JPPT | Retrospective Clinical Investigation

Evaluation of Melatonin Practices for Delirium in Pediatric Critically Ill Patients

Thomas W. Laudone, PharmD; Shawna D. Beck, PharmD; and Hubert J. Lahr, PharmD

OBJECTIVE To determine the use of melatonin and its role in therapy for pediatric delirium (as either prophylaxis or treatment for delirium) in an academic medical center's PICU.

METHODS This retrospective, single-center study reviewed patients between 1 and 18 years of age admitted to the PICU between April 1, 2014, and February 29, 2019. Patients were included if they were admitted for greater than 48 hours and received melatonin for the indication of "delirium." Patients were excluded if melatonin was a home medication. Data collected included baseline characteristics, sedation and antipsychotic usage, assessment scores, and admission overview data. Descriptive statistics were used to report categorical data as percentages.

RESULTS A total of 63 patients were included. Thirty-nine patients (62%) required antipsychotics post–melatonin exposure, with risperidone being the most frequently used agent. The average cumulative antipsychotic exposure pre– and post–melatonin initiation was 2 versus 13 days. The average cumulative exposure to sedating agents, including opioids, benzodiazepines, ketamine, dexmedetomidine, and propofol, pre– and post–melatonin initiation was 13 versus 10 days. The average hospital and PICU lengths of stay were 54 and 39 days, respectively. The initiation of melatonin was also associated with lighter levels of sedation and decreased pain scores.

CONCLUSION Although the initiation of melatonin does not appear to decrease antipsychotic use, the results of this study may suggest a potential prophylactic effect in reducing the days of sedation the patient receives while inpatient.

ABBREVIATIONS EMR, electronic medical record; FLACC, Face, Legs, Activity, Cry, Consolability Scale; ICU, intensive care unit; PICU, pediatric intensive care unit; RASS, Richmond Agitation-Sedation Scale

KEYWORDS antipsychotic; delirium; melatonin; pediatric intensive care unit; prophylaxis; sedation

J Pediatr Pharmacol Ther 2021;26(4):361–365

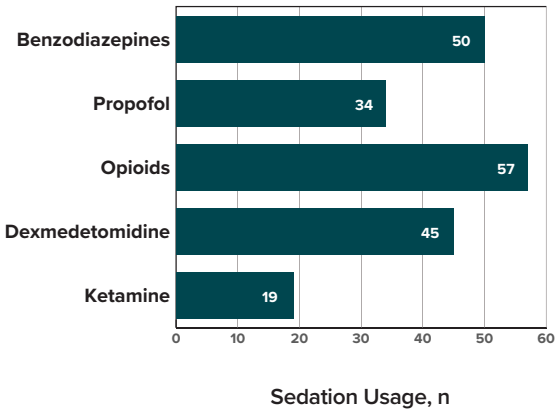
DOI: 10.5863/1551-6776-26.4.361

Introduction

Delirium is a well-known problem in the adult critically ill population. More than 30% of all critically ill adults develop delirium during their intensive care stay.[1,2] Emerging literature[1-3] suggests that as is the case with adults, pediatric delirium occurs frequently, with prevalence rates of between 12% and 65% in PICUs. The same categories of delirium observed in adults are also seen in pediatric patients and are characterized as hypoactive or decreased responsiveness, hyperactive or agitation, or mixed (combination of both).[4] To date, the largest multicenter pediatric delirium study[3] assessed 994 patients from 25 different PICUs and found a 25% overall delirium rate.

As defined in the Society of Critical Care Medicine Pain, Agitation, and Delirium Guidelines,[5] *delirium* is a syndrome characterized by the acute onset of cerebral dysfunction, with a change or fluctuation in baseline mental status, inattention, and either disorganized thinking or an altered level of consciousness. Sleep and delirium disturbances are notoriously difficult to both assess and recognize in the pediatric population, which has ultimately led to the development of pediatric-specific delirium tools. There are 3 validated tools that are frequently used: the Confusion Assessment Method for the ICU for children older than 5 years, the Preschool Confusion Assessment Method for the ICU for children aged 6 months to 5 years, and the Cornell Assessment of Pediatric Delirium for children aged 0 to 21 years.[4] Sleep deprivation is a known risk factor for ICU-associated delirium, and improvement in sleep quality is an important preventative intervention.[6,7] Melatonin is a vital component of the sleep-wake cycle because it is a neuro-hormone produced by the pineal gland during hours of darkness and provides multiple biological effects, including the regulation and synchronization of circadian rhythms.[7] To date, no trials have evaluated melatonin use in delirium in critically ill pediatric patients. The aim of this study is to determine melatonin's role in therapy for pediatric delirium as either

Figure. Most used sedative agents in the study population.



a prophylactic or a first-line or second-line treatment for delirium in the PICU at a large academic medical center. It is hypothesized that patients will be started on melatonin as a predominantly second-line treatment option and that the results will demonstrate a reduction in antipsychotic use.

Materials and Methods

This study was a retrospective, single-center chart review of patients who were between 1 and 18 years of age and admitted to the PICU from April 1, 2014, through February 29, 2019. This timeframe was selected to provide a sample of patients in a 5-year time block that correlated with the implementation of a new EMR database. Patients were included if they were admitted for greater than 48 hours and received melatonin for the indication of delirium. Patients were excluded if melatonin was a home medication, if they were younger than 1 year of age, or had one-time or as-needed melatonin orders. Patients who had no clear documentation or mention of delirium or altered mental status 1 week prior to initiating melatonin were also excluded because this suggests that melatonin was added for an indication other than delirium. *The International Classification of Diseases, Tenth Revision*[8] codes used to identify delirium were the following: F19.921, F11.20, R41.82, R41.0, F41.9, R45.1, F11.221, F05, F13.239, J96.01, F43.20, F13.231, F13.20, F43.21, F43.22, and F39.

Data collected included demographic information; hospital admission date; PICU admission date; use of and cumulative exposure to either typical or atypical antipsychotics; melatonin dose, frequency, and timing of administration; PICU and hospital length of stay; in-hospital mortality; and cumulative exposure to sedating agents. Additionally, average days on sedation, Richmond Agitation-Sedation Scale (RASS) and Face, Legs, Activity, Cry, Consolability Scale (FLACC) scores were recorded both a minimum of 5 days pre– and post–melatonin initiation. Assessment of these scores was conducted multiple times each day by the nursing staff. All scores for each day were averaged together, and this was done for the 5 days preceding and following initiation of melatonin. The primary outcome was defining melatonin therapy use and its current role in PICU-related delirium as either a prophylactic (prior to delirium development) or a first-line or second-line treatment after antipsychotic use. Secondary outcomes included both hospital and PICU length of stay, in-hospital mortality, and average RASS and FLACC scores pre- and post-initiation of melatonin. Additional secondary outcomes included identifying the most frequently used antipsychotic and sedation agents and determination of whether the addition of melatonin led to an overall reduction in their use. Descriptive statistical analysis was used to report categorical data as percentages. p values were used to detect statistical significance of secondary outcomes. A p value of ≤0.05 was considered significant, and 95% confidence intervals were computed with Prism 6 software (GraphPad Software, San Diego, CA) and unpaired *t*-test.

Results

One hundred and thirteen patients were screened between April 2014 and February 2019, and 63 patients met inclusion criteria. Fifteen patients were excluded because they were in the PICU for <48 hours; 13 patients were excluded owing to no mention of altered mental status or delirium in their EMR; 14 patients were excluded because melatonin was a continuation of their home dose or it was started in the hospital but outside the PICU; and 7 patients were excluded because they received as-needed or one-time doses of melatonin.

When evaluating the entire study population, 52% were female, and the mean age was 8 years, with the most often identified ethnicity being white or Caucasian (Table 1). Seventy-six percent of patients had a clear diagnosis related to delirium, and the 15 patients who did not have a relevant diagnosis code had clear documentation of delirium in the provider progress notes within the EMR. Weight, height, and body mass index were also reported for the study population (Table 1). Of the 63 patients included in the study, 39 of them had antipsychotic use post–melatonin exposure. Twenty-six patients received 1 antipsychotic, and 7 patients received 2 or more antipsychotics. Risperidone (n = 19) was the most frequently given antipsychotic, followed by haloperidol (n = 8), quetiapine (n = 3), and olanzapine (n = 3). When compared with pre–melatonin initiation, cumulative antipsychotic exposure was significantly longer post–melatonin use (Table 2.) Fifty-six (89%) patients received sedation during their stay in the PICU, and average cumulative sedation exposure pre– and post–melatonin initiation was not statistically different (Figure; Table 2). The average hospital and

Table 1. Baseline Characteristics of Patients Included in the Study

Baseline Characteristics	Patients (N = 63)
Age, mean ± SD, yr	8 ± 5.6
Sex, n (%), female	33 (52)
Race, n (%)	
White/Caucasian	39 (61.9)
Black/African American	9 (14.3)
Hispanic/Latino	6 (9.5)
Other/unknown	9 (14.3)
Delirium-associated diagnosis, n (%)	48 (76.2)
Length of stay, mean ± SD, days	
ICU	39.2 ± 36.1
Hospital	53.5 ± 55
Weight, mean ± SD, kg	30.3 ± 19.9
Height, mean ± SD, cm	119.2 ± 32.4
Body Mass Index ± SD, kg/m^2	19.3 ± 5.3

PICU lengths of stay were 53.5 ± 55 and 39.2 ± 36.1 days, respectively.

The average RASS scores pre– and post–melatonin initiation were significantly different (Table 2). However, the average FLACC scores pre- and post-melatonin were not significantly different (Table 2).

Discussion

Pediatric delirium continues to be a condition that is difficult to both diagnose and effectively manage in the ICU environment. Delirium is not a single entity but rather a global encephalopathic process that may result from a variety of causes, ranging from medications to the environment. It presents acutely with impairment of attention and consciousness, abnormalities of the sleep-wake cycle, and disturbances in thought and behavior.[1,3] Delirium in hospitalized patients has been linked to a number of adverse outcomes, including increases in length of stay, duration of mechanical ventilation, medical cost, in-hospital mortality, and long-term cognitive impairment.[6,9] Melatonin is believed to help improve delirium through its hypnotic effects by accelerating sleep initiation and improving sleep maintenance and efficacy.[7] Additionally, melatonin and melatonin agonists have the potential to decrease the incidence and severity of delirium through their sedative-sparing effects, which in turn may improve health outcomes.[9] We hypothesized that this study would validate the place of melatonin in the management of delirium, whether it be useful as a prophylactic or as a first-line or second-line treatment option. As a result, this would minimize the use of antipsychotics, which are known to have detrimental side effects, as well as decrease the ICU and hospital lengths of stay.

When reviewing the results of the primary outcome, the initiation of melatonin did not decrease the cumulative days of antipsychotic exposure, and more than half of the patients required antipsychotics in conjunction with melatonin. After initiation of melatonin there was a decrease in cumulative days of sedation exposure. Additionally, initiation of melatonin was also associated with a lighter level of sedation, according to the RASS scores, and with a decrease in pain, based on the improvement in FLACC scores. We hypothesize that this may lead to less delirium because both prolonged deeper levels of sedation and pain are risk factors for the development of delirium. However, it is possible that the changes in RASS and FLACC scores are directly attributable to the changes in the analgesic and sedative agents and not necessarily a result of the melatonin initiation. Without a tool to directly assess delirium, recognition becomes more challenging in the PICU when the patient has an underlying disease process or if the patient is receiving a sedative or analgesic medication that can contribute to alterations in level of consciousness.

These pediatric patients are already at increased risk for significant disturbances in sleep quality and quantity and are at risk for alteration of the sleep-wake pattern.[6] Two studies[7,10] in the pediatric ICU setting found fragmented sleep and absence of diurnal variation (daily cycle). Marseglia et al[11] also found altered circadian rhythm in mechanically ventilated children based on repeated measures of serum melatonin. It is difficult to correlate a specific demographic patient population that may be at a greater risk for delirium because the sex was about evenly split, and except for Caucasian being the predominant ethnicity identified, the remaining breakdown of ethnicities were relatively well distributed. Additionally, there was no subgroup

Table 2. Primary and Secondary Outcomes of Cumulative Antipsychotic and Sedation Exposure and Risk Factors Associated With the Development of Delirium Post–Melatonin Initiation

Outcome	Patients	CI (p value)
Primary outcomes		
Post-melatonin antipsychotic use, n (%)	39 (62)	
Cumulative antipsychotic exposure, mean ± SD, days		
Pre–melatonin exposure	2 ± 3.9	−17.605 to −4.395
Post–melatonin exposure	13 ± 15.5	(p = 0.0015)
Cumulative sedation exposure, mean ± SD, days		
Pre–melatonin exposure	13.2 ± 12	−2.820 to 7.620
Post–melatonin exposure	10.8 ± 13.5	(p = 0.3636)
Secondary outcomes		
Average RASS score, mean ± SD		
Five days pre–melatonin initiation	−0.8 − ± 0.9	0.106 to 0.694
Five days post–melatonin initiation	−0.4 ± 0.7	(0.0081)
Average FLACC score, mean ± SD		
Five days pre–melatonin initiation	0.6 ± 1	−0.125 to 0.525
Five days post–melatonin initiation	0.4 ± 0.8	(0.2249)
In-hospital mortality, n (%)	6 (9.5)	

FLACC, Face, Legs, Activity, Cry, Consolability Scale; RASS, Richmond Agitation-Sedation Scale

analysis conducted to stratify the effect of melatonin among different age groups. Although delirium can be associated with higher mortality, we attributed the deaths of 6 patients in this study to the underlying conditions that led to their PICU admissions. Underlying illness was not a data point that was collected and therefore is not reported.

Further studies would be beneficial to assess if melatonin assists in decreasing the use of a specific sedative agent or antipsychotic. Risperidone was the most frequently used antipsychotic, and opioids and benzodiazepines were the most common sedative agents used in this study. Because benzodiazepines are also associated with causing delirium it would be helpful to evaluate if melatonin could decrease the use of these agents for sedation. This study only evaluated cumulative days of sedation pre- and post-initiation of melatonin and did not stratify based on specific agents. The most common dose and frequency of melatonin was 3 mg by mouth nightly. This study was not designed to detect a clinical difference between the doses of melatonin, and therefore there may be a greater impact on decreasing delirium with higher doses of melatonin, but further studies are needed to confirm this theory.

There were many limitations of this study, one of which involved the use of a single center. The retrospective design prevents us from evaluating the efficacy of melatonin in the treatment of delirium compared with a specific antipsychotic agent. The study population was likely smaller than anticipated because there were several patients that were excluded from the study because of poor documentation of delirium or altered mental status within the EMR. Although the initiation of melatonin demonstrated a decrease in the amount of sedation received, this result was not statistically significant, nor can we solely attribute it to the initiation of melatonin. There were many confounders that were not accounted for in the study design, including average duration of intubation, reporting delirium scores, dexmedetomidine versus benzodiazepine use, duration of benzodiazepine use, and reporting average doses of sedation pre– and post–melatonin exposure. Additionally, RASS and FLACC scores were used as surrogate markers to identify the impact melatonin has on delirium because these are known risk factors for the development of delirium. A better indicator of melatonin's effect on delirium would be to evaluate the change in the Confusion Assessment Method for the ICU, Preschool Confusion Assessment Method for the ICU, or Cornell Assessment of Pediatric Delirium scores. These scores were not available because the study institution does not currently use any pediatric delirium scoring tools.

Conclusion

The initiation of melatonin does not appear to prevent delirium or decrease antipsychotic use. We were also unable to support a correlation between melatonin and decrease in pain or sedation. The role of melatonin in the treatment of pediatric delirium remains unclear because it was not compared directly to the use of antipsychotics. No comparison can be made between melatonin and its effects on sedation and pain because there was no analysis of disease severity and underlying sedative or analgesic doses and duration. Based on the results of this study, we do not recommend any changes in prescribing practices for the management of delirium in critically ill pediatric patients at this time.

Further studies are needed to evaluate the role of melatonin in the therapy for pediatric delirium by prospectively evaluating its effects compared with those of antipsychotics using a validated pediatric delirium scoring tool.

Article Information

Affiliations. Department of Pharmacy, University of North Carolina Children's Hospital, Chapel Hill, NC.

Correspondence. Thomas W Laudone, PharmD; tlaudone@msn.com

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the nature of this study, the project was exempt from informed consent.

Acknowledgments. The whole paper was virtually presented on May 2, 2020, at the PPA Annual Meeting, Bruce Parks Memorial Residency Showcase.

Submitted. May 3, 2020

Accepted. January 27, 2021

References

1. Malas N, Brahmbhatt K, McDermott C, et al. Pediatric delirium: evaluation, management, and special considerations. *Curr Psychiatry Rep*. 2017;19(9):65. doi:10.1007/s11920-017-0817-3
2. Patel AK, Bell MJ, Traube C. Delirium in pediatric critical care. *Pediatr Clin North Am*. 2017;64(5):1117–1132.
3. Traube C, Silver G, Reeder RW, et al. Pediatric delirium in critically-ill children: an international point prevalence study. *Crit Care Med*. 2017;45(4):584–590.
4. Capino AC, Thomas AN, Baylor S, et al. Antipsychotic use in the prevention and treatment of intensive care unit delirium in pediatric patients. *J Pediatr Pharmacol Ther*. 2020;25(2):81–95.
5. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825–e873.
6. Calandriello A, Tylka JC, Patwari PP. Sleep and delirium in pediatric critical illness: what is the relationship? *Med Scim (Basel)*. 2018;6(4):90. doi:10.3390/medsci6040090
7. Martinez FE, Anstey M, Ford A, et al. Prophylactic melatonin for delirium in intensive care (Pro-MEDIC): study protocol for a randomised controlled trial. *Trials*. 2017;18(1):4. doi:10.1186/s13063-016-1751-0
8. World Health Organization. *International Classification of Diseases, Tenth Revision (ICD-10)*. WHO.
9. Foster J, Burry LD, Thabane L, et al. Melatonin and melatonin agonists to prevent and treat delirium in critical illness: a systematic review protocol. *Syst Rev*. 2016;5(1):199. doi:10.1186/s13643-016-0378-2
10. Carno MA, Hoffman LA, Henker R, et al. Sleep monitoring in children during neuromuscular blockade in the pediatric intensive care unit: a pilot study. *Pediatr Crit Care Med*. 2004;5(3):224–229.
11. Marseglia L, Aversa S, Barberi I, et al. High endogenous melatonin levels in critically ill children: a pilot study. *J Pediatr*. 2013;162(2):357–360.