Child Neurology Open
Volume 10: 1-8

DOI: 10.1177/2329048X231194251
journals.sagepub.com/home/cno

Efficacy of Melatonin for Inducing Sleep in Pediatric Electroencephalogram Recordings: A Single-Blind Randomized Controlled Pilot Study

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Abstract

Objective To compare the efficacy of melatonin, melatonin with sleep deprivation, and chloral hydrate with sleep deprivation on sleep induction in Asian children. **Methods:** For this randomized single-blind controlled trial, we recruited 45 children aged 1–5 years and older who were not cooperative on electroencephalogram (EEG) recordings, randomly allocated to three groups: melatonin (group A), melatonin and sleep deprivation (group B), or chloral hydrate and sleep deprivation (group C). Between-group comparisons were performed using the Kruskal–Wallis and Mann–Whitney U tests. **Results:** Stage II sleep was achieved in 92.8%, 100%, and 100% of participants in groups A, B, and C, respectively. Sleep latency was significantly shorter in Group C than in Groups A ($p = .022$) and B ($p = .027$), while Group C had better sleep efficacy than Groups A ($p = .02$) and B ($p = .04$). **Conclusion:** Melatonin with sleep deprivation is less effective at inducing sleep than combined chloralhydrate and sleep deprivation.

Keywords

chloral hydrate, electroencephalography, melatonin, non-rapid eye movement sleep, sleep deprivation

Received March 28, 2023. Received revised June 17, 2023. Accepted for publication July 2, 2023.

Introduction

Successful electroencephalogram (EEG) recordings require patient cooperation, which can be a problem with children and toddlers, who sometimes find it difficult to remain still for a sustained amount of time. Epileptiform discharges often increase during sleep, which increases the chance of detecting EEG abnormalities.[1,2] Therefore, pediatric patients with suspected epilepsy usually undergo EEG recordings with sedation to induce sleep.

Chloral hydrate is an organohalide developed by Justin Liebig in 1832, which was first used as a sedative drug in 1869.[3] The exact mechanism of action of chloral hydrate is unknown; however, trichloroethanol and trichloroacetic acid are known to be the active metabolites. Trichloroethanol plays a crucial role in the sedative effect of chloral hydrate. Although chloral hydrate is not a Food and Drug Administration-approved drug, it is nevertheless widely used to induce sleep in pediatric subjects during EEG recordings in Thailand. However, several side effects have been reported, including nausea, vomiting, ataxia, restlessness, deep/prolonged sedation,[4] delayed apnea events,[5] gastric irritation, and teratogenic effects.[3] Accordingly, chloral hydrate should be used with caution, and should be avoided in patients with gastritis, gastric ulcers, liver disease, and porphyria, as well as in

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patients with a high risk of respiratory failure, those receiving anticoagulant drugs, or those who at risk of an allergic reaction.[3]

Melatonin is a hormone released from the pineal gland whose secretion is controlled by external factors, most notably light. This hormone induces sleep by acting on the suprachiasmatic nucleus (SCN) of the hypothalamus.[6] Melatonin is widely used to treat jet lag syndrome, insomnia, and circadian rhythm disorder.[7] The side effects of melatonin include headache, dizziness, hypothermia, and fatigue.[8]

Pediatric patients, especially those of preschool age and with delayed developmental status, often do not cooperate well during EEG recordings. Thus, the protocol is sometimes difficult with sleep deprivation. Currently, chloral hydrate used in combination with sleep deprivation is the standard method to induce sleep prior to EEG recording at the Division of Pediatric Neurology, King Chulalongkorn Memorial Hospital. However, the aforementioned side effects of chloral hydrate necessitate close monitoring, particularly deep or prolonged sedation and delayed apnea events in patients with severe developmental delays and respiratory symptoms. As such, in the present study, we propose melatonin as a potentially advantageous sedative medication with fewer side effects than chloral hydrate.

In 2009, Ashrafi et al. reported no significant differences in sleep latency between melatonin and chloral hydrate use with combined sleep deprivation.[9] Similar results were reported by several subsequent studies.[10–13] In 2017, Ibekwe et al.[12] reported that melatonin induced sleep in 86% of patients, which was a lower rate than chloral hydrate (95%); these results agree with those of a previous study in 2012. Furthermore, in 2015, Dirani et al.[10] compared the efficacy of melatonin, hydroxyzine, and chloral hydrate for sleep induction. They found that combined melatonin, hydroxyzine, and chloral hydrate treatment induced a significantly longer sleep duration than chloral hydrate alone.[10] However, Ashrafi et al. reported that the sleep duration and drowsiness time were longer for chloral hydrate combined with sleep deprivation than for melatonin alone.[9] In 2019, Alix et al.[14] reported that melatonin combined with sleep deprivation resulted in shorter sleep onset latency and longer sleep duration than either melatonin or sleep deprivation alone.

This study aimed to compare the efficacy of melatonin alone, melatonin combined with sleep deprivation, and chloral hydrate combined with sleep deprivation. Given that different ethnicities have different melatonin metabolism rates,[15] and that the majority of existing studies examined only Caucasian participants, we anticipated potential differences in the efficacy of melatonin in our Asian pediatric population.

Methods

Participants

We recruited patients who underwent an EEG appointment at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, from May 2019 to January 2020. Patients aged 1 to 5 years, as well as those who were older but not cooperative for EEG recordings, were included in this study. The exclusion criteria were: a history of allergy to melatonin or chloral hydrate, current respiratory infection or respiratory symptoms and signs, alterations of consciousness, inability to follow the sleep deprivation protocol, contraindications for enteral feeding, and/or clinical seizures during the EEG recording due to undetermined sleep stages. This study was approved by the Ethics Committee of the Faculty of Medicine at Chulalongkorn University. Written informed consent was obtained from the parents of all patients.

Patients were randomized into the following three groups using a computerized block of six randomizations: the melatonin group (Group A), combined melatonin and sleep deprivation group (Group B), and combined chloral hydrate and sleep deprivation control group (Group C). All three groups were managed in accordance with the protocols described below.

Sleep Deprivation Protocol

- The night before the EEG procedure, the patient went to sleep 2 h later than usual and woke up at their usual rising time.
- If a patient had an EEG scheduled in the afternoon, they would not sleep during the day.

Group A Protocol

- Patients did not follow the sleep deprivation protocol.
- Patients were asked to refrain from consuming food and drink for at least 4 h prior to the EEG procedure.
- Melatonin was purchased in a capsule form (Swanson®, manufactured by Swanson Health Products, USA; 3 mg/capsule). When administering melatonin to the patients, the capsule was removed, and the 3 mg of melatonin powder was dissolved in water. If the patient did not sleep, they received a second dose of melatonin 60 min after the first dose. If patients still did not sleep after the second dose of melatonin, they received a dose of chloral hydrate (25 mg/kg) 60 min after the second dose of melatonin.

Group B Protocol

- Patients followed the sleep deprivation protocol.
- Patients were asked to refrain from consuming any food and drink for at least 4 h before the EEG procedure.
- The melatonin was contained in a capsule (Swanson®; 3 mg/capsule). When giving this to the patients, the capsule was removed, and the 3 mg of melatonin powder was dissolved in water. If the patient did not sleep, they received a second dose of melatonin 60 min after the first dose. If patients did not sleep after the second dose of melatonin, they received a dose of chloral hydrate (25 mg/kg) 60 min after the second dose of melatonin.

Group C Protocol

- Patients followed the sleep deprivation protocol.

- Patients were asked to refrain from consuming food and drink for at least 4 h before the EEG procedure.
- Syrup chloral hydrate (Pharmaceutical Group, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 500 mg/5 mL) (maximum dosage was less than 1.2 g) was administered to the patients at 50 mg/kg/dose. If the patient did not sleep, they received a second dose of chloral hydrate (25 mg/kg) 60 min after the first dose.

The patients were administered their medication as usual. Patients who experienced type I hypersensitivity symptoms (acute urticaria or anaphylaxis), or any other severe adverse reactions, were withdrawn from the study.

EEG electrodes were applied after the patients received medication and felt sleepy. The EEG room was maintained dark and quiet, and the recordings lasted from 30 min to 2 h. A 19-channel system was used, and electrodes were placed according to the International 10–20 system. Demographic data, including sex, age, diagnosis before the EEG recording, and developmental status, were recorded. EEG data, including sleep-onset latency and sleep efficacy, were recorded.

Sleep onset latency was defined as the duration from the first dose of sedation to the time when non-rapid eye movement (NREM) stage II sleep was observed on EEG. NREM stage II sleep was defined as sleep spindles at 12–15 Hz lasting for at least 0.5 s, or the observation of K-complexes or vertex sharp waves over the central and paracentral areas. Sleep efficacy was calculated as the percentage of sleep time, including sleep stage NREM I-III (positive occipital sharp transients (POSTs), vertex sharp transients, sleep spindles, K-complexes, and slow-wave sleep), and rapid eye movement sleep.

The EEG data was interpreted by a pediatric neurologist and sleep medicine specialist with seven years of experience in EEG and polysomnography. This was a single-blind randomized controlled trial for which the researchers interpreting the EEG data were blinded to the patients' information.

Our study team recorded the occurrence of any side effects, including nausea, vomiting, abdominal discomfort due to gastric irritation, ataxia, and deep/prolonged sedation in the chloral hydrate group and headaches, dizziness, hypothermia, and fatigue in the melatonin groups.

Statistical Analyses

Statistical analyses were performed using the SPSS/PC software (version 22; SPSS Inc., Chicago, IL, USA). Qualitative data are described as the median, interquartile range (IQR), and range, owing to the non-normal distribution of the data. Fisher's exact test was used to perform between-group comparisons of qualitative data. For quantitative comparisons, we used the Pearson's correlation test, non-parametric Kruskal–Wallis test, and Mann–Whitney U test.

Results

Forty-five patients were enrolled between May 2019 and January 2020. Two patients met the exclusion criteria: one due to missing EEG data and another because we could not determine sleep stages due to a seizure. Therefore, the data of only 43 patients were analyzed.

Demographic Data

Demographic data and EEG recordings were obtained for 43 patients (65% male). The median age of patients was 2.5 years (IQR = 1.7-3.8, range = 1.0-8.7 years). The demographic data are presented in Table 1. There were no significant differences in sex, age, developmental status, diagnosis prior to EEG, or EEG performance time before 12:00 PM (AM) versus after 12:00 PM (PM).

Drug Doses and Correlation Between age and Developmental status in Each Group

In groups A and B, 4/14 patients (28.6%) and 2/12 patients (14.3%) required two or more doses of melatonin, respectively. One patient (7.1%) each in groups A and B required chloral hydrate administration, while one patient (6.7%) in Group C required two doses of chloral hydrate. There was no significant between-group difference in the drug dose ($p = .57$; Fisher's exact test; Figure 1). Furthermore, there was no significant correlation between drug dose and patients' age ($p = .27$), or between the developmental status and severity of global delay development (GDD) (mild GDD and normal development vs moderate and severe GDD) ($p = .78$).

Achievement of Sleep, Sleep Latency, and Sleep Efficacy

Stage II sleep was achieved in of 13/14 patients (92.8%) in group A, 14 patients in group B (100%), and 15 patients in group C (100%).

The sleep latency was measured in minutes. The median sleep latency was 57.00 (IQR = 40.50-83.00) in group A, 52.50 (IQR = 39.75-76.25) in group B, and 35.00 (IQR = 30.00-54.00) in group C. There was a significant difference in the median sleep latency ($p = .032$; Kruskal–Wallis test). Post-hoc testing showed that sleep latency was significantly shorter in group C than in groups A ($p = .022$) and B ($p = .027$). Furthermore, sleep latency was not significantly different between Groups A and B ($p = .904$) (Figure 2).

According to the patients' developmental status, the median sleep latency was 49.00 (IQR = 35.00-74.00) in the mild GDD and normal development groups and 47.00 (IQR = 33.00-75.00) in the moderate and severe GDD groups. No significant difference in sleep latency was found according to the patient's developmental status ($p = .933$).

Sleep efficacy was recorded as the percentage (%) of the total sleep duration during the recording. The median sleep efficacy percentage was 100.00% (IQR = 68.60-100%) in Group A, 99.50% (IQR = 84.24-100%) in Group B, and 100% (IQR = 100-100%) in Group C. Significant differences were found in the median sleep efficacy ($p = .039$; Kruskal–Wallis Test). Post Hoc test revealed that sleep efficacy was significantly better in group C than in groups A ($p = .020$) and B ($p = .044$). However, there was no significant difference in sleep efficacy between Groups A and B ($p = .729$) (Figure 3).

Table 1. Demographics Data.

	Total (n = 43)	Melatonin (A) (n = 14)	Melatonin with sleep deprivation (B) (n = 14)	Chloral hydrate with sleep deprivation (C) (n = 15)	*p*-value
Gender; n (%)					
Males	28 (61.1)	10 (71.4)	9 (64.3)	9 (60.0)	.809[a]
Females	15 (38.9)	4 (28.6)	5 (35.7)	6 (40.0)	
Age; years (Range)	2.9 (1.0-8.6)	2.6 (1.3-5.5)	3.8 (1.7-8.7)	2.4 (1.0-5.0)	.07[b]
Developmental status					
Mild GDD and normal	32 (74.4)	12 (85.7)	9 (64.3)	11 (73.3)	.427[a]
Moderate to severe GDD	11 (25.6)	2 (14.3)	5 (35.7)	4 (26.7)	
Diagnosis prior EEG recording					
Epilepsy	9 (20.9)	2 (14.3)	5 (35.7)	2 (13.3)	.253[a]
Non-epilepsy[c]	34 (79.1)	12 (85.7)	9 (64.3)	13 (86.7)	
EEG performing times					
AM (before 12 pm)	22 (51.2)	7 (50.0)	6 (42.9)	9 (60.0)	.650
PM (after 12 pm)	21 (48.8)	7 (50.0)	8 (57.1)	6 (40.0)	

Data is presented as number (percentage)
Abbreviations: GDD, global delay development; EEG, electroencephalography.
[a]Fisher's Exact test.
[b]Kruskal-Wallis test
[c]Non-epilepsy included recurrent febrile seizure, paroxysmal event, developmental regression, first episode unprovoked seizure, and tuberous sclerosis or polymicrogyria patients who never had seizure.

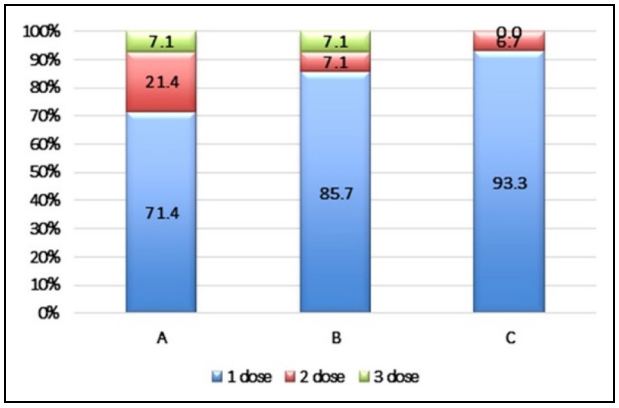

Figure 1. Number of drug doses in the melatonin group (A), melatonin and sleep deprivation group (B), and chloral hydrate and sleep deprivation group (C).

According to the patients' developmental status, the median sleep efficacy was 100.00 (IQR = 86.69-100.00) in the mild GDD and normal development groups and 100.00 (IQR = 73.80-100.00) in the moderate and severe GDD groups. Overall, there was no significant difference in the patients' developmental status ($p = .652$).

Comparison of Sleep Latency and Sleep Efficacy According to EEG Performing Time

We further stratified patients into two groups based on the EEG recording time; before 12:00 PM (AM) and after 12:00 PM (PM). The median sleep latency was 50.50 (IQR = 34.50-75.00) in the AM group and 49.00 (IQR = 34.75-74.25) in the PM group. There was no significant difference in median sleep latency between the AM and PM EEG performance times.

In patient group A, the median sleep latency was 58.00 (IQR = 38.00-80.00) in the AM group and 52.50 (IQR = 38.50-94.50) in the PM group. In patient group B, the median sleep latency was 51.00 (IQR = 38.75-73.25) in the AM group and 52.50 (IQR = 42.00-144.75) in the PM group. In patient group C, the median sleep latency was 35.00 (IQR = 27.50-64.00) in the AM group and 36.00 (IQR = 28.75-54.75) in the PM group. There was no significant difference in the median sleep latency or EEG performance time between groups A and B ($p = .731$), B ($p = .573$), and group C ($p = .955$).

In terms of sleep efficacy, the median sleep efficacy was 100.00 (IQR 75.57-100.00) in the AM group and 100.00 (IQR = 90.02-100.00) in the PM group. There was no significant difference in the median sleep efficacy between the AM and PM EEG times ($p = .202$). In patient group A, the median sleep efficacy was 76.17 (IQR 60.20-100.00) in AM group and 100.00 (IQR 83.65-100.00) in PM group. In patient group B, the median sleep efficacy was 86.68 (IQR 73.03-99.25) in the AM group and 100.00 (IQR 90.02-100) in the PM group. In patient group C, the median sleep efficacy was 100.00 (IQR 100.00-100.00) in the AM group and 100.00 (IQR 92.14-100.00) in the PM group. There was no significant difference in terms of sleep efficacy or EEG performance time among groups A ($p = .234$), B ($p = .059$), and C ($p = .607$).

However, when we compared the median sleep efficacy in each group for EEG performance times, we identified a significant difference in the median sleep efficacy between A,B and C for morning EEG group. ($p = .01$). The post-hoc test sleep

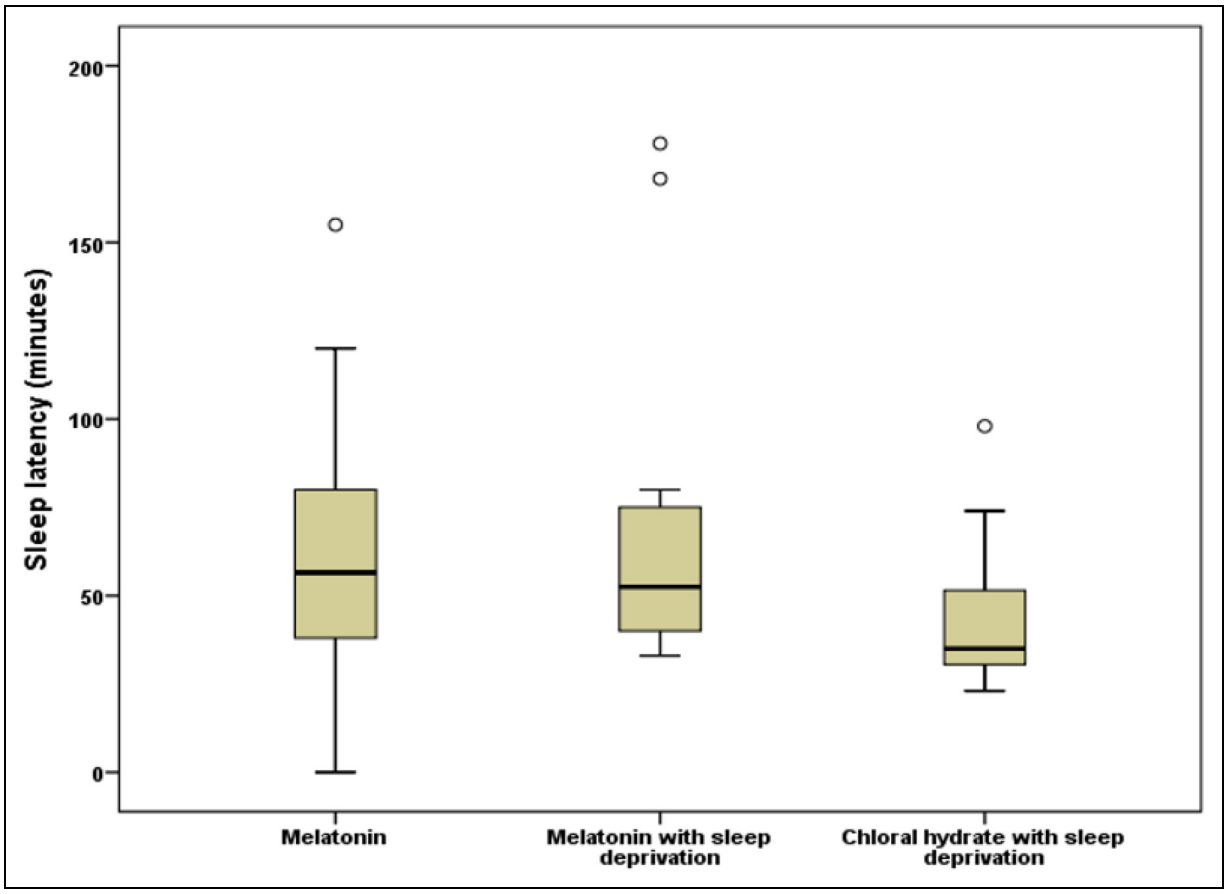

Figure 2. Sleep latency in groups A, B, and C, expressed in minutes.

efficacy was superior in group C than in groups A ($p = .011$) and B ($p = .01$).

Comparison of Sleep Latency and Sleep Efficacy According to age and Developmental status

There was no significant correlation between age and sleep latency ($p = .539$), as shown in Figure 4. However, there was a negative correlation between patient age and sleep efficacy ($r = -0.317$, $p = .041$), with sleep efficacy found to be poorer in older patients; however, there was no significant correlation between the subgroups (A, B, and C), as shown in Figure 4.

There was no significant between-group difference in terms of sleep latency ($p = .93$) (Table 2) or sleep efficacy ($p = .65$) (Table 3) when compared with the patients' developmental status (mild GDD and normal development vs moderate and severe GDD).

None of the study participants reported any side effects, including the any of the previously-published side effects, such as nausea, vomiting, abdominal discomfort due to gastric irritation, ataxia, or deep/prolonged sedation caused by chloral hydrate and headaches, dizziness, hypothermia, and fatigue due to melatonin.

Discussion

Overall, the results of the present study showed that melatonin alone was as effective as melatonin in combination with sleep deprivation to induce sleep prior to pediatric EEG recordings. However, its efficacy was less than that of chloral hydrate combined with sleep deprivation, which was especially true for achieving sleep, sleep latency, and sleep efficacy. These results agree with those of a previous study conducted in 2017 by Ibekwe et al.[12] In terms of EEG performance time, there was no significant difference in sleep latency or sleep efficacy between patients who underwent EEG in the morning or afternoon. Nevertheless, when we compared sleep efficacy between each group, we found it to be better in the combined chloral hydrate and sleep deprivation group who underwent EEG monitoring in the morning. Overall, our results agree with those of a previous study by Kurth et al which measured the sleep duration in children under five years, finding decreased sleep duration in the afternoon nap group compared with the morning nap group.[16] However, there were no significant between-group differences in drug doses. Further, in the present study, the sleep efficacy was better in younger patients. We hypothesized that the melatonin doses in each patient were followed by age, regardless of body weight and small sample size. Therefore, the combined chloral hydrate and sleep

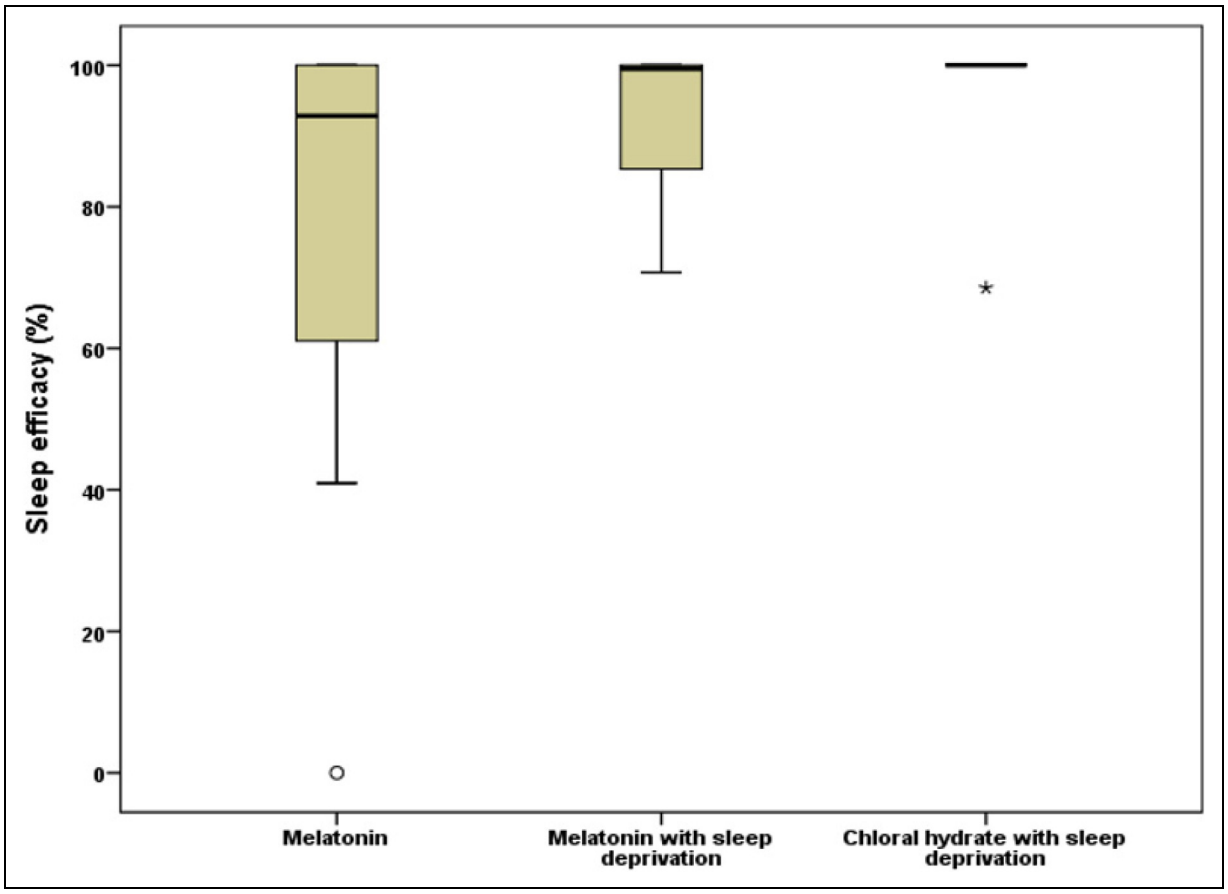

Figure 3. Sleep efficacy in groups A, B, and C, expressed as percentages.

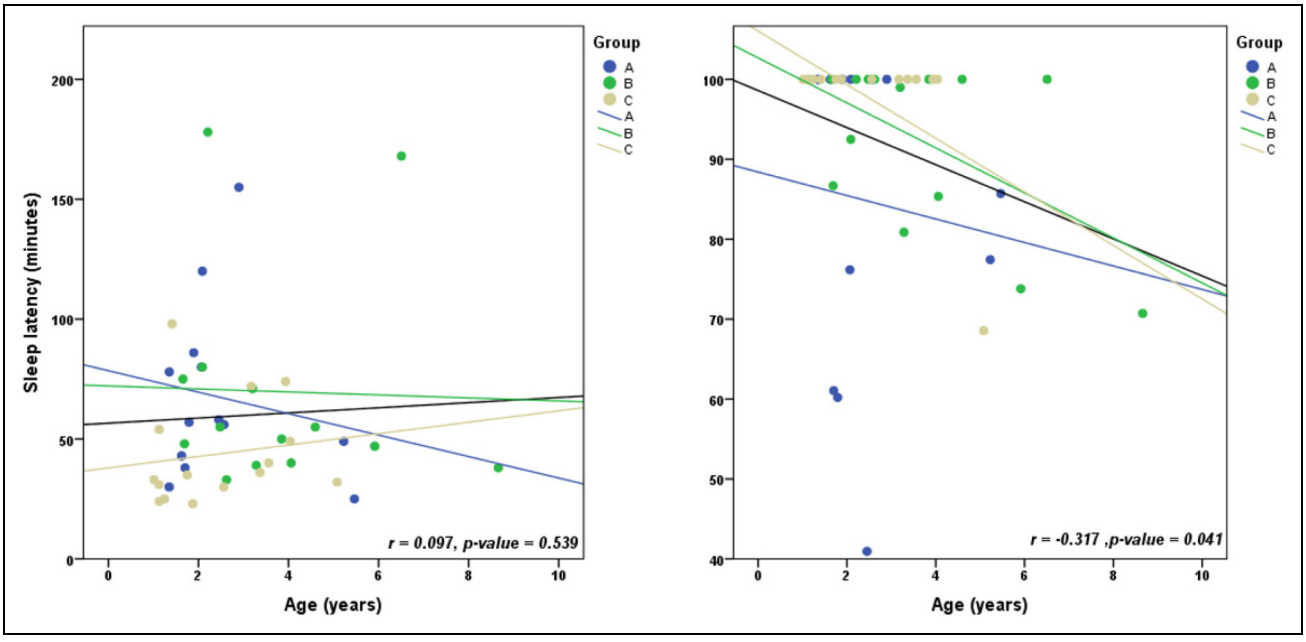

Figure 4. (Left) Correlation between sleep latency (minutes) and age in groups A (blue line), B (green line), and C (light brown line). (Right) The correlation between sleep efficacy (%) and age in groups A (blue line), B (green line), and C (light brown line).

Table 2. Comparison of the Sleep Latency in Each Groups, EEG Time and Development.

Factors		Sleep latency	p-value
Group			
	A	57.00 (40.50-83.00)	.032
	B	52.50 (39.75-76.25)	
	C	35.00 (30.00-54.00)	
EEG time			
	AM	50.50 (34.50-75.00)	.753
	PM	49.00 (34.75-74.25)	
Developmental status	Mild GDD and normal	49.00 (35.00-74.00)	.933
	Moderate and severe GDD	47.00 (33.00-75.00)	

Data is presented as median (IQR).

Table 3. Comparison of the Sleep Efficacy in Each Groups, EEG Time and Development.

Factor		Sleep efficacy	p-value
Group			
	A	100.00 (68.61-100.00)	.039
	B	99.50 (84.24-100.00)	
	C	100.00 (100.00-100.00)	
EEG time			
	AM	100.00 (75.57-100.00)	.202
	PM	100.00 (90.02-100.00)	
Developmental status	Mild GDD and normal	100.00 (86.69-100.00)	.652
	Moderate and severe GDD	100.00 (73.80-100.00)	

Data is presented as median (IQR)

deprivation method showed an improved effect. Patients in this group were administered the chloral hydrate dosage in mg/kg/dose,[9] which could explain why younger patients had better sleep efficacy when their body weight was lower than that of older patients. However, the melatonin dosage is widely calculated based on the patient's age, not body weight. Melatonin is also commonly used in the sleep medicine field, where patients are also prescribed a melatonin dosage based on their age.[10,11]

No side effects of chloral hydrate have been reported at our institution. However, previous studies have reported that some patients may experience gastric irritation, vomiting, oxygen desaturation, paradoxical excitation, prolonged sedation, hypotension, and cardiac arrhythmia.[3] The pharmacokinetic lifetime of melatonin, including Tmax, ranged from 15 min (2 mg oral) to 210 min (10 mg oral), or approximately 50 min following oral immediate-release formulation of melatonin; the half-life ranged from 28 min (0.005 mg IV) to 126 min (4 mg oral), and the bioavailability of oral melatonin ranged from to 9–33%.[16] Moreover, a previous study showed that melatonin has a significantly shorter half-life and a lower area under the curve in prepubertal subjects.[17] In the present study, we recruited pediatric patients aged 1–5 years, and found that melatonin could have a shorter half-life, which would explain the fewer sleep-related side effects, shorter sleep duration, and/or worse sleep efficacy than chloral hydrate. The altered pharmacokinetics probably resulted from altered CYP1A2 activity, which plays a vital role in melatonin metabolism. Asian individuals generally have lower CYP1A2 activity than Caucasians.[15] Therefore, sleep latency and sleep duration induced by melatonin may differ according to ethnicity.

A recent prospective study that collected data from 688 patients from 51 neurophysiologic centers in the United Kingdom used their own sleep-induction protocol, which divided patients into the melatonin, sleep deprivation, and combined intervention groups. They found that a combined intervention was more effective than either intervention alone. However, this was not a randomized controlled trial.[14]

Overall, the present study had some limitations. First, the sample size was small, and the data were collected over a short period. Future studies should investigate the effect of melatonin on seizure activity and the effect of medication on the beta frequency.

In conclusion, the results of this study melatonin treats sleep deprivation less effectively than combined chloral hydrate and sleep deprivation methods. However, our results also show that it should be administered in a mg/kg/dose to achieve the highest efficacy.

Acknowledgements

We would like to thank Ms. Dollapas Punpanich of the Biomedical Research and Development Center, Phramongkutklao Hospital, who served as our statistical consultant.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the the Ratchadapiseksompotch Fund, (grant number RA 62/064)

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