JPPT | Single Center Retrospective Study

Melatonin Use in Infants Admitted to Intensive Care Units

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OBJECTIVES Sleep deprivation is a risk factor for delirium development, which is a frequent complication of intensive care unit admission. Melatonin has been used for both delirium prevention and treatment. Melatonin safety, efficacy, and dosing information in neonates and infants is lacking. The purpose of this study was to describe melatonin use in infants regarding indication, dosing, efficacy, and safety.

METHODS This descriptive, retrospective study included infants <12 months of age admitted to an intensive care unit receiving melatonin. Data collection included demographics, melatonin regimen, sedative and analgesic agents, antipsychotics, and delirium-causing medications. The primary objective was to identify the melatonin indication and median dose. The secondary objectives included change in delirium, pain, and sedation scores; change in dosing of analgesic and sedative agents; and adverse event identification. Wilcoxon signed rank tests and linear mixed models were employed with significance defined at $p < 0.05$.

RESULTS Fifty-five patients were included, with a median age of 5.5 months (IQR, 3.9–8.2). Most (n = 29; 52.7%) received melatonin for sleep promotion. The median body weight–based dose was 0.31 mg/kg/dose (IQR, 0.20–0.45). There was a statistical reduction in cumulative morphine equivalent dosing 72 hours after melatonin administration versus before, 17.1 versus 21.4 mg/kg ($p = 0.049$). No adverse events were noted.

CONCLUSIONS Most patients (n = 29; 52.7%) received melatonin for sleep promotion at a median dose was 0.31 mg/kg/dose. Initiation of melatonin was associated with a reduction of opioid exposure; however, there was no reduction in pain/sedation scores.

ABBREVIATIONS CAPD, Cornell Assessment of Pediatric Delirium; CICU, cardiovascular intensive care unit; EMR, electronic medical record; FLACC, Faces, Legs, Arms, Cry, and Consolability; MME, morphine milligram equivalents; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; RASS, Richmond Agitation-Sedation Scale; SBS, State Behavioral Scale

KEYWORDS critical care; delirium; melatonin; pediatrics

J Pediatr Pharmacol Ther 2023;28(7):635–642

DOI: 10.5863/1551-6776-28.7.635

Introduction

Melatonin is a vital neurotransmitter produced by the pineal gland and is responsible for the body's circadian rhythm.[1] Exogenous melatonin, available as a natural supplement, has been gaining popularity in the outpatient setting for promoting sleep. Popularity has increased despite both a lack of rigorous potency and purity testing and a paucity of data regarding the long-term safety profile of melatonin use. A cross-sectional study of 871 school-aged children in the Netherlands found that 6.1% (n = 53) of participants used melatonin over the counter at least once a week for sleep disturbances.[2] The theory of using melatonin for sleep promotion has expanded past the outpatient setting into the inpatient setting. Procaccini and Kudchadkar[3] described inpatient melatonin use at a tertiary children's hospital; most patients (95.3%) receiving melatonin were >1 year of age. They noted a 246% increase from 2016 to 2020, and the authors inferred the indication was to ensure adequate sleep.

Melatonin has also been proposed to be beneficial in the setting of delirium prevention and treatment.[4] Delirium is a complication of intensive care unit admission that is related to negative outcomes, such as increased mortality, extended hospital stays, and cognitive deficits.[4] The recent practice guidelines on the Prevention and Management of Pain, Agitation, Neuromuscular Blockage and Delirium in Critically Ill Pediatric Patients with Consideration of the ICU Environment and Early Mobility suggest minimization of sedation exposure to decrease occurrence and severity of delirium, and the guidelines note that melatonin has decreased emergence delirium after general anesthesia in pediatric patients.[5] Laudone and colleagues[6] retrospectively evaluated 63 pediatric patients ages 1 to 18 years (mean ± SD age, 8 ± 5.6) that used melatonin for the prophylaxis or treatment of delirium in the pediatric intensive

care unit (PICU) and concluded that melatonin did not appear to prevent delirium, decrease pain, or reduce the use of antipsychotics and/or sedatives. Similarly, a recent meta-analysis of 80 studies evaluated various pharmacologic and nonpharmacological interventions to prevent delirium in critically ill patients ≥16 years of age, which included melatonin use in 225 patients.[7] The authors of this meta-analysis concluded that melatonin did not have a statistically significant effect in delirium occurrence, duration of mechanical ventilation, intensive care unit or hospital length of stay, or mortality in adults. Despite the lack of evidence, melatonin is still often employed inpatient at a range of doses for varying indications.

There are currently no studies examining the use of melatonin in neonates and infants. In the aforementioned studies by Procaccini and Kudchadkar[3] and Laudone and colleagues,[6] there were few patients ages <1 year who received melatonin. As a result, there are still very few data regarding efficacy, safety, and dosage strategies in this population. The purpose of this study is to describe melatonin use in infants <12 months of age regarding indication of use, dosing, efficacy, and safety.

Materials and Methods

Study Design. This was a retrospective cohort study of infants <12 months of age admitted to the PICU, cardiovascular intensive care unit (CICU), or the neonatal intensive care unit (NICU) at a tertiary care, academic health system from January 1, 2019, through August 31, 2021, that were initiated on melatonin. Patients were identified using the electronic medical record (EMR), Meditech (Medical Information Technology Inc, Westwood, MA). Patients were excluded if melatonin was a home medication or if the indication for use was not explicitly stated for one of the following: sleep promotion, or prevention or treatment of delirium. Indication of use was collected from patient care notes in the EMR. Delirium was determined by use of the Cornell Assessment of Pediatric Delirium (CAPD) scoring tool or documentation from the providers for the suspicion of delirium based on clinical symptoms in the EMR. The CAPD scoring tool is validated for delirium identification in children ages 0 to 21 years.[5,8] Patients with a CAPD ≥9 were designated as having delirium. Patients were also excluded if they only received 1 dose of melatonin or were admitted to a non–critical care service.

Study Objectives and Data Collection. Data collection included baseline demographic data, indication for melatonin, melatonin regimen, and analgesia and sedation used 72 hours prior to and after melatonin initiation. Any additional agents used for sleep (e.g., trazadone) within the 72-hour premelatonin and postmelatonin administration were collected. Opioids that were used for analgesia and sedation were converted to morphine milligram equivalents (MMEs) to allow more direct comparison (i.e., 0.1 mg of fentanyl and 1.5 mg of hydromorphone = 10 mg of morphine).[9] Data were collected on antipsychotics initiated for delirium in the inpatient setting if the agent was started within a month of melatonin initiation or if the patient remained on an antipsychotic agent during melatonin therapy. Additionally, the use of gabapentin was collected. Agents that are known to cause delirium, including benzodiazepines, corticosteroids, and anticholinergics, were collected in the 72-hour window before and after melatonin initiation.[5,10]

Analgesia, sedation, and pain scores used in the intensive care units were collected. The EDIN score is a validated tool to assess pain in neonates and is routinely used in the NICU setting and assessed every 3 to 4 hours.[11] The Faces, Legs, Arms, Cry, and Consolability (FLACC) and State Behavioral Scale (SBS) scores are validated tools for pain and sedation, respectively, that are recommended for assessment in critically ill children.[5] In the CICU and PICU, the FLACC scores are recorded every 4 hours, whereas the SBS scores are assessed every 2 hours by the patient's bedside staff trained in the use of these instruments. For those patients with CAPD scores, the highest CAPD scores per 24 hours (e.g., 0–24, 24–48, 48–72) were collected for each patient within the 24-hour period before melatonin and 72 hours after melatonin initiation. The EMR was screened for mention of adverse events related to melatonin administration as well as if delirium/agitation resolved or worsened or if sleep improved.

The primary objective of this study was to identify melatonin indication and median dose used. The secondary objectives included change in pain and sedation scores, cumulative dosing of analgesic and sedative agents (when available) 72 hours before and after melatonin initiation, and identification of documented adverse events noted with melatonin use in the providers' EMR notes. In those patients who were initiated on melatonin for prevention or treatment of delirium, an additional secondary objective was to identify melatonin's place of therapy with regard to other pharmacologic agents (e.g., antipsychotics, gabapentin). An additional secondary objective was to identify the change in CAPD scores in patients 24 hours before melatonin versus 72 hours after melatonin initiation.

Statistical Analysis. Descriptive statistics were used to summarize patient and clinical characteristics. Categoric variables were reported as frequency (percent) and continuous variables were reported as mean ± SD or median (IQR). Wilcoxon signed rank tests were used to make comparisons for changes in sedative and analgesic total dose before and after melatonin administration. Linear mixed models were used to estimate conditional means for pain and sedation scores.[12] Hourly time intervals were modeled as a random effect using a first-order autoregressive covariance structure, and time frame (prior to or after

melatonin administration) was modeled as a fixed effect conditional means, and slopes for pain and sedation scores were calculated using model estimates and compared between time frames using contrasts. Alpha was set to 0.05 for all analyses, which were conducted using SAS STAT software for Windows version 9.4 (Statistical Analysis System, Cary, NC), whereas figures were created using Tableau Desktop v2022.1 (Tableau, Seattle, WA).

Results

During the study period, 75 infants <12 months of age received melatonin during their hospital admission. Twenty patients were excluded for the following reasons: receipt of 1-time melatonin dose (n = 10), melatonin being a home medication (n = 7), and admission to general pediatric floor (n = 3). Baseline demographics for the 55 included patients are listed in Table 1. Most patients (n = 43; 78.2%) were mechanically intubated at the time of melatonin initiation and were admitted for a medical admission diagnosis (n = 31; 56.4%). Forty-four patients (80%) received ≥1 medication known to cause delirium, including benzodiazepines, corticosteroids, or anticholinergics. Eleven patients (20%) did not receive a medication associated with delirium prior to or after melatonin initiation. The median age at time of melatonin initiation was 5.5 months (IQR, 3.9–8.2), and there was a similar distribution of melatonin initiation between the PICU, CICU, and NICU. Most patients (n = 29; 52.7%) received melatonin for promotion of sleep. No patients received additional medications for sleep other than melatonin. Twenty-six patients (47.3%) received melatonin for delirium prevention (n = 3) or treatment (n = 23). No adverse events were noted.

Table 1. Patient Demographics (N = 55)

Variable	Value
Age at melatonin administration, median (IQR), mo	5.5 (3.9–8.2)
Biologic sex, female, n (%)	22 (40.0)
Weight, median (IQR), kg	5.5 (4.3–7.5)
Race/ethnicity, n (%)	
White	39 (70.9)
Black	7 (12.7)
Indigenous American	5 (9.1)
Other	3 (5.5)
Asian	1 (1.8)
Admission diagnoses, n (%)	
Medical	31 (56.4)
Surgical	24 (43.6)
Intensive care unit location	
Pediatric intensive care unit	22 (40.0)
Neonatal intensive care unit	18 (32.7)
Cardiovascular intensive care unit	15 (27.3)
Received agent known to cause delirium, n (%)*	
Anticholinergics	6 (10.9)
Benzodiazepines	15 (27.3)
Corticosteroids	33 (60)
Melatonin administration indication, n (%)	
Sleep promotion	29 (52.7)
Delirium treatment	23 (41.8)
Delirium prevention	3 (5.5)

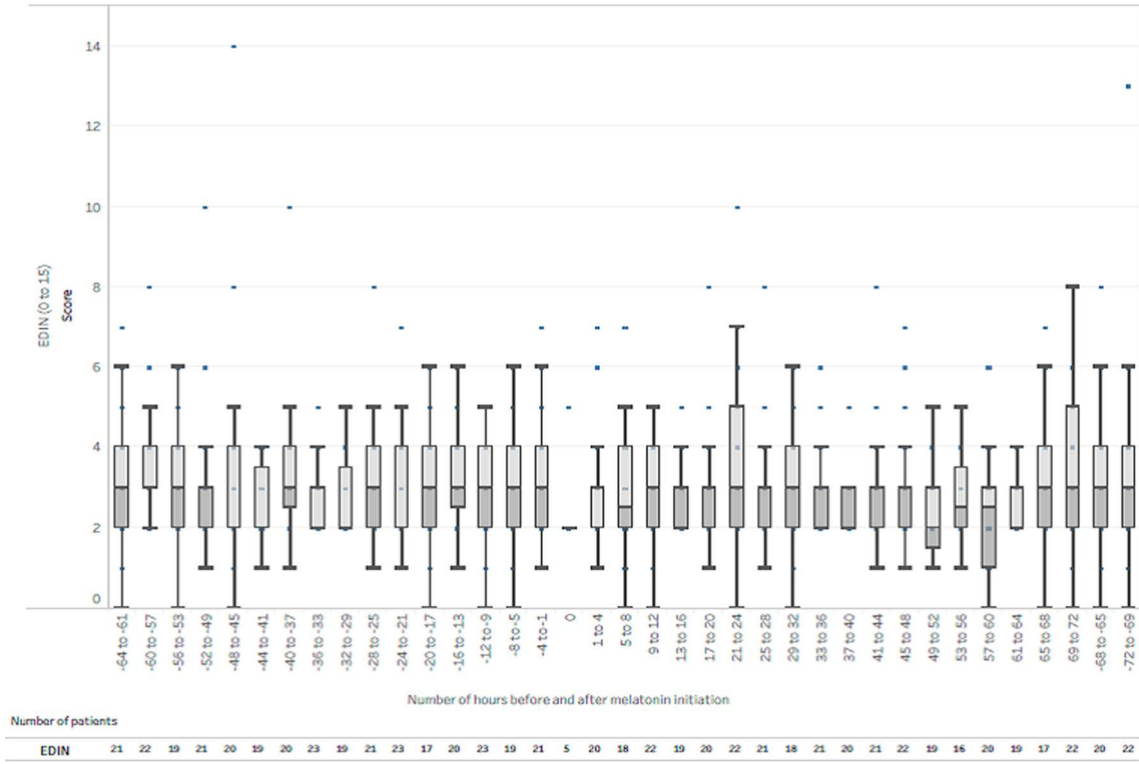
* Forty-four patients received ≥1 agent known to cause delirium.

The median weight-based dose was 0.31 mg/kg/dose (IQR, 0.20–0.45). The median fixed dose was 1.5 mg (IQR, 1.0–3.0). All patients received melatonin in the formulation of a 3-mg tablet, which was consistent with the institution's medication formulary at the time of the study. All doses <3 mg were achieved through splitting the tablet with a tablet-splitter by nursing staff. Thirteen patients (23.7%) initially received a full 3-mg tablet, and 10 patients (18.2%) initially received one half (1.5 mg) of a 3-mg tablet. Eighteen patients (32.7%) initially received doses that were not easily measurable increments of the 3-mg tablet (e.g., 1 mg), thus making it difficult to administer the prescribed dose. The most common dosing frequency for scheduled (n = 41) and as-needed (n = 14) doses was once daily in the evening at varying times. When examining all frequencies, the median number of doses administered was 11 (IQR, 4.0–32.0).

Twelve patients received a melatonin dose increase to a median dose of 0.45 mg/kg (IQR, 0.23–0.56), and the median number of doses administered of the increased dose was 20.5 (IQR, 11.5–60). Five of these patients were receiving melatonin for delirium treatment, whereas the remaining 7 patients received melatonin for sleep. Of these 12 patients, 10 received scheduled dosing of melatonin, and the remaining 2 patients received as-needed dosing. Time between the original dose and the increased dose varied, with 5 patients receiving a dose increase <1 week from the date of original dose initiation (i.e., 1–3 days); 4 of these patients had their dose increased from 1 to 1.5 mg to allow for a measurable dose using the 3-mg tablets. Three patients received a dose increase at 10 to 15 days, and the remaining patients experienced a dose increase at 28 to 70 days status after melatonin initiation.

Six patients had a decrease in their initial melatonin dose to a median dose of 0.24 mg/kg/dose (IQR, 0.20–0.48), and the median number of doses administered of the decreased dose was 5.5 (IQR, 3.0–17.0). Of these 6 patients, 3 received melatonin scheduled dosing once daily, with the remaining patients receiving melatonin as needed once daily. Time between original dose and the decreased dose varied, with 4 patients experiencing a dose decrease within 1 to 2 days of melatonin. The remaining 2 patients had a dose decrease at 34 and 45 days status after melatonin initiation.

Figure 1. Box plot of EDIN pain scores in 4-hour segments before and after melatonin administration.



The box plot displays distribution of pain scores in four-hour segments before and after melatonin administration. The box displays the median and interquartile range which is the middle 50% of data. The dark grey box represents the lower portion, and the light grey represents the upper portion. The whiskers display the upper and lower quartiles, while the dots represent outliers.

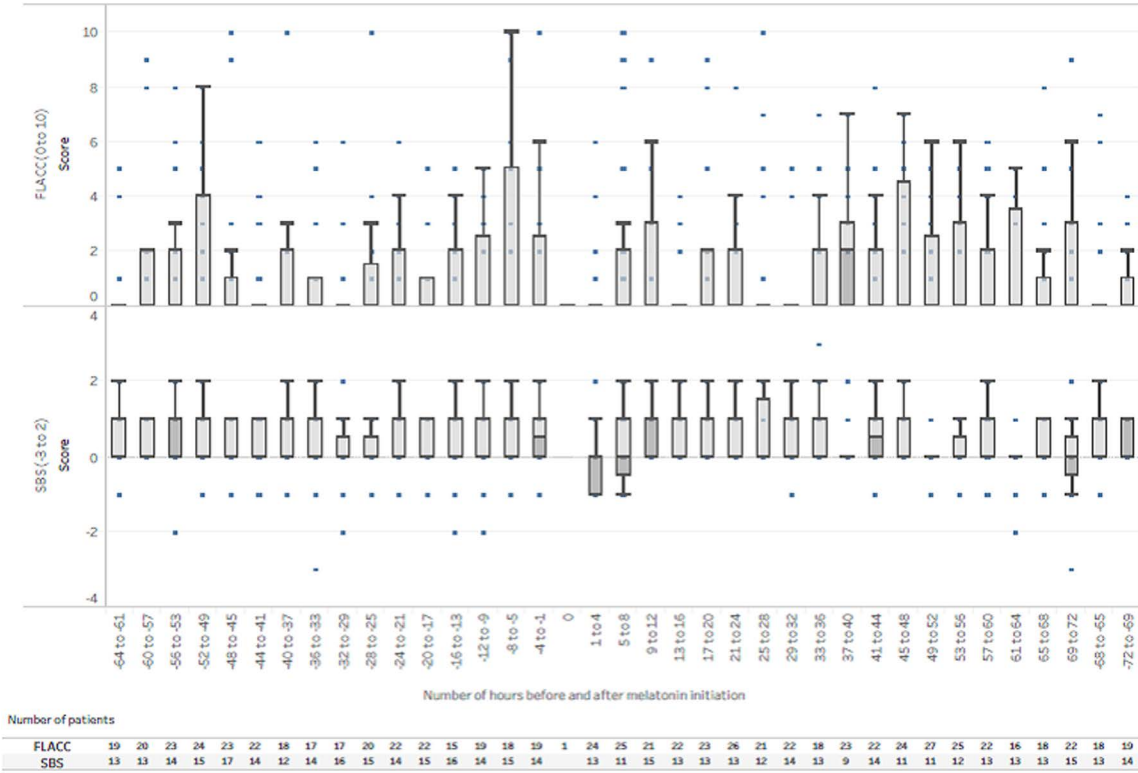
Sedation and pain scores were collected for all patients enrolled. The change in EDIN scores in the NICU during the 72-hour time frame prior to melatonin administration and 72-hour time frame after melatonin administration are included in Figure 1. The mean ± SD EDIN score prior versus after melatonin administration was 3.37 ± 3.17 versus 2.74 ± 3.22, respectively, with a slope of −0.62 (p = 0.073). The changes in FLACC and SBS scores in patients admitted to the CICU or PICU during the 72-hour time frame prior to melatonin administration and 72-hour time frame after melatonin administration are included in Figure 2. The mean ± SD FLACC score prior versus after melatonin administration was 1.55 ± 4.7 versus 0.95 ± 4.1, respectively, with a slope of −0.57 (p = 0.144). The mean SBS score prior versus after melatonin administration was 0.29 ± 1.45 versus 0.41 ± 1.65, respectively, with a slope of 0.104 (p = 0.580). Improvement in sleep was noted by providers for 5 patients (9.1%) in their EMR patient care notes.

Sedative and analgesic medications were collected for 72 hours prior and after melatonin administration. The difference in doses required between the 2 time periods as well as the number of patients that received each sedative/analgesic are illustrated in Table 2. There was statistical reduction in cumulative MME in the 72 hours after melatonin administration versus before at 17.1 versus 21.4 mg/kg (p = 0.049).

Gabapentin was administered to 10 patients during melatonin therapy at an initial dose of 5 mg/kg/dose every 8 to 12 hours. Seven of these patients were initiated on melatonin for delirium treatment, with the remaining 3 patients receiving melatonin for sleep. Seven patients were receiving gabapentin at least a week prior to melatonin start date, and 1 patient received 1 dose of gabapentin before starting melatonin. Of these 8 patients, the gabapentin dose was decreased in 2 patients, increased in 2 patients, and remained the same in 6 patients in the 72 hours prior versus after melatonin initiation. Two patients were started on gabapentin 9 to 10 days after melatonin initiation; thus, these patients are not represented in the comparison of 72 hours prior and after melatonin initiation reported in Table 2.

Of the 23 patients initiated on melatonin for delirium treatment, melatonin was initiated as a first-line agent for delirium in 14 (60.9%), and 9 received melatonin as a second-line agent after the initiation of an antipsychotic. Of the 14 patients who received melatonin as a first-line delirium treatment, 4 were subsequently initiated on an antipsychotic. This resulted in 13 patients who received both melatonin and an antipsychotic for delirium treatment. An additional 3 patients who received

Figure 2. Box plot of Faces, Legs, Arms, Cry, and Consolability (FLACC) pain and State Behavioral Scale (SBS) sedation scores in 4-hour segments before and after melatonin administration.



The box plot displays distribution of pain or sedation scores in four-hour segments before and after melatonin administration. The box displays the median and interquartile range which is the middle 50% of data. The dark grey box represents the lower portion, and the light grey represents the upper portion. The whiskers display the upper and lower quartiles, while the dots represent outliers.

Table 2. Concomitant Sedative and Analgesic Medications During a 72-Hour Period Before and After Initiating Melatonin

Medications	72 hr Prior to Melatonin Initiation		72 hr After Melatonin Initiation		p value
	Median (IQR)	n	Median (IQR[a])	n	
Opioids, MME/kg	21.4 (7.9–59.9)	44	17.1 (4.8–56.6)	42	0.049*
Dexmedetomidine, mcg/kg	43.2 (24.6–79.4)	27	43.3 (26.0–72)	26	0.798*
Clonidine, mcg/kg	15.0 (9.1–22.5)	25	15.9 (9.4–25)	27	0.155*
Midazolam, mg/kg	3.9 (1.9–10.0)	18	3.7 (2.4–6.4)	17	0.375*
Diazepam, mg/kg	0.6 (0.2–2.0)	16	0.7 (0.4–1.6)	19	0.232*
Lorazepam, mg/kg	0.3 (0.2–0.3)	14	0.3 (0.1–0.4)	13	0.845*
Gabapentin, mg/kg	39.4 (27.0–42.3)	8	41.6 (36.1–46.1)	8	—N/A
Ketamine, mg/kg	12.1 (7.5–557.0)	5	8.4 (2.6–1080)	3	N/A
Propofol, mcg/kg	47360	1	0	0	N/A
Phenobarbital, mg/kg	68.2 (53.9–82.5)	2	68.5 (54.6–82.5)	2	N/A

MME, morphine milligram equivalents N/A, nt applicable

* Wilcoxon signed rank test used for analysis.

melatonin for sleep also received antipsychotics for delirium treatment. For the 16 patients who received antipsychotics, irrespective of melatonin indication, the antipsychotics were initiated at different points during melatonin therapy including prior to melatonin initiation (n = 10), concomitantly with melatonin (n = 2), and after melatonin initiation (n = 4).

Ten patients (18.2%) had delirium scores documented in the 24 hours prior to melatonin initiation. Two patients had CAPD scores <9. For the remaining 8 patients, the median CAPD score was 12.5 (IQR, 11.5–15.5). At 24 hours after melatonin initiation, 7 of these patients had a CAPD score ≥9 with a median score of 13 (IQR, 9–15.5). These 7 patients continued to have CAPD scores ≥9 at 48 hours after melatonin initiation, with a median score of 14 (IQR, 10–21). At 72 hours, 5 of these patients continued to have a CAPD score ≥9, with a median score of 16 (IQR, 14–17).

Discussion

To our knowledge, this is the first study focused on melatonin's role in sleep promotion and delirium prevention and treatment in infants. Melatonin was most commonly used for sleep (52.7%) and delirium treatment (41.8%) in the intensive care units. It was difficult to determine the exact reason for the initiation of melatonin for sleep versus delirium, because some providers may have initiated melatonin to help improve sleep as to prevent or treat delirium.[3] The indication for the initiation of melatonin in our study does differ from those in previous studies[3,6] because of the age of the patients included. The study by Laudone and colleagues,[6] which included patients ages 1 to 18 years noted that 48 (76.2%) had a concomitant delirium diagnosis and were initiated on melatonin for delirium prevention or treatment. In contrast, Procaccini and Kudchadkar[3] included all pediatric patients ages <18 years, but only 4.7% of the patients included were infants; they noted that 98% of melatonin was administered for sleep regulation.

We noted that the median initial weight-based dose of our patients was 0.31 mg/kg/dose (IQR, 0.2–0.45). Some sources recommend dosing of 0.05 to 0.2 mg/kg/dose.[13,14] A study conducted by Van Geijlswijk and colleagues[14] found no clinical difference in outcomes between children ages 6 to 12 years with insomnia at sleep onset who received 0.05, 0.1, and 0.15 mg/kg/dose melatonin. The authors recommended using the smallest effective dose starting at 0.05 mg/kg/dose. It is difficult to compare the dosing used in their study with school-age children because of the paucity of efficacy and safety data with melatonin in infants that were included in our study. The weight-based dose our patients received was likely a result of the fixed dosage of a 3-mg tablet on our formulary at the time of the study. Laudone and colleagues[6] noted that the most common dosage form their patients received was also a 3-mg tablet. The median age and weight in their study were 8 years and 30.3 kg, and using the 3-mg tablet, the approximate mg/kg dose was 0.1 mg/kg/dose. Therefore, in the infants included in our study, the use of the 3-mg tablets did not allow for easy customization of doses to fall within this recommended dosage of 0.05 to 0.2 mg/kg/dose.[13,14]

Our study found a relationship between melatonin use for any indication and a decrease in MME dosing when comparing the 72-hour window prior to and after melatonin (21.4 [7.9–59.9] versus 17.1 [4.8–56.6] MME/kg; p = 0.049). This could be important given that employing strategies to decrease overall sedation exposure has been associated with decreased occurrence and severity of delirium.[5] The study by Laudone and colleagues[6] did not find a statistically significant decrease in the number of days requiring sedation, classified as receipt of either benzodiazepines, propofol, opioids, dexmedetomidine, or ketamine (13.2 ± 12 vs 10.8 ± 13.5, p = 0.364). Dosing and length of individual medications were not disclosed; therefore, it is unknown if a significant decrease in opioid usage was seen after melatonin initiation in their study. Our study did not find a difference in cumulative dose between the 72 hours before versus after melatonin in any of the other individual medications. Our study did not demonstrate a statistically significant change in SBS, FLACC, or EDIN scores. However, Laudone and colleagues[6] noted a lighter level of sedation required after melatonin initiation, with a significant decrease in Richmond Agitation-Sedation Scale scores (p = 0.008) and no significant change in FLACC scores after melatonin initiation. It is difficult to compare our study with their study. First, our PICU and CICU use SBS instead of FLACC scores to assess sedation. The NICU uses EDIN scores instead of FLACC scores to assess pain. With the small number of patients included, it limits the power for analysis of these data.

Twenty-three of our patients were initiated on melatonin for delirium treatment. Fourteen patients had melatonin as first-line delirium treatment, and 9 patients received melatonin as a second-line therapy after the initiation of an antipsychotic. Of the fourteen patients who received melatonin as a first-line agent, 4 (28.6%) required initiation of an antipsychotic to manage their delirium. The escalation of therapy to an antipsychotic in our study was less frequent than the frequency seen in the study by Laudone and colleagues,[6] with 61.9% of their patients starting an antipsychotic after melatonin initiation. This difference in frequency could be due to the small number of patients that received melatonin as a first-line agent for delirium treatment in our study, but it may also be attributed to our study population having a median age of 5.5 months. Delirium scoring tools have the least amount of data in those <6 months of age; they also have higher interrater variability in infants and lack validation, specifically within the NICU setting.[5,8,15]

The lack of objective identification may have played a significant role in our population not experiencing therapy escalation as often as the population in the aforementioned study. Notably, very few of our patients underwent consistent CAPD scoring prior versus after melatonin administration.

As mentioned, no adverse events associated with melatonin use were identified within our study. Because melatonin falls under the umbrella of a dietary supplement, the adverse event profile associated with melatonin is relatively unknown. A recent cross-sectional study by Lelak and colleagues[16] reported an uptick in melatonin ingestions reported to poison control centers around the United States, with 5 children requiring mechanical ventilation and 2 children dying secondary to melatonin overdoses from 2012 to 2021. Other adverse events reported included gastrointestinal, cardiovascular, and central nervous system symptoms.[16] Additionally, a study by Zhdanova and colleagues[17] found an association between melatonin doses greater than 3 mg and increased rates of hypothermia in geriatric patients. The most commonly reported adverse events that would prove problematic in the infant population include drowsiness, rash, diarrhea, and hypothermia.[18] Melatonin is currently being explored with varying results in multiple different infantile disease states, including hypoxic ischemia, seizures, sepsis, and lung injury in preterm infants, with limited acute adverse events noted.[19] Clinicians should be mindful when using melatonin and screen for the above-mentioned adverse events.

It is important to note that melatonin is not regulated, and thus purity and potency cannot be guaranteed. A study conducted by Erland and Saxena[20] found melatonin potency ranged from −83% to 478% of the labeled dose. This variability was not dependent on manufacturer or product type, and it remained when examining different lots within the same manufacturer. The least amount of variability was noted with melatonin tablets, which our population did receive. The infants within our study received a median initial dose above the proposed mg/kg/dose dosing range. This is without accounting for the wide range of potency between different lots and manufacturers. As noted, larger doses of melatonin may be related to increased frequency of adverse events. Even if the proposed dosing of 0.05 to 0.2 mg/kg/dose is used, there is no way for the clinician to know the true dose of melatonin the infant is receiving unless the product undergoes additional testing, like US Pharmacopeia testing. Products that are US Pharmacopeia verified may or may not be available from the institution's supplier.

A number of limitations with this study should be noted. First, this study was conducted at a single center, and thus these results may not be reproducible at other institutions. Second, the retrospective study design made it difficult to determine components of melatonin efficacy and safety. We only noted 5 of the 29 patients that received melatonin for sleep had documentation in their EMR for improved sleep. With the lack of an objective scoring tool and the potential for inconsistent documentation, it is difficult to confirm if the other patients initiated on melatonin for sleep also had improvement in their sleep patterns. We were also unable to elucidate why melatonin doses were increased or decreased because of inconsistent documentation. In addition, we did not note any documentation of adverse events with melatonin. For the assessment of adverse events, we reviewed the providers' notes in the EMR, so it is plausible that there may have been adverse events that were not captured.

Third, CAPD scoring was not available for all of our patients. Routine CAPD scoring was not used in all units at the time of the study. A fourth limitation was the inclusion of patients from the NICU, CICU, and PICU; each unit employs different sedation and/or pain scoring tools. It is possible that if this study was conducted at another institution with different scoring tools, then there could be different results noted. Finally, there may be other plausible explanations for the decrease in MME seen within our study. It is possible that providers may have been tapering the continuous infusions of sedative and/or opioid infusions around the time that melatonin was initiated. To account for this, we collected all sedative and opioids 72 hours before and after melatonin initiation, and we did not note a reduction in cumulative dosing of sedatives. We recommend further studies using our results to explore the potential opioid-sparing effects of melatonin. We also recommend more rigorous testing of melatonin when supplied for use in the inpatient setting to ensure safe and accurate dosing.

Conclusion

Most patients (n = 29; 52.7%) received melatonin for sleep promotion, and the median dose was 0.31 mg/kg/dose. There was a significant decrease in the cumulative MME dosing 72 hours after melatonin administration when compared to the 72 hours before melatonin administration, 17.1 versus 21.4 mg/kg (p = 0.049), with no other difference found in other sedatives or analgesics. Pain and sedation scores were not statistically different before and after melatonin initiation. No adverse events were noted. Future prospective studies should assess the efficacy and safety of melatonin in infants <12 months of age for the indication of sleep promotion, delirium prevention, and delirium treatment.

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Disclosure. 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.

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 has been approved by our institution review board. Given the nature of this study, informed consent, assent, and parental permissions were not required.

Acknowledgments. At the time of this study CB was a PGY2 Pediatric Pharmacy Resident at the University of Oklahoma College of Pharmacy. We would like to thank Meera Vijayan, PharmD student, and Madison Casten, PharmD student, at the University of Oklahoma College of Pharmacy, for their assistance with the data collection.

Submitted. August 31, 2022

Accepted. March 4, 2023

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