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Opioid Use Is Associated with ICU Delirium in Mechanically Ventilated Children

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Abstract

Introduction: Pediatric delirium is a significant problem when encounterd in an intensive care unit (ICU). The pathophysiology of pediatric delirium is complex and the etiology is typically multifactorial. Even though various risk factors associated with pediatric delirium in a pediatric ICU have been identified, there is still a paucity of literature associated with the condition, especially in extremely critically ill children, sedated and mechanically ventilated. **Aim of the study**: To identify factors associated with delirium in mechanically ventilated children in an ICU. **Material and Methods**: This is a single-center study conducted at a tertiary care pediatric ICU. Patients admitted to the pediatric ICU requiring sedation and mechanical ventilation for >48 hours were included. Cornell Assessment of Pediatric Delirium scale was used to screen patients with delirium. Baseline demographic and clinical factors as well as daily and cumulative doses of medications were compared between patients with and without delirium. Firth's penalized maximum likelihood logistic regression was used on a priori set of variables to examine the association of potential factors with delirium. Two regression models were created to assess the effect of daily medication doses (Model 1) as well as cumulative medication doses (Model 2) of opioids and benzodiazepines. **Results**: 95 patient visits met the inclusion criteria. 19 patients (20%) were diagnosed with delirium. Older patients (>12 years) had higher odds of developing delirium. Every 1mg/kg/day increase in daily doses of opioids was associated with an increased risk of delirium (OR=1.977, p=0.017). Likewise, 1 mg/kg increase in the cumulative opioid dose was associated with a higher odds of developing delirium (OR=1.035, p=0.022). Duration of mechanical ventilation was associated with the development of delirium in Model 1 (p=0.007). **Conclusions**: Age, daily and cumulative opioid dosage and the duration of mechanical ventilation are associated with the development of delirium in mechanically ventilated children.

Keywords: pediatric delirium, mechanically ventilated children, intensive care unit

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Introduction

Delirium is a significant problem in a pediatric intensive care unit (PICU), with a prevalence ranging from 25-50% [1,2]. It is characterized by acute to sub-acute onset of altered and fluctuating consciousness and cognition, and may be associated with a reduced awareness of the environment, impaired attention, and disorganized thinking [3-5]. It can present as three subtypes – hyperactive, hypoactive and mixed, with hypoactive and mixed conditions being more common in critically ill children [6,7]. Delirium is often associated with significant short and long-term consequences including prolonged mechanical ventilation, increased hospital and PICU length of stay [8-11], increased healthcare costs [12,13] long-term cognitive impairment, physical disability and mortality [6,14].

The pathophysiology of pediatric delirium is complex and the etiology is typically multifactorial [8,15]. Factors associated with delirium include the use of benzodiazepines, opioids, steroids and anti-cholinergic agents, prolonged period of immobilization in an ICU, the presence of invasive lines and monitors, and the disruption of the patient's sleep-wake cycle [1,16]. Recently significant advances have been made in an attempt to diagnose and manage pediatric delirium.

A single center prospective study by Silver et al. (2015) reported factors that predicted delirium which included preschool age (2-5 years), developmental de-

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lay and requirement for mechanical ventilation [8]. Various validated delirium screening tools have been developed recently for screening of delirium in critically ill children including Cornell Assessment of Pediatric Delirium (CAPD) [17] and Pediatric Confusion Assessment Method for Intensive Care Unit (pCAM-ICU) scales [18].

Despite these developments, there is still a paucity of significant literature in pediatric delirium, especially in a subset of mechanically ventilated and sedated children in an ICU, who are the most critically ill. Moreover, while most studies look at the association of daily use of medications, especially benzodiazepines and opioids, and delirium [19], the effect of cumulative doses of these medications which could possibly be related to a higher risk of delirium, has rarely been reported [20]. Children on mechanical ventilation is a subset of pediatric patients found in an ICU, which often requires the use of increased opioid and benzodiazepine doses for prolonged period [21]. This places the children at a higher risk of developing delirium. Given the higher exposure of these delirigenic medications, it is reasonable to consider the effect of cumulative doses of these medications on the development of delirium in this patient population.

The aim of the study was to identify factors associated with delirium in this high-risk pediatric ICU population including demographics, admission diagnosis, daily and cumulative doses of potentially deliriogenic medications, length of pediatric ICU stay, duration of mechanical ventilation and severity of illness.

The Null hypotheses are:

1. There is no significant difference between the daily and cumulative doses of various medications received by patients with delirium and those without delirium.

2. There is no significant difference between the baseline characteristics and length of mechanical venilation, length of ICU stay and severity of illness between the patients with delirium and those without delirium.

Materials and Methods

Design and setting

A prospective cohort study was carried out on sedated and mechanically ventilated pediatric patients admitted to an ICU at the Children's of Alabama (COA) Hospital in Birmingham, Alabama.

The study was approved by the University of Alabama at Birmingham's Institutional Review Board.

Inclusion and exclusion criteria

Inclusion criteria

- Patients up to 21 years of age admitted to the pediatric ICU
- Patients receiving either continuous infusion or "as needed" sedatives
- Patients requiring mechanical ventilation for more than 48 hours

Exclusion criteria

- Patients who were extubated within 48 hours of admission
- Patients requiring sedation for less than 48 hours after admission
- Patients transferred from the pediatric ICU to another ICU while still being sedated and mechanically ventilated

Clinical endpoint

The primary endpoint was the identification of delirium in the defined patient population.

Implementation of delirium protocol

In August 2017, for delirium screening in the pediatric ICU, the revised CAPD scale [17] was implemented as the standard of care.

The revised scale was completed by the patient's nurse using a paper checklist. To assure uniformity in scoring, the pediatric ICU nursing staff underwent a formal training on the pertinent aspects of the scale and scoring system prior to implementation of the CAPD. CAPD screening was completed for all study patients twice a day between 04:00 and 16:00 hours.

Our pediatric ICU staff uses the State Behavioral Scale (SBS) for monitoring sedation, thus Richmond Agitation Sedation Scale (RASS) score in the CAPD scale was substituted with SBS score [17]. RASS scores of -4 and -5 are considered equivalent to SBS scores of -2 and -3, thus on the CAPD scale, if SBS was -2 or -3, scoring was not undertaken.

Once delirium was confirmed, patients underwent environmental modifications like establishing daily routine including sleep hygiene, clustering care before and after sleep, promoting parental involvement and using communication aides; and were started on treatment with anti-psychotic medications whenever applicable.

CAPD scoring continued until patients reached the point of pediatric ICU discharge.

Data collection

All the data were collected from the medical records of eligible patients and who received the CAPD scoring. CAPD scores for all the included patients were collected and stored through to the end of the study period. Patients' demographic data and comorbidities were recorded.

Age was divided into 4 categories for analysis (< 2 years, 2 years to 4.9 years, 5 years to 11.9 years and ≥12 years). Age <2 years was used as a reference group.

Comorbidities were defined as presence of any co-existing acute or chronic conditions in patients unrelated to the admission diagnosis.

Daily and cumulative doses of suspected deliriogenic medications, opioids, benzodiazepines, dexmedetomidine, anti-cholinergic medication and steroids received by patients during their entire pediatric ICU stay were also documented.

Given that patients received different medications in a particular category, medication dosing was standardized using the equivalent dose of a reference medication, e.g. morphine for opioids, midazolam for benzodiazepines, atropine for anticholinergics/antihistaminics and dexamethasone for steroids. This was calculated using appropriate equivalent conversion calculators available online and verified by the pediatric clinical pharmacist.

Data on use of vasoactive medications, length of mechanical ventilation, ICU length of stay and severity of illness using the Pediatric Index of Mortality (PIM) 3 Risk of Mortality (ROM) were obtained.

The number of patients diagnosed with delirium was also logged.

Statistical analysis

Subjects were divided into two groups based on the presence of delirium: 'Delirium' and 'No delirium'.

Categorical data were compared using Pearson Chi-square test or Fisher's exact test. Continuous data were compared using a Wilcoxon rank-sum test due to non-normal distribution of the data.

To reduce the small sample bias of maximum likelihood estimation, the Firth's penalized maximum likelihood logistic regression statistic was used [22].

Two separate regression models were constructed, one with daily medications (Model 1) and another using cumulative doses of medications (Model 2).

The models used a priori set of variables found to be statistically different among the two groups. Due to collinearity between ICU length of stay and time on a ventilator, only time on the ventilator was used in both models.

Data management and analysis were conducted using Stata SE 16 software. The significance level was set at $\alpha = 0.05$.

Results

A total of 95 patient visits met the inclusion criteria. 53 patients (56%) were males. With respect to ethnicity, 49 patients (52%) were white and 40 patients (42%) were African American (Table 1).

The most common diagnosis for admission to the PICU was respiratory failure (61%) followed by septic shock (14%). 69% patients had some comorbidity and 31% had developmental delay (Table 1).

The overall prevalence of delirium in the study was 20%.

Factors associated with delirium were age (Fisher's exact test: p= 0.012), use of vasoactive medications (58% versus 30%, Chi-square test: p= 0.033), duration of mechanical ventilation (349 hours in the delirium group versus 153 hours in no delirium group, Wilcoxon rank-sum test: p<0.001) and median PICU length of stay (16 days versus 8 days, Wilcoxon rank-sum test: p<0.001).

When compared to those without delirium, children with delirium had received a higher daily dose of opioids (3 mg/kg/day versus 1 mg/kg/day, Wilcoxon rank-sum test: p= 0.023), and benzodiazepines (2 mg/kg/day versus 1 mg/kg/day, Wilcoxon rank-sum test: p= 0.009), as well as a higher cumulative dose of opioids (37 mg/kg versus 13 mg/kg, Wilcoxon rank-sum test: p<0.001) and cumulative benzodiazepine dose (33 mg/kg versus 9 mg/kg, Wilcoxon rank-sum test: p<0.001).

There was no difference among the two groups with respect to the severity of illness based on the PIM scores (Wilcoxon rank-sum test: p=0.527), daily steroid dose (Wilcoxon rank-sum test: p=0.154), daily (Wilcoxon rank-sum test: p=0.941) or cumulative (Wilcoxon rank-sum test: p=0.177) dexmedetomidine dose.

Table 1. Descriptive statistics of patients

	Overall (N=95) Frequency (%)/ Median (IQR)	No Delirium (n=76) Frequency (%)/ Median (IQR)	Delirium (n=19) Frequency (%)/ Median (IQR)	p-value
Age				
< 2 years	37 (39)	35 (46)	2 (11)	**0.012**
2-4.9 years	12 (13)	9 (12)	3 (16)	
5-11.9 years	22 (23)	17 (22)	5 (26)	
≥ 12 years	24 (25)	15 (20)	9 (47)	
Sex				
Female	42 (44)	35 (46)	7 (37)	0.470
Male	53 (56)	41 (54)	12 (63)	
Ethnicity				
White	49 (52)	39 (51)	10 (53)	
Black	40 (42)	34 (45)	6 (32)	0.163
Hispanic	4 (4)	2 (3)	2 (11)	
Asian	2 (2)	1 (1)	1 (1)	
Comorbidity				
No	29 (31)	26 (34)	3 (16)	0.166
Yes	66 (69)	50 (66)	16 (84)	
Anticholinergic use				
No	29 (31)	25 (33)	4 (21)	0.410
Yes	66 (69)	51 (67)	15 (79)	
Vasoactive use				
No	61 (64)	53 (70)	8 (42)	**0.033**
Yes	34 (36)	23 (30)	11 (58)	
Developmental delay				
No	66 (69)	50 (66)	16 (84)	0.120
Yes	29 (31)	26 (34)	3 (16)	
Diagnosis				
Respiratory failure	58 (61)	48 (63)	10 (53)	
Septic shock	13 (14)	9 (12)	4 (21)	0.673
Status epilepticus	7 (7)	6 (8)	1 (5)	
Other	17 (18)	13 (17)	4 (21)	
Time spent on ventilator (hours)	171 (102-360)	153 (94-282)	349 (171-987)	**<0.001**
Length of PICU stay (days)	9 (6-18)	8 (5-14)	16 (9-41)	**<0.001**
Daily benzodiazepine dose (mg/kg/day)	2 (0-3)	1 (0-3)	2 (2-4)	**0.009**
Cumulative benzodiazepine dose (mg/kg)	15 (2-34)	9 (2-28)	33 (18-77)	**<0.001**
Daily opioid dose (mg/kg/day)	2 (1-3)	1 (0-3)	3 (1-4)	**0.023**
Cumulative opioid dose (mg/kg)	16 (4-33)	13 (3-24)	37 (24-70)	**<0.001**
Daily dexmedetomidine dose (mcg/kg/day)	4 (0-10)	4 (1-9)	2 (0-10)	0.941
Cumulative dexmedetomidine dose (mcg/kg)	36 (5-91)	35 (3-84)	60 (11-118)	0.177
Daily steroid dose (mg/kg/day)	0 (0-1)	0 (0-0)	0 (0-0)	0.154
Cumulative steroid dose (mg/kg)	2 (1-4)	2 (1-4)	3 (0-5)	0.434
PIM 3 ROM	2 (1-3)	1 (1-3)	2 (1-4)	0.527

Table 2 shows the results of Firth's multivariable logistic regression including the daily dose of opioids and benzodiazepines, among other variables, as predictors of delirium. Although a higher Odds Ratio was noted with increasing age, this was statistically significant only for the age group >12 years (Firth's logistic regression: p= 0.004).

Compared to the reference group (i.e. < 2 years), this age group had 25 times higher odds of developing delirium. (OR=25.326, 95% CI 2.8-227, p=0.004).

With respect to medications, 1 mg/kg/day increase in the daily opioid dose was associated with 97% increase in the development of delirium (OR 1.97, 95% CI= 1.129–3.463, Firth's logistic regression: p=0.017). Increase in daily dose of benzodiazepines was not associated with delirium. Increase in one hour spent on ventilator was associated with a 0.4% rise in development of delirium (OR 1.004, 95% CI=1.001-1.01, Firth's logistic regression: p=0.007).

Table 3 shows the results of Firth's multivariable logistic regression including cumulative doses of opioids and benzodiazepines, among other variables, as predictors of delirium.

Similar to Model 1, increasing age was associated with delirium. For example, age greater than 12 years was associated with increased odds of development of delirium compared to those younger than 2 years (OR=13.122, 95% CI 1.8-93, Firth's logistic regression: p=0.01).

With respect to medications, 1 mg/kg increase in the cumulative opioid dose was associated with 3.5% increase in the development of delirium (Firth's logistic regression: p=0.022).

Upon multivariate regression, cumulative benzodiazepine dose (Firth's logistic regression: p= 0.401) and time spent on ventilator (Firth's logistic regression: p= 0.143) were not associated with delirium.

Table 2. Firth's Penalized Maximum Likelihood Logistic Regression (Model 1) evaluating association of delirium with daily medication doses

Variables	Odds Ratio (OR)	95% CI	p-value
Age			
<2 years	ref		
2-4.9 years	3.759	0.379-37.240	0.258
5-11.9 years	6.515	0.812-52.269	0.078
≥12 years	25.326	2.818-227.635	**0.004**
Vasoactive use			
No	ref		
Yes	0.361	0.066-1.974	0.240
Time spent on ventilator (hours)	1.004	1.001-1.007	**0.007**
Daily benzodiazepines dose (mg/kg/day)	1.060	0.691-1.625	0.791
Daily opioid dose (mg/kg/day)	1.977	1.129-3.463	**0.017**

Table 3. Firth's Penalized Maximum Likelihood Logistic Regression (Model 2) evaluating association of delirium with cumulative medication doses

Variables	Odds Ratio (OR)	95% CI	p-value
Age			
<2 years	ref		
2-4.9 years	2.055	0.210-20.070	0.536
5-11.9 years	4.330	0.617-30.386	0.140
≥12 years	13.122	1.842-93.487	**0.010**
Vasoactive use			
No	ref		
Yes	0.445	0.085-2.330	0.338
Time spent on ventilator (hours)	1.002	0.999-1.004	0.143
Cumulative benzodiazepine dose (mg/kg)	1.003	0.995-1.012	0.401
Cumulative opioid dose (mg/kg)	1.035	1.005-1.066	**0.022**

Discussion

Delirium is a common problem in a pediatric ICU. Although several studies have shown mechanical ventilation to be an independent risk factor for the development of delirium, there is little reported in the literature of other factors associated with delirium in this vulnerable patient population [23]. Identifying these risk factors is important for timely diagnosis and early management, as well as to prevent the development of delirium in this patient population. The prevalence of delirium in the present study (20%) was similar to those previously reported [1,6].

The present study showed several factors that were associated with delirium. Firstly, daily as well as cumulative doses of opioids were associated with delirium. Although the association of daily opioid use has been established in the literature, the association of cumulative opioid dosage with delirium has not been previously described [20]. This association, though minimal, a 3.5% increase in risk of delirium with an increase in opioid use by 1 mg/kg was reported, it is of clinical importance and may be considerd as a means of reducing the incidence of delirium by using the lowest possible dose of opioids.

Another factor associated with development of delirium was time spent on mechanical ventilation. Although this was highlighted in the multivariate logistic regression statistics using daily medication as the predictor, similar results were not observed when cumulative medication was used as the predictor.

In the current study, neither daily nor cumulative use of benzodiazepines were associated with delirium using multivariate regression analysis. This particular finding is in contrast to previously published literature where both daily as well as cumulative doses of benzodiazepines have been associated with delirium [21]. The findings of this study require additional explanation. Firstly, sedation practices have changed over time with a considerable decrease in the use of benzodiazepines and an increasing use of dexmedetomidine as well as opioids. Also, easily available tools such as CAPD help with the early identification of patients with delirium and consequently, prompt treatment. Recently, the use of dexmedetomidine for sedation has increseed in the pediatric ICU setting. In this study, although dexmedetomidine use, daily as well as cumulative, was not associated with delirium, the cumulative dose was higher in the delirium group. This could be explained by the fact that many patients showing signs of delirium were weaned off benzodiazepines and opioids by substituting these with dexmedetomidine. This could also explain our study's contentious results with respect to benzodiazepines.

There are increasing reports, specifically related to adult treatment, alluding to the beneficial effect of dexmedetomidine on delirium in ICU patients including reduced incidence, more delirium free days and longer ventilator-free time [24-26]. Likewise, Smith et al. (2011) reported shorter stay in the ICU in pediatric patients exposed to dexmedetomidine[19]. Further studies are needed to determine the long-term effects of dexmedetomidine on delirium in patients in the PICU.

Another factor associated with delirium in this study was age. In an attempt to maintain uniformity with previous studies, age groups were chosen which were similar to those categorized in these studies [1,8]. Children greater than 12 years had increased odds of developing delirium compared to those < 2 years old. This is in contrast to the majority of the previous results reported in the literature [1,8]. However, a systematic review by Holly et al. (2018) showed a higher prevalence of delirium in 16-18 years old children compared to ≤3 years olds [27,28].

Our study did not show any association between delirium and gender, anticholinergic use, severity of disease or the presence of comorbidities. Although many studies [8,28], including a recently published systematic review, have shown a correlation between developmental delay and delirium, this was not the case in the present study. This might reflect the challenges in appropriately diagnosing delirium in developmentally delayed patients, even with the use of a validated delirium screening tool. This could reflect a potential limitation of the CAPD scale to appropriately identify delirium in developmentally delayed children and those with sensory deficits [17].

Although CAPD was used for the diagnosis of delirium, the findings from the current study do reflect an issue related to the implementation of this scale, especially in children with developmental delay. The original study, which validated CAPD, showed a poor performance in children with developmental delay, with specificity reaching only 51%, thus indicating a significantly high number of false positives [17]. Moreover, the utility of CAPD in the diagnosis of delirium in mechanically ventilated patients is not completely

understood. CAPD was originally validated using DSM-IV criterion as the gold standard for delirium diagnosis. However, assessing altered consciousness in mechanically ventilated patients is often difficult due to the sedation and analgesia they receive. Thus, the newer DSM-5 criteria, which include disturbance in awareness and attention, seems to be more appropriate for diagnosing delirium in ventilated patients [29,30]. Ideally, a modification of CAPD to reflect the changes in these DSM criteria seems a more plausible solution to this issue.

The present study has several strengths. Being conducted in a tertiary care center, it reflects a population with a myriad of varied etiologies. A subset of the pediatric ICU population was studied which represents the most vulnerable cohort to develop delirium and the least reported in the literature. Another strength of the study is that it looked at the effect of cumulative doses of potentially deliriogenic medications and the development of delirium. To our knowledge, previous studies have not looked at this in detail or reported the effect of cumulative does of opioids.

As with other observational studies, it is prone to bias. Actual patients' weights were used to calculate the cumulative and daily medication doses instead of ideal body weight which might have falsely underestimated the medication doses in patients with obesity. Nor did the study distinguish between hypoactive and hyperactive delirium preventing further analysis between these delirium subtypes. Due to the small sample size of our data, the current findings may not be generalizable. A larger, multi-center study is needed to identify the factors associated with delirium in this subset of the population. A retrospective power analysis was performed based on the current sample using GPower [31]. Using the asymptotic relative efficiency method of Wilcoxon rank-sum test power analysis, we found that the power (1-β error prsobability) ranged from 0.1 to 0.9 when testing the hypotheses.

Conclusions

Age, daily and cumulative opioid dosage were associated with delirium in sedated and mechanically ventilated children in the pediatric ICU. This has practical implications for practitioners and supports the efforts of ICU Liberation goals currently being employed across the country [32]. While recent focus has been on limiting benzodiazepine use as an effective strategy to reduce the incidence of ICU delirium, the study has additionally identified the need for reducing opioid use to the lowest effective dose. This additional strategy may aid in decreasing the incidence of delirium in this most at-risk population.

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Conflict of interest

None to declare.

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