fold increase in VAE in the subjects treated with long sedation protocols and ventilated for >7 d.[5] Interestingly, neuromuscular blockade was not identified as an independent risk factor for VAE in the adult cohort or for pediatric VAE in our cohort, in contrast to another study in children[6] but in agreement with a recent meta-analysis.[20]

Analysis of our data in children found use of short-term sedative-analgesic agents to be a strong protective factor against VAE (HR, 0.06). Classically, these drugs were mostly used in the subjects scheduled for fast-track extubation or for neurological evaluation in the subjects with previously altered level of consciousness. Current guidelines argue against deep sedation and promote early mobility to shorten the period of mechanical ventilation and avoid complications.[21] Our results agree with these recommendations. According to our findings, a good sedation strategy for limiting pediatric VAE development would be to use only short-acting drugs, even in children ventilated for > 48 h.

Another interesting result was that the use of only long-acting sedative-analgesic agents or benzodiazepines for >3 d did not seem to be a risk factor for pediatric VAE, in contrast to findings in the adult population.[5] In recent years, benzodiazepine use has been related to poor outcomes and, therefore, has been discouraged.[22] Classically, midazolam has been defined as a short-acting sedative drug but its pharmacokinetics is not the same in patients in critical care as when it is applied for a short time in previously healthy individuals (eg, in surgical procedures). The use of continuous intravenous

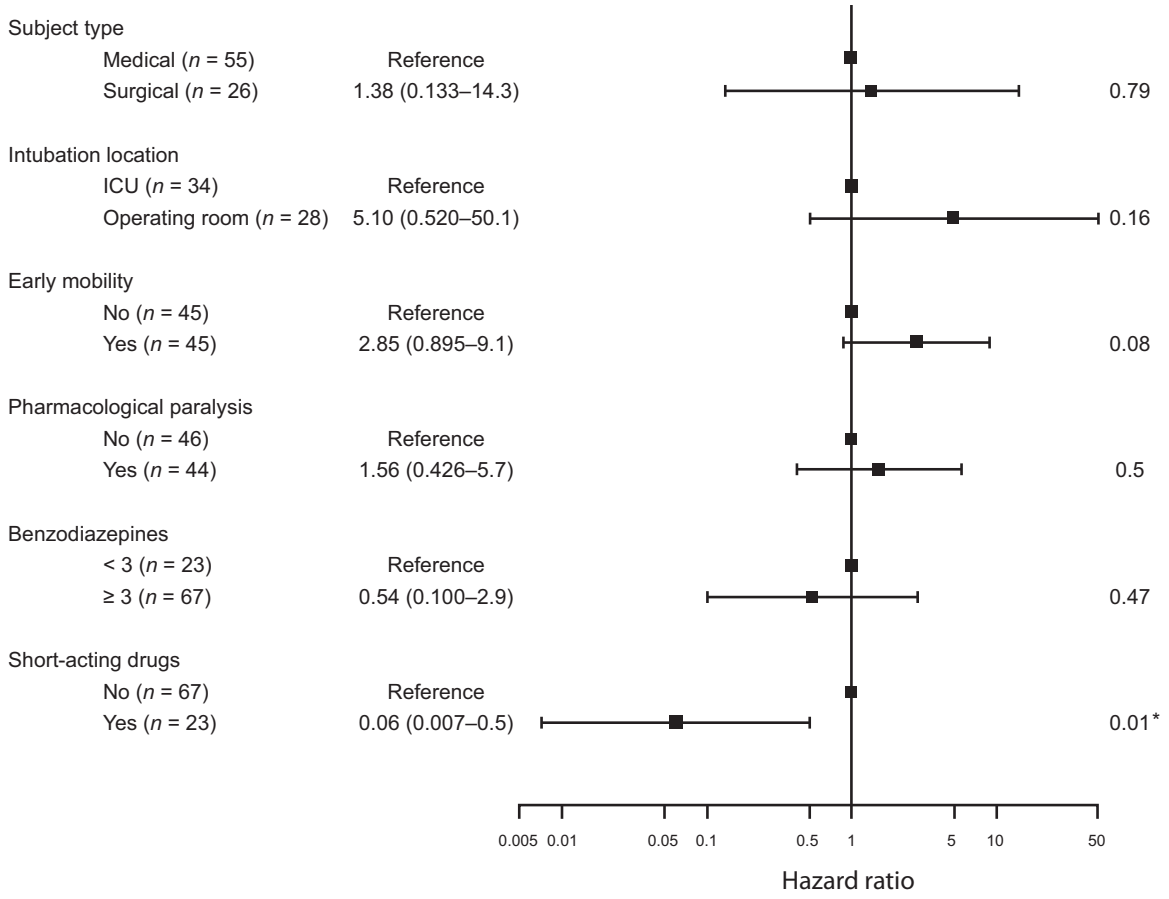

Fig. 1. Factors associated with pediatric ventilator-associated event: multivariate Cox proportional hazards model ($N = 90$).

infusions of midazolam for several days in patients who are critically ill, who commonly experience multiorgan failure, frequently results in accumulation and oversedation.[23] As Wyncoll and McKenzie[24] noted, this may be the main reason for harm caused by benzodiazepines rather than their pharmacodynamics.

Delirium has historically been underestimated and frequently limited to the hyperactive type; today, however, there is an awareness of the risk of hypoactive delirium associated with deep sedation in both adults[25] and children.[26] In this regard, other novel molecules, for example, remimazolam, an ultra-short-acting benzodiazepine with organ-independent metabolism, may be a promising new sedative agent.[27] Thus, a possible explanation of the lack of association between benzodiazepine use for >3 d and pediatric VAE in our pediatric cohort may be the different pharmacokinetics in most children who are critically ill or in those who are less prone to renal failure, or, alternatively, its use in combination with short-acting sedative-analgesic agents throughout the ventilatory period.

Formerly, continuous benzodiazepine infusion was used as the main sedative at the initiation of mechanical ventilation, particularly in patients prone to unstable hemodynamics. Propofol stills tends to be avoided in these patients due to the need for more vasopressors to treat hypotension events. In addition, children and infants may be at risk of developing propofol infusion syndrome, and so its use in long-term sedation in children has been discouraged.[28] However, it has been reported that short-term propofol infusion as an adjunct to extubation may allow time for opiates and benzodiazepines infused over a long period to be metabolized.[29]

On the other hand light sedation with dexmedetomidine or inhalational sedation with sevoflurane is promoted nowadays in the ICU in both adults and children.[30-33] However, a withdrawal syndrome has been associated with prolonged dexmedetomidine infusion in children who were critically ill, as has been found with prolonged opioid or benzodiazepine use,[34] despite the rapid onset and offset of dexmedetomidine action and its short-half life (2 h). Interestingly, Haenecour et al[35]

attributed this to a change in the pharmacokinetic profile of dexmedetomidine after a prolonged infusion and to its reduced clearance in infants.

In light of our findings, we cannot argue against benzodiazepine or neuromuscular blockade use in children who are unstable and with hypoxemic respiratory failure and/or an expected mechanical ventilation period of >5–7 d. Analysis of our findings suggests that it would be advisable to adjust long-acting sedative-analgesic agents to a minimum effective dose and to switch them quickly to short-acting drugs once respiratory and/or hemodynamic stability is achieved, to decrease the risk of pediatric VAE. In fact, decreasing the ventilation period is a major factor in preventing VAE or pediatric VAE. This statement could also be applied to infectious ventilator-associated complications (which account for >60% in our cohort, in agreement with some of the literature),[4,7-9,36,37] rather than focusing only on pathophysiologic measures.[8,36,37] Thus, our findings add evidence to support a strategy of sedation control, which should be a cornerstone in pediatric ventilatory management.[37,38]

This study has several limitations. First, the pediatric VAE criteria used in this paper does not align with that used by the U.S. Centers for Disease Control and Prevention in the United States. Second, the sample size was small and further large multicenter trials need to be performed. Moreover, excluding subjects who had had a previous episode of mechanical ventilation may have underestimated the number of VAE episodes. Third, there was no objective score for assessing delirium or multiorgan or renal failure in this cohort. Dexmedetomidine or inhalational sedation with sevoflurane were not properly evaluated due to their low levels of use in the participating ICUs during the study period, and further studies are needed to identify their potential effects. Fourth, this study was conducted in Europe, and the interpretations may not be applicable to other geographic regions due to the large variation in therapeutic strategies, case mix, and duration of mechanical ventilation. Fifth, other potentially relevant variables, such as fluid balance, average gastric retention monitoring, and selective oral and/or digestive decontamination, were not evaluated. Sixth, we considered the entire period from the start of mechanical ventilation to pediatric VAE development or extubation; other variables may be relevant if the time span is limited or if subsequent episodes of ventilation are addressed.

Conclusions

Our study found that the prescription of only short-acting drugs as continuous sedative-analgesic agents is a strong protector against the development of pediatric VAE. Recommendations for preventing pediatric VAE should include short-acting sedative-analgesic use, even in children ventilated for > 48 hours.

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