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Original Article

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Delirium in Pediatric Patients With Respiratory Insufficiency Requiring Noninvasive Ventilation

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Abstract

Background: Delirium is associated with increased length of stay, duration of mechanical ventilation, in-hospital mortality, and cost. Independent predictors of delirium include age < 2 years, developmental delay, severity of illness, mechanical ventilation, and administration of benzodiazepines and anticholinergic medications. Although patients receiving noninvasive ventilation (NIV) may have been included in prior studies, there are no data specifically focusing on delirium in children receiving NIV. Our primary aim was to investigate the prevalence of delirium in patients on NIV in the pediatric intensive care unit (PICU) and evaluate potentially modifiable risk factors for delirium.

Methods: This was a single-center, retrospective study evaluating the prevalence of delirium as established by the Cornell Assessment of Pediatric Delirium (CAPD). We evaluated PICU patients ≤ 18 years old with respiratory insufficiency requiring ≥ 48 h of NIV. Patients receiving invasive mechanical ventilation were excluded from the analysis.

Results: There were 202 patients that received ≥ 48 h of NIV during the study period. Of these patients, 43 patients had at least one CAPD score documented while on NIV. There were a total of 143 days on NIV and 137 days with CAPD documentation. The prevalence of delirium, defined as a CAPD score ≥ 9, was 67.4% (29 of 43 patients). Sixty-nine percent of the patients who experienced delirium received benzodiazepines, compared with 14% who did not experience delirium (P = 0.001). Most patients (83.7%) in this cohort received dexmedetomidine. Of patients who received dexmedetomidine and had delirium, 68% received benzodiazepines compared to 25% in the non-delirious group (P = 0.046).

Conclusions: Delirium is common in young pediatric patients receiving NIV. As previously shown in the invasive mechanical ventilation population, benzodiazepine exposure continues to be a potentially modifiable risk factor for delirium.

Keywords: Delirium; Noninvasive ventilation; Benzodiazepines; Dexmedetomidine

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Introduction

Delirium is a disturbance in attention or awareness that develops over a short period of time. It represents a change from baseline attention and awareness and tends to fluctuate in severity throughout the day [1]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) recognizes three major subtypes of delirium including hyperactive (agitation, restlessness, hypervigilance, combative behavior), hypoactive (lethargy, inattention, decreased responsiveness), and mixed-type [1]. While delirium can occur in any setting, it is most prevalent in the inpatient setting, especially in the intensive care unit (ICU) [2]. Independent predictors of delirium include age less than 2 years, developmental delay, severity of illness, mechanical ventilation, coma, and administration of benzodiazepines or anticholinergic medications [3].

Delirium is a common complication of critical illness in infants and children and is known to be associated with increased pediatric ICU length of stay (LOS), increased duration of mechanical ventilation, in-hospital mortality, and hospital cost [3-8]. While long-term pediatric outcomes data remain limited, a minority of pediatric patients with delirium reported post-traumatic stress symptoms months after hospitalization [9]. Additionally, recent studies have demonstrated an association between pediatric delirium and decreased quality of life after hospital discharge, even after controlling for severity of illness [10, 11]. The Cornell Assessment of Pediatric Delirium (CAPD) is a well-validated eight-item observational screening tool that was created to detect delirium in children. A score ≥ 9 is considered a positive screen, indicative of delirium [12]. The CAPD is valid and reliable for identifying all types of delirium, can be used in children less than 2 years of age, and in children with developmental delay [12-14].

To the best of our knowledge, there are currently no studies of delirium that specifically focus on children requiring noninvasive ventilation (NIV) in the pediatric ICU. The primary objective of this study is to investigate the prevalence of delirium in our pediatric ICU population supported with NIV

for treatment of acute respiratory insufficiency. Additionally, we sought to evaluate potentially modifiable risk factors for delirium in this population.

Materials and Methods

The study was approved by the Institutional Review Board at Nationwide Children's Hospital in Columbus, Ohio. As a retrospective study, the need for informed consent was not deemed necessary. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

We conducted a single-center retrospective study to evaluate the prevalence of delirium (defined as a CAPD score ≥ 9) in pediatric ICU patients with respiratory insufficiency requiring NIV. We included patients ≤ 18 years of age admitted to the pediatric ICU between June 1, 2018 and June 30, 2020 with respiratory insufficiency that received ≥ 48 h of NIV and had CAPD documentation in the electronic medical record. Secondly, we evaluated the association of medications, type of respiratory support, and duration of NIV with the development of delirium in this population. At our institution, CAPD scores are to be performed by the bedside nurse twice a day on all ICU patients with an ordered State Behavioral Scale (SBS) score goal of 0 or -1 (excludes patients who are responsive only to noxious stimuli or unresponsive) [15].

The NIV modalities included were bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC). Study variables collected included age, gender, race, primary diagnosis (etiology of respiratory insufficiency), comorbid conditions, baseline developmental delay status, hospital LOS, pediatric ICU LOS, type of NIV utilized, duration of NIV, reason for NIV discontinuation, use of supplemental oxygen, CAPD scores, SBS scores, and all medications received while on NIV. We excluded patients with a pre-existing tracheostomy, home supplemental oxygen, home invasive or noninvasive ventilation. Additionally, we excluded patients that received NIV after tracheal extubation as these patients would be at risk of delirium from their time on mechanical ventilation and increased sedation. Although we intended to include patients who progressed to endotracheal intubation and invasive mechanical ventilation after the use of NIV, we ultimately did not have any of these patients in our cohort.

For demographic and clinical characteristics, we calculated number and frequency for categorical variables and the median and range for continuous variables. Patients who experienced delirium were compared to those who did not experience delirium using Fisher exact test or Wilcoxon rank sum test depending on the type of data. A subset analysis was performed on patients receiving dexmedetomidine, stratifying the group further based on whether or not they received benzodiazepines. All analyses were performed using SAS 9.4 (Cary, NC).

Results

There were 202 patients that received ≥ 48 h of NIV during the study period. However, as CAPD scoring was not uniformly applied, only 43 patients formed the cohort for the study. All 43 patients in our NIV cohort were successfully weaned off respiratory support and did not require endotracheal intubation and invasive mechanical ventilation. The demographic data are listed in Table 1. Patients ranged in age from < 1 to 17 years of age, with most patients on NIV being less than 2 years old (83.7%). Reasons for needing for NIV included viral bronchiolitis, pneumonia, influenza A infection, and status asthmaticus.

There were a total of 143 days on NIV in our study cohort. The number of days on NIV varied from 2 to 12 days per patient. Of the 143 days on NIV, CAPD scores were documented on 137 of the days. Delirium, defined as screening positive for delirium with at least one CAPD score ≥ 9, was noted in 29 of 43 patients (67.4%). The percentage of delirious days in the cohort while on NIV, defined as each day with at least one CAPD score documented ≥ 9 during NIV, was 51.7% (74 of 143 days). Of those who screened positive for delirium, the median number of days with delirium was 2 days (range 1 - 6 days). Data on hospital LOS, pediatric ICU LOS, duration of NIV, type of NIV, and days with delirium are shown in Table 2.

There was no clinically meaningful difference between the delirious and not delirious groups when it came to demographic data including age, gender, and race. Of the 29 patients who screened positive for delirium, three had a baseline developmental delay (zero patients in the not delirious group). There was no statistical difference in hospital LOS or pediatric ICU LOS between the two groups in our NIV cohort. Medications received by the patients in our cohort while on NIV are listed in Table 3. Of the 29 patients who screened positive for delirium, 20 of them (69%) received benzodiazepines, compared to only two of the 14 patients (14%) who did not screen positive for delirium (P = 0.001). Of note, 83.7% of patients in the entire cohort received dexmedetomidine during the study period. Of the 29 patients who screened positive for delirium, 28 of them (97%) received dexmedetomidine, compared to eight of the 14 patients (57%) who did not screen positive for delirium (P = 0.003). Therefore, Table 4 focuses on the patients in our cohort who received dexmedetomidine (n = 36). Of these patients, there remained a significant difference between the delirious and not delirious groups with benzodiazepine exposure. Of the 28 patients who received dexmedetomidine and screened positive for delirium, 19 of them also received benzodiazepines (68%, P = 0.046).

Discussion

In this select cohort of patients in whom delirium screening was performed, we found that delirium is a common problem in patients on NIV for acute respiratory insufficiency in the pediatric ICU. To the best of our knowledge this is the first study of pediatric delirium in children requiring NIV in the pediatric ICU. Our cohort revealed that 67.4% of the pediatric patients requiring NIV screened positive for delirium. In many patients who screened positive for delirium, it persisted and was noted on more than 1 day, with a median of 2 days with

Table 1. Demographic Data of Patients With and Without Delirium[a]

Variable	No delirium (n = 14)	Delirium[a] (n = 29)	P value
Age (years)	0 (0, 10)	1 (0, 17)	0.631
< 1	8 (57%)	14 (46%)	0.965
1 - 2	4 (29%)	10 (35%)	
2 - 4	1 (7%)	3 (11%)	
5 - 9	0	1 (4%)	
≥ 10	1 (7%)	1 (4%)	
Gender			0.099
Female	11 (79%)	14 (48%)	
Male	3 (21%)	15 (52%)	
Race			0.475
White	10 (71%)	22 (76%)	
Black	2 (14%)	6 (21%)	
Other	2 (14%)	1 (3%)	
Baseline developmental delay	0	3 (11%)	
Primary diagnosis			1.000
Viral bronchiolitis	13 (93%)	25 (86%)	
Pneumonia	0	3 (10%)	
Influenza A	1 (7%)	0	
Status asthmaticus	0	1 (3%)	
Type of gastric tube			0.308
None	11 (79%)	17 (59%)	
Nasogastric tube	3 (21%)	12 (41%)	
Daily feeding			1.000
Enteral	4 (29%)	7 (24%)	
None	10 (71%)	22 (76%)	

Data are presented as median (range) and n (%). P values are calculated using Wilcoxon rank sum test or Fisher's exact test. [a]Positive delirium screen based on CAPD ≥ 9. CAPD: Cornell Assessment of Pediatric Delirium.

delirium. This prevalence is higher than what has been previously reported in the general pediatric ICU population. Traube et al reported an incidence of delirium of 17.3% (267 of 1,547 patients); however, their cohort included all patients admitted to the pediatric ICU for more than 24 h [3]. Forty-two percent of their study subjects required mechanical ventilation with a smaller percentage, only 46%, having a primary diagnosis of respiratory failure [3]. Other studies in the pediatric population have estimated the prevalence of delirium to vary between 10-44% [8, 16-18]. It is important to note that our cohort was assessed for delirium on multiple occasions compared to some of these studies which were single point-prevalence. Additionally, in contrast to other studies, we did not note a significant impact on hospital or pediatric ICU LOS in our population [3].

Consistent with the prior literature, our cohort revealed an association with benzodiazepine use and the development of delirium. It is known that there are several medications and situations in the pediatric ICU that are associated with an increased incidence or worsened manifestations of delirium. Consistent with the adult literature, Traube et al found that delirium was five times more likely in pediatric patients who received benzodiazepines [3]. Similarly, Mody et al showed an independent, temporal, and dose-response relationship between benzodiazepine use and subsequent development of pediatric delirium [19]. The biologic mechanisms underlying the association between benzodiazepines and delirium are multifactorial. Benzodiazepines activate γ-amino butyric acid (GABA) receptors in the central nervous system, altering levels of neurotransmitters believed to be deliriogenic [20]. Benzodiazepines disrupt the normal sleep cycle (shown on electroencephalography and functional magnetic resonance imaging) which contribute to development of delirium in the ICU setting [21-23]. Additionally, benzodiazepines have anticholinergic properties and potentiate the anticholinergic effect of other medications resulting in an increased risk of delirium.

Multiple studies, primarily in adult patients, have demonstrated a potential protective effect of sedation with dexmedetomidine. These studies show dexmedetomidine to be less likely to cause delirium when compared to other sedatives, while still achieving the desired level of sedation [24-30]. Un-

Table 2. Outcome and Additional Clinical Data of Patients With and Without Delirium[a]

Variable	No delirium (n = 14)	Delirium[a] (n = 29)	P value
Number of days in the hospital	5.5 (3, 10)	6 (3, 14)	0.535
Total number of days in the hospital	83	191	
Number of days in the PICU	3 (1, 6)	3 (2, 13)	0.053
Total number of days in the PICU	43	123	
Number of days on NIV	2 (2, 5)	3 (2, 12)	0.152
Total number of days on NIV	39	104	
Type of NIV			
BiPAP	5 (35%)	21 (72%)	0.044[b]
CPAP	0	2 (7%)	1.000[b]
HFNC	11 (79%)	16 (55%)	0.187[b]
Average daily inspired oxygen concentration (%)	26 (19 - 33)	26 (18 - 34)	0.864
Reason for NIV discontinuation			
Weaned off	14 (100%)	29 (100%)	
Number of days with delirium[a]	0	2 (1, 6)	
Total number of days with delirium[a]	0	74	
Number of days CAPD documented	2 (1, 4)	3 (2, 9)	
Total number of days CAPD documented	31	106	

Data are presented as median (range) and n (%). When considering the type of NIV, the values may add up to more than the n as a single patient may have transitioned from one type of NIV to another during their hospital course. P values are calculated using Wilcoxon rank sum test or Fisher's exact test. [a]Positive delirium screen based on CAPD ≥ 9. [b]P values comparing the no delirium and delirium groups on each modality of NIV. PICU: pediatric intensive care unit; NIV: noninvasive ventilation; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; HFNC: high-flow nasal cannula; CAPD: Cornell Assessment of Pediatric Delirium.

like the effects of benzodiazepines described above, dexmedetomidine does not disrupt sleep cycles and facilitates non-rapid eye movement sleep patterns. Given our usual clinical practice, dexmedetomidine was a common medication used to provide sedation and facilitate acceptance of NIV in our patient cohort, with 83.7% of the patients on NIV receiving dexmedetomidine. Despite previous studies in adults demonstrating a protective effect on delirium, we noted a greater prevalence of delirium in patients on NIV who received dexmedetomidine. Twenty-eight of 29 patients (97%) who screened positive for delirium also received dexmedetomidine compared to eight of the 14 non-delirious patients (57%). However, a large percentage of these patients also received benzodiazepines. Of the patients who received dexmedetomidine and screened positive for delirium, 68% had benzodiazepine exposure (lorazepam or midazolam), compared to only 25% in the non-delirious group. These data suggest the potential impact of benzodiazepine administration on delirium even with the concomitant administration of dexmedetomidine.

In addition to benzodiazepines, there are multiple other medications with anticholinergic properties that are frequently used in the pediatric ICU setting. The "Anticholinergic Drug Scale" (ADS) has been used as a tool to quantify the anticholinergic medication burden in the pediatric ICU cohort; and found to be even higher than previously documented in the adult population [21, 31]. Traube et al found that anticholinergic medication use was an independent predictor of delirium in pediatric ICU patients [3]; however, this association has not been uniformly reproduced and reported by other studies [32]. Increased awareness of these potential effects has led to investigation of alternatives to those medications with associated anticholinergic properties aside from their therapeutic effects. In our cohort, 79% of patients with delirium while on NIV had received one or more of the medications included in the ADS (median ADS = 2.0). However, we did not identify a difference between the delirious and non-delirious groups in the use of these medications or their ADS [21, 31].

In addition to medication risk factors, it has been shown that there is a higher risk for delirium in patients requiring supplemental oxygen, with the highest risk in those on invasive mechanical ventilation [16]. For patients supported with NIV, the goal is to provide adequate sedation to tolerate the external device and promote synchrony with the respiratory support, while limiting delirium [33]. Meyburg et al studied risk factors for pediatric postoperative delirium and found the highest CAPD scores in patients with devices connected to the head (CPAP, nasal cannula, nasogastric tube, internal jugular central venous catheter) or hands (arterial catheter) [34]. In our cohort, we did not find a difference between the delirious and not delirious groups when it came to duration of NIV, presence of a nasogastric tube, or addition of enteral nutrition. Sixty percent of our cohort was supported with BiPAP and 72% of this group experienced delirium during their time on NIV. Sixty-three percent of our cohort was supported with HFNC and 55% of them experienced delirium. While we were unable to differentiate whether patients were more delirious while on

Table 3. Medications received by patients with and without delirium[a]

Medications	No delirium (n = 14)	Delirium[a] (n = 29)	P value
Benzodiazepines	2 (14%)	20 (69%)	0.001
Lorazepam	2 (14%)	19 (66%)	
Midazolam	0	2 (7%)	
Diazepam	0	1 (3%)	
Dexmedetomidine	8 (57%)	28 (97%)	0.003
Melatonin	1 (7%)	1 (3%)	1.000
Risperidone	0	1 (3%)	1.000
Famotidine	2 (14%)	7 (24%)	0.693
Albuterol	12 (86%)	27 (93%)	0.586
Ipratropium	1 (7%)	7 (24%)	0.240
Corticosteroids	3 (21%)	9 (31%)	0.720
Prednisolone	2 (14%)	6 (21%)	
Methylprednisolone	2 (14%)	8 (28%)	
Hydrocortisone	0	1 (3%)	
Antibiotics	5 (36%)	10 (34%)	1.000
Chloral hydrate	3 (21%)	13 (45%)	0.187
Clonidine	2 (14%)	5 (17%)	1.000
Anticholinergic agents	7 (50%)	23 (79%)	0.077
ADS score	1.5 (1, 3)	2 (1, 6)	0.292

Data are presented as median (range) and n (%). P values are calculated using Wilcoxon rank sum test or Fisher's exact test. [a]Positive delirium screen based on CAPD ≥ 9. ADS: Anticholinergic Drug Scale; CAPD: Cornell Assessment of Pediatric Delirium.

BiPAP than HFNC, these results are consistent with the prior literature showing devices connected to the head may be a risk factor for delirium. However, the current study has a limited cohort size and is not powered to evaluate these differences. A larger cohort will be needed to further define the relationship of the type of NIV (HFNC versus BiPAP) to delirium.

Our study is limited by its retrospective cohort design and a relatively small cohort size due to limited compliance with CAPD scoring and documentation. For our retrospective review, we included only patients who received standardized delirium assessment with CAPD scoring. The use of CAPD scoring was unfortunately not consistent in the study cohort as only 43 of a total of 202 patients who received NIV had appropriate scoring recorded in the medical record. Our results may be limited by selection bias, as patients who exhibit symptoms concerning for delirium may be more likely to get CAPD scores documented thereby overestimating the prevalence of delirium. The limited compliance with scoring may be related to a lack of appreciation that despite the use of NIV versus invasive mechanical ventilation, these patients remain critically ill with many of the same risk factors for delirium as patients requiring endotracheal intubation. Additionally, formal severity of illness scoring was not available or collected thereby limiting analysis based on the nature of the critical illness and its severity. Given these concerns, it may not be feasible to apply these data to all patients receiving NIV.

We were unable to perform time to event analysis due to our limited sample size, so we are unable to confirm that risk factor exposure preceded the positive delirium screen. Additionally, patients without delirium had fewer CAPD measurements documented than patients who screened positive for delirium, which could result in an additional source of bias. Additional data with a more universal approach to delirium scoring are needed. As our practice with NIV continues to grow, we are able to support more patients with significant respiratory involvement on NIV, including those of a younger age. As such, ongoing delirium screening is necessary in this cohort of patients. As demonstrated by our cohort, there is a significant prevalence of delirium in patients requiring NIV.

Lastly, we did not assess the different subtypes of delirium in this cohort and included three patients who had a baseline developmental delay. Kaur et al showed that fluctuation in the Richmond Agitation Sedation Scale (RASS) score in conjunction with the CAPD is a sensitive and specific tool for detecting delirium in patients with developmental delay [13, 35]. Our institution does not utilize RASS scoring and therefore we were unable to incorporate this into our analysis. Future studies are required to further evaluate preventable risk factors for pediatric delirium in the ICU setting.

Conclusions

Our data from this retrospective cohort demonstrate a significant prevalence of delirium in infants and children requiring

Table 4. Benzodiazepine Exposure In Patients With and Without Delirium[a] Who Received Dexmedetomidine (N = 36)

Medications	No delirium (n = 8)	Delirium[a] (n = 28)	P value
Benzodiazepines	2 (25%)	19 (68%)	0.046
Lorazepam	2 (25%)	19 (68%)	
Midazolam	0	2 (7%)	
Diazepam	0	0	
Total number of lorazepam bolus doses	0.5 (0, 3)	2.8 (0, 10)	
Total number of midazolam bolus doses	-	0.07 (0, 1)	

Data are presented as median (range) and n (%). P values are calculated using Wilcoxon rank sum test or Fisher's exact test. [a]Positive delirium screen based on CAPD ≥ 9. CAPD: Cornell Assessment of Pediatric Delirium.

NIV. As with previous studies, we noted an association with benzodiazepine use, providing at least one potentially modifiable risk factor. These data demonstrate the need for ongoing and consistent delirium screening for all patients in the ICU setting.

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Conflict of Interest

None to declare.

Informed Consent

As a retrospective study, the need for informed consent was not deemed necessary.

Author Contributions

Claire E. Christian: data acquisition, manuscript writing (original, revisions, and final version); Stephani S. Kim: data analysis, manuscript preparation and review; Joseph D. Tobias: manuscript preparation and review (drafts and final version).

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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