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ORIGINAL ARTICLE

Comparison of sedative drugs (chloral hydrate, hydroxyzine, and melatonin) and natural sleep used in sleep transition before electroencephalogram exposure in children: A randomized controlled trial

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ABSTRACT

Objectives: This study aimed to evaluate the effects of sedative drugs and natural sleep on sleep success, duration of falling asleep, and the baseline for electroencephalogram (EEG) recording in children, as well as adverse effects.

Patients and methods: This single-blind, randomized controlled clinical study was conducted with 180 children (113 males, 67 females; mean age: 41.66 ± 25.34 months; range, 1 to 7 years) between January and December 2021. The study comprised two stages: Stage I, preliminary preparation, and Stage II, procedure preparation and EEG recording.

Results: The sedative drug groups had a significant difference in the duration of falling asleep ($p < 0.001$). The duration was the shortest in the chloral hydrate group, and it was the longest in the natural sleep group. Excessive fast act patterns were highest in the chloral hydrate group and significantly lower in the natural sleep group ($p = 0.042$). While frequency values differed significantly among the groups, the frequency value in the hydroxyzine group was significantly higher than that in the melatonin group ($p = 0.001$).

Conclusion: In conclusion, while our study provided clear evidence that melatonin offered a safer sedation alternative with minimal EEG interference, the challenge of developing universally applicable sedation protocols remains. Future research should focus on multicenter trials, innovative sedative combinations, and integrating technological advances to improve both the safety and diagnostic accuracy of pediatric EEG.

Keywords: Electroencephalogram, natural sleep, pediatric neurology, sedative drugs.

Electroencephalogram (EEG) is important for making the correct diagnosis in children, providing appropriate intervention, and predicting the prognosis in the long term.[1-3] The quality of the EEG recording is determined by the absence of environmental and technical artifacts.[4] It is important for the child to remain still during the EEG recording to ensure the successful completion of the neurodiagnostic procedure.[5] Therefore, sedation is administered to children before EEG recordings to prevent muscle artifacts and to facilitate the sleep period, which increases the efficiency of detecting interictal epileptiform abnormalities.[6-9]

A range of sedative agents is utilized in pediatric sedation practices. The selection of the sedative and the desired depth of sedation are determined by the nature of the procedure and the child's underlying medical condition.[10] For pediatric patients, it is crucial that the ideal

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sedative agent has a rapid onset of action, minimal side effects, is easy and painless to administer, maintains sedation throughout the procedure, has minimal impact on hemodynamics, does not suppress abnormal EEG activity, and provides sedation without causing alterations in the EEG background.[11-17] It has been reported that both benzodiazepines and barbiturates, among the sedative drug groups, possess antiepileptic properties, can alter EEG background activity, and may hinder the detection of abnormal discharges, thereby complicating the interpretation of the EEG.[2,7,11,12] Due to these effects of benzodiazepines and barbiturates, their use is not preferred in EEG diagnostic procedures, and alternative sedative drugs are favored instead.[18,19] Although usage frequency varies across clinical settings, chloral hydrate, melatonin, and hydroxyzine are the most commonly used drugs to induce sleep for EEG recording in children.[20]

Chloral hydrate is one of the first synthetic sedative drugs recognized as a sedative agent for imaging in pediatric patients. It is widely used due to its rapid absorption when administered orally or rectally, its fast metabolism in the liver, and its successful compatibility with other sedative medications.[18,21] A meta-analysis study indicated that chloral hydrate, at therapeutic doses, is a suitable and effective drug for sedation in children.[22] However, chloral hydrate was reported to cause side effects such as apnea, desaturation, hypotension, vomiting, and prolonged sedation in infants under six months of age. Its bitter taste and the gastric irritation that can induce vomiting are considered its main disadvantages.[18,21]

Another drug that can be considered an alternative to chloral hydrate is hydroxyzine. Hydroxyzine is a long-acting, first-generation H1 antagonist with central nervous system depressant activity. Hydroxyzine is as effective as chloral hydrate in inducing sleep before EEG in children, while being more successful in minimizing adverse effects on the EEG.[16] A study reported that although chloral hydrate had a higher sedation success rate compared to hydroxyzine, more side effects (e.g., vomiting, hypotension, and agitation) were observed in the chloral hydrate group, highlighting the need for further research on this topic.[23]

According to the International League Against Epilepsy, partial sleep deprivation or the use of melatonin is recommended for EEG recordings in children under 12 years of age.[24] A study reported that the sedation success rates of melatonin and chloral hydrate were similar, no significant side effects were observed with either drug, mild nausea and vomiting were occasionally noted in the chloral hydrate group, and both medications could be used for sedation in EEG recordings.[25] In another study comparing melatonin, chloral hydrate, and hydroxyzine, it was noted that chloral hydrate was more effective in inducing sleep; however, further prospective studies are needed.[20] Considering these findings, it is evident that further research is needed to support clinical decision-making in the selection of an ideal sedative drug for EEG recordings in children.[11,13-15,17,20] In this context, the purpose of this study was to evaluate the effects of natural sleep versus chloral hydrate, hydroxyzine, and melatonin, which are used as sedative agents before EEG recording in children, on sleep success, the duration of falling asleep, the EEG baseline, and adverse effects. We hypothesized that natural sleep and the sedative drugs (chloral hydrate, hydroxyzine, and melatonin) administered to children in their transition to sleep before the EEG recording would have no difference in their effects on sleep success, the duration of falling asleep, and the EEG baseline.

PATIENTS AND METHODS

This single-blind, randomized controlled clinical study was conducted in the Pediatric Neurology Outpatient Clinic of Antalya Training and Research Hospital between January and December 2021. The study included all children who had EEG recordings available. The sample consisted of 180 children (113 males, 67 females; mean age: 41.66 ± 25.34 months; range, 1 to 7 years) who met the inclusion criteria and were evaluated in terms of epilepsy, suspected epilepsy, headache, syncope, and visual aura. According to the classification determined by the American Society of Anesthesiologists (ASA)[26,27] the children in the ASA I group (normal healthy individuals) and those in the ASA II (those with mild systemic diseases) risk group and who came to the recording in accordance with the training steps provided by the EEG nurse were included in the study. The exclusion criteria of our study were determined based on the literature. Chloral hydrate is contraindicated in cases of respiratory failure, renal and hepatic dysfunction, gastrointestinal diseases (e.g., gastritis, esophagitis, and peptic ulcer), adenoid hypertrophy, porphyria, and the use of anticoagulants.[18]

Melatonin is not recommended for patients who are using medications for narcolepsy, antihypertensives, or immunosuppressants due to potential drug interactions.[28] Hydroxyzine may cause side effects such as motor coordination impairment, confusion, dizziness, tachycardia, and gastrointestinal symptoms; its use is not recommended in individuals with tics, behavioral disorders, or anxiety disorders.[29] Additionally, in children with neurodevelopmental disorders, sedation procedures can be challenging due to factors such as the risk of paradoxical reactions to sedative drugs, sensory sensitivities, and communication barriers, often requiring additional interventions.[30] Accordingly, children with neurological disorders (e.g., autism, Down syndrome, cerebral palsy, and mental retardation), leukemia, autoimmune diseases, tic disorders, behavioral and anxiety disorders, and cardiac, respiratory, metabolic, and gastrointestinal system diseases were excluded from the study. Additionally, those with known hypersensitivity to the sedative drug, those who vomited after drug administration, those who woke up during the recording, those who were unable to achieve adequate sleep, and cases found to be inadequately prepared according to the preprocedural preparation training provided by the EEG nurse were also excluded. These comprehensive exclusion criteria were established to obtain a homogeneous sample group for evaluating the safe and effective use of sedative agents. Written informed consent was obtained from the parents of all children. The study protocol was approved by the Antalya Training and Research Hospital Clinical Research Ethics Committee (Date 02.03.2020, Decision no: 4/3). This randomized controlled clinical trial was registered at ClinicalTrials.gov (ID: NCT05492812). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Melatonin was administered orally at a dose of 3 mg in children up to 15 kg and at a dose of 6 mg after 15 kg.[31] Hydroxyzine was administered orally to children at a dose of 1–2 mg/kg.[32] Chloral hydrate was administered orally to children at a dose of 25–50 mg/kg.[18]

The children scheduled for EEG recording were assigned to the study groups according to the randomization scheme of the study. Due to the nature of the study, blinding could not be applied as parents and children were informed about the sedative drug to be used; however, the pediatric neurologists evaluating the EEG recordings were not provided with information about the sedative drugs during the assessment.

The researchers prepared Children's Information Form, which consisted of 17 questions, including the children's clinical information (age, weight, sex, drugs used, reason for EEG ordered, risk score, sedative substance and dose used, the duration of falling asleep, sleep duration, drug side effects, and EEG baseline and result).

Ramsay Sedation Score measurement tool was developed by Ramsay et al.[33] in 1974. The first three items of the six-item scale evaluate the patients' wakefulness levels, and the other three items evaluate the patients' sleep levels. Wakefulness levels were identified as follows: 1 = patient anxious and agitated, restless, or both; 2 = patient is cooperative, orientated, and tranquil; and 3 = patient responds to commands only. Sleep levels were dependent on the patient's response to a light glabellar tap or a loud auditory stimulus: 4 = a brisk response, 5 = a sluggish response, and 6 = no response.

Steward Recovery Score was developed by Steward[34] in 1975 to evaluate the recovery status of the patient after anesthesia. It consists of three items on a scale of 0 to 2: (1) consciousness (0 = not responding, 1 = responding to stimuli, 2 = awake), (2) airway (0 = airway requires intervention, 1 = maintaining good airway, 2 = coughing on command or crying), and (3) movement (0 = not moving, 1 = nonpurposeful movements, 2 = moving limbs purposefully). The total score obtained from the scale varies from 0 to 6.

The data collection process comprised two stages. In Stage I, the preliminary stage of the study, the recording appointments of the children who were requested to have the EEG were scheduled in the outpatient clinic. The EEG nurse provided the children and their parents with information about the procedure, along with a standard training booklet prepared by the researchers. The content of the training included information about the requirement of clean hair (e.g., no hair gel) and the duration of sleep deprivation specified in the literature as suitable for all age groups.[35]

The parents were informed about the following sleep deprivation periods: (1) children aged 15 to 18 months must be awake at least 1 h before the EEG; children between 19 and 35 months must be put to sleep 2 h later than normal sleep times and wake up at the normal waking time; (2) for

children aged 36 months and over, normal sleep time must be shortened up to 4 h.

In Stage II, the recording appointment was predetermined. The caregivers and the children who had received training in preliminary preparation were evaluated in terms of hours of sleep deprivation by the nurse who would perform the recording procedure. The individuals who did not properly complete their preparations were excluded from the study, and routine outpatient recording procedures were performed. In line with the training given, the children who were ready for the procedure and their caregivers were informed about the recording, and informed consent was obtained from the caregivers. The sedation procedure was prepared by the nurse in accordance with the children's developmental age (using the picture booklet), and sedative medication was administered to the children in the intervention group. After the sedative drug administration, the children and their caregivers were taken to a quiet and dark sleep room in the outpatient clinic to enable the children to fall asleep. In this process, the children were evaluated by the nurse using the Ramsay Sedation Score every 5 min.[33] The children with scores of 4 to 6 were taken to the EEG room for recording. While sedated, the children's blood pressure, oxygen saturation, and pulse were checked every 5 min. Electroencephalogram electrodes were placed in accordance with the international 10–20 system. On average, a 30-min EEG recording was made for each patient. The awakening process of the children whose EEG recordings were completed was evaluated with the Steward Recovery Score.[36] The individuals with a score of 6 were accepted as awake, and each one's procedure was completed. The process steps are summarized in Figure 1. The EEG recordings obtained within the scope of our study were interpreted by two pediatric neurologists. The interpretation of the recordings was performed according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events.[36]

Statistical analyses

The power analysis of the study was carried out using G*Power version 3.1.9.2 (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany).[37] Since there were four study groups, the F test was chosen as the test type, and fixed-effects, one-way analysis of variance was selected as the method of analysis. The effect size was calculated using the time it took for each group to fall asleep; the data were obtained from a pilot study.[38] The common standard deviation value was taken as 10 min, and the effect size was calculated as d = 0.521. The minimum sample size for the four groups was determined as 168, with a power value

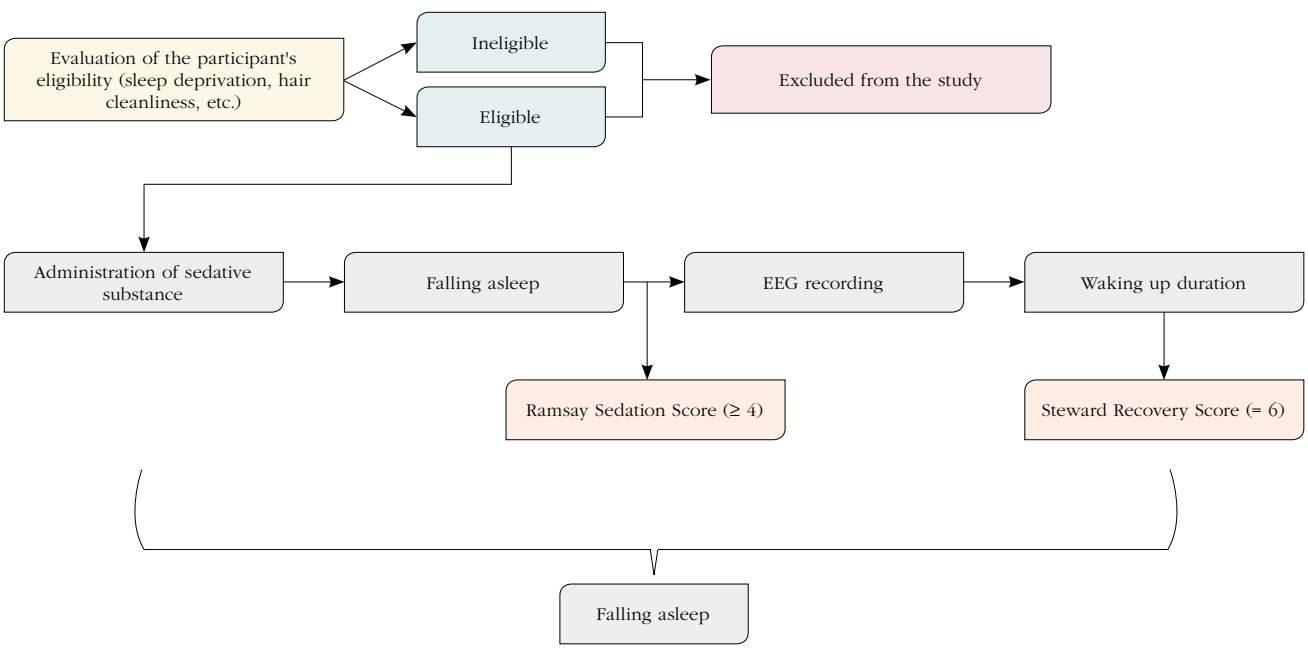

Figure 1. Procedure steps.
EEG, electroencephalogram.

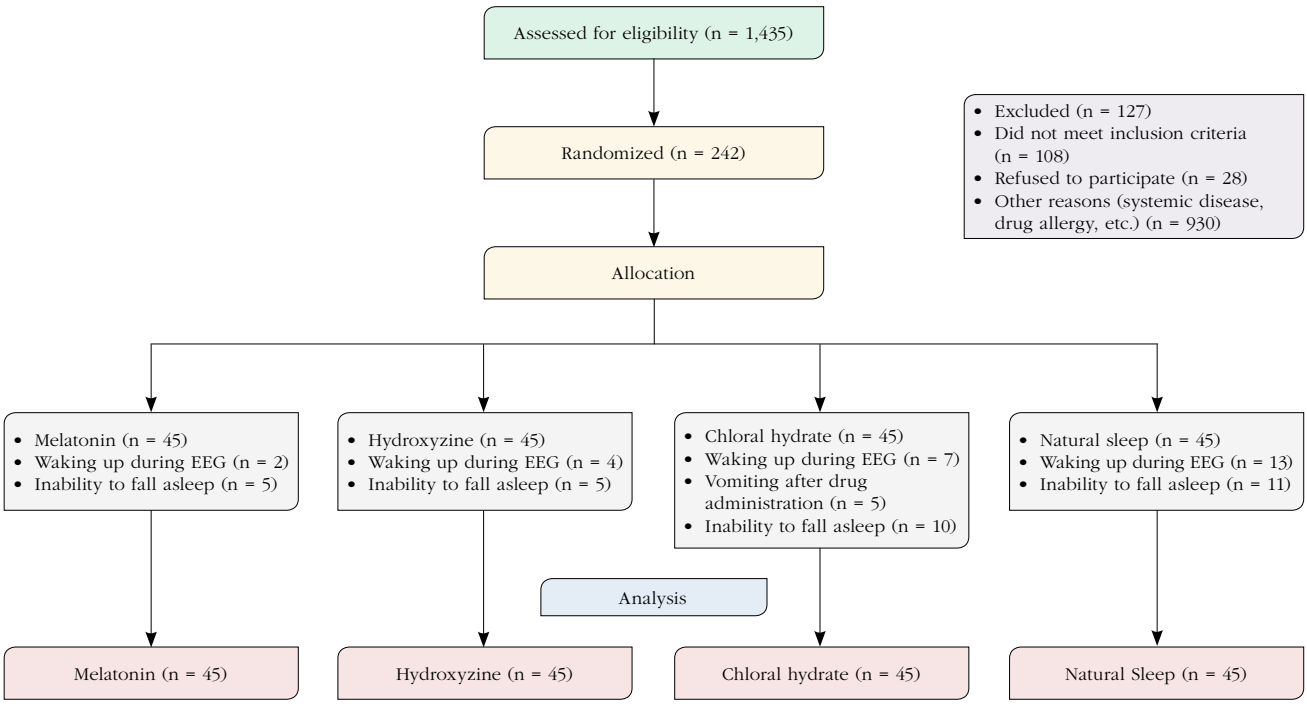

Figure 2. CONSORT flow chart.
EEG, electroencephalogram.

of 95% and an error rate of 5%. The number of patients, which was initially determined as 42 per group, was adjusted to 45 per group, taking into account the missing observation rate, and the study was completed with a total of 180 patients. The blocking randomization method was used to provide an equal number of samples for all four groups (chloral hydrate, hydroxyzine, melatonin, and natural sleep) in the study and to avoid bias (Figure 2).[38] The number of blocks was four, and each block size was determined as 45. The sequence was as follows: 1 = melatonin, 2 = hydroxyzine, 3 = chloral hydrate, and 4 = natural sleep. The sorting was done online (https://www.randomizer.org/). A four-group randomization table was created by entering the sample number on the specified website, and assignments to sample groups were made accordingly.

Statistical analyses were performed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive measurements were presented as frequency (percentage) for categorical variables and mean ± standard deviation and median (interquartile range) for numerical variables. The continuous numerical measurements' conformity to the normal distribution was tested using the Kolmogorov-Smirnov method; however, it was determined that they did not fit the normal distribution ($p < 0.05$). The Kruskal-Wallis test was used to find whether there were statistically significant differences between the distributions of four groups. The categories that were found significant as a result of pairwise comparisons are shown using the same exponential letters. The chi-square test with Monte Carlo exact simulation was applied to determine the relationships between the categorical measurements. Significantly different categories were indicated by symbols. A multinomial logistic regression model was established to determine which properties of the sedative substances were effective. A p-value < 0.05 was considered statistically significant.

RESULTS

Some of the children who were assigned to the melatonin, hydroxyzine, and chloral hydrate groups woke up during the recording after the drug was administered, others could not fall asleep even after the drug was administered, and some vomited after the drug was administered. These children were not included in the research groups (Figure 2). The median weight of the children was 15 kg. An EEG was ordered for 78.9% of the

patients for suspected epilepsy or due to prior epilepsy diagnosis. Antiepileptic drugs were used in patients diagnosed with epilepsy. Vomiting was observed as a sedative side effect in five patients in the chloral hydrate group. Oxygen saturation was over 90% in all children, and supplemental oxygen was never required. Vital signs remained stable in all patients during the recording. The median value of the time it took for the patients to fall asleep was 22 min.

The pediatric patients' demographic and clinical characteristics were compared according to the sedative substances used, and no significant difference was found between sex distribution and sedative substances (p = 0.053). Although the median age of the children who received hydroxyzine was higher than that of the other groups, there was no significant difference in the ages of the patients assigned to any of the four groups (p = 0.346). There was no significant difference between the sedative substance groups in the presence of epilepsy and antiepileptic medication. Although the rate of epileptic anomaly was lower (13.3%) in the children using melatonin, no significant difference was observed among the three substance groups (p = 0.519). The sedatives' adverse effects occurred only in the patients who were administered chloral hydrate (11.1%); however, there were no significant difference between the groups. The groups showed a significant difference in the duration of falling

TABLE 1
Demographic characteristics of the children according to sedative substance types

Sedative substance	Melatonin	Hydroxyzine	Chloral hydrate	Natural sleep	Total	p
Sex, n (%)						
Girl	13 (28.9)	17 (37.8)	13 (28.9)	24 (53.3)	67 (37.2)	0.053
Boy	32 (71.1)	28 (62.2)	32 (71.1)	21 (46.7)	113 (62.8)	
Antiepileptic drug use, n (%)						
Yes	10 (22.2)	6 (13.3)	8 (17.8)	14 (31.1)	38 (21.1)	0.198
No	35 (77.8)	39 (86.7)	37 (82.2)	31 (68.9)	142 (78.9)	
Epilepsy types, n (%)						
Focal	5 (13.2)	3 (7.9)	4 (10.5)	7 (18.4)	19 (50.0)	
Generalize	3 (7.9)	2 (5.3)	3 (7.9)	5 (13.2)	13 (24.2)	0.890
Mixed/syndromic	2 (5.3)	1 (2.6)	1 (2.6)	2 (5.3)	6 (15.8)	
Reason for EEG, n (%)						
Headache	10 (22.2)	11 (24.5)	10 (22.2)	9 (20.0)	40 (22.2)	
Syncope	3 (6.7)	8 (17.7)	4 (8.9)	5 (11.1)	20 (11.1)	
Visual aura	10 (22.2)	7 (15.6)	8 (17.8)	5 (11.1)	30 (16.7)	0.278
Suspect seizures	12 (26.7)	13 (28.9)	15 (33.3)	12 (26.7)	52 (28.9)	
Epilepsy	10 (22.2)	6 (13.3)	8 (17.8)	14 (31.1)	38 (21.1)	
Epileptic anomaly, n (%)						
Yes	6 (13.3)	11 (24.4)	10 (22.2)	11 (24.4)	38 (21.1)	0.519
No	39 (86.7)	34 (75.6)	35 (77.8)	34 (75.6)	142 (78.9)	
Sedative adverse effect, n (%)						
Yes	0	0	5 (11.1)	0	5 (2.8)	0.312
No	45 (100.0)	45 (100.0)	40 (88.9)	45 (100.0)	175 (97.2)	
Age (month), Mean ± SD, median; Q1-Q3	41.27 ± 25.16 32.0; 18.0–63.0	46.44 ± 23.91 43.0; 24.5–69.0	39.20 ± 26.84 30.0; 15.5–63.5	39.73 ± 25.59 34.0; 15.5–60.0	41.66 ± 25.34 36; 18–62	0.346
Weight (kg), Mean ± SD, median; Q1-Q3	16.11 ± 4.74 15.0; 12.5–20.0	17.61 ± 6.78 17.0; 12.0–20.5	15.40 ± 5.91 14.0; 10.5–19.0	15.77 ± 6.23 15.0; 10.0–18.5	16.22 ± 5.97 15; 12–20	0.262
Falling asleep duration (min), Mean ± SD, median; Q1-Q3	22.44 ± 8.75[a] 21.0; 15.0–27.5	24.77 ± 9.89 24.0; 16.5–31.0	20.60 ± 10.83[b] 18.0; 12.5–26.0	33.88 ± 16.94[a,b] 32.0; 18.0–47.5	25.42 ± 12.98 22.0; 15-32	<0.001*

SD, standard deviation; Q, quartiles; *, According to Kruskal-Wallis analysis results, it shows significance at 0.05 level; [a, b], according to K-W critical value pairwise comparisons same superscript letters denote the significant pairwise comparisons

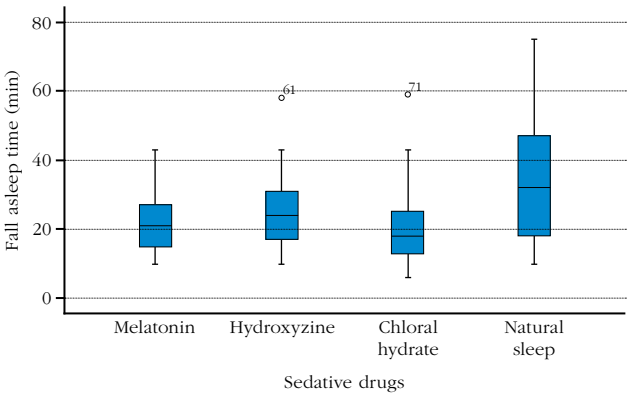

Figure 3. Falling asleep times according to sedative substance groups.

asleep ($p < 0.001$), with 32 min for the natural sleep group, 18 min for the group that used chloral hydrate, and 21 and 24 min for those using melatonin and hydroxyzine, respectively (Table 1; Figure 3).

The EEG findings and clinical results related to the sleep stage were compared among the sedative substances (Table 2). Vertex sharp waves (focal sharp transients typically best observed during nonrapid eye movement sleep, represented in the transition from Stage I to Stage II of sleep) was observed at high rates in patients. Rates were slightly higher in the melatonin and chloral hydrate groups compared to the hydroxyzine and natural sleep groups ($p = 0.326$). The presence of sleep spindles (observed in EEG in the sleep state) was frequent and similar between the groups ($p = 0.877$). The K-complex ratios (high amplitude [> 100 µV], wide [> 200 msec], diphasic transition, frontocentral location, and most midline markers associated with sleep spindles) were moderate, and the groups showed similar results ($p = 0.131$). An excessive fast activity (a characteristic electrophysiological pattern of low voltage [rapid EEG ictal activity] in focal epileptic seizures, commonly appearing at the seizure onset) was found at the highest rate (28.9%) in the chloral hydrate group; similar rates were noted in the melatonin and hydroxyzine groups, but the natural sleep group showed a significantly lower rate ($p = 0.042$). The groups had similar rates of Stage II sleep, but the rate of Stage III sleep was found to be higher in the hydroxyzine group,

TABLE 2
Sleep characteristics of the children according to sedative substance types

Sedative substance	Melatonin	Hydroxyzine	Chloral hydrate	Natural sleep	Total	*p*
Vertex sharp						
Yes	41 (91.1)	36 (80.0)	41 (91.1)	38 (84.4)	156 (86.7)	0.326
No	4 (8.99)	9 (20.0)	4 (8.9)	7 (15.6)	24 (13.3)	
Sleep spindles						
Yes	44 (97.8)	43 (95.6)	42 (93.3)	42 (93.3)	171 (95.0)	0.877
No	1 (2.2)	2 (4.4)	3 (6.7)	3 (6.7)	9 (5.0)	
K-complex						
Yes	29 (64.4)	34 (75.6)	32 (71.1)	24 (53.3)	119 (66.1)	0.131
No	16 (35.6)	11 (24.4)	13 (28.9)	21 (46.7)	61 (33.9)	
Excessive fast act						
Yes	11 (24.4)	12 (26.7)	12 (28.9)	3 (6.7)†	39 (21.7)	**0.042***
No	34 (75.6)	33 (73.3)	32 (71.1)	42 (93.3)‡	141 (78.3)	
Sleep stage						
Stage II	43 (95.6)	40 (88.9)	38 (84.4)	42 (93.3)	163 (90.6)	
Stage III	2 (4.4)	5 (11.1)	0	1 (2.2)	8 (4.4)	0.206
Stage II-III	0	0	7 (15.6)	2 (4.4)	9 (5.0)	
Frequency, Mean ± SD, median; Q1-Q3	4.48 ± 0.44[a] 4.5; 4.0–5.0	4.87 ± 0.52[a] 5.0; 4.5–5.0	4.54 ± 0.46 4.5; 4.0–5.0	4.62 ± 0.50 5.0; 4.3–5.0	4.62 ± 0.49 5; 4–5	**0.001****
Amplitude, Mean ± SD, median; Q1-Q3	34.92 ± 9.34 35.8; 27.8–40.3	40.89 ± 13.23 43.5; 29.9–49.3	37.25 ± 12.72 36.1; 28.7–44.6	41.50 ± 14.11 39.3; 30.7–49.8	38.64 ± 12.67 36.8; 29.4–46.1	0.053

SD, standard deviation; Q, quartiles; *, according to Chi-square analysis results, it shows significance at 0.05 level, †, ‡, according to z proportion test of pairwise comparison results, it shows the significantly different ratio from others; **, according to Kruskal-Wallis analysis results, it shows significance at 0.05 level, a, according to K-W critical value pairwise comparisons same superscript letters denote the significant pairwise comparisons.

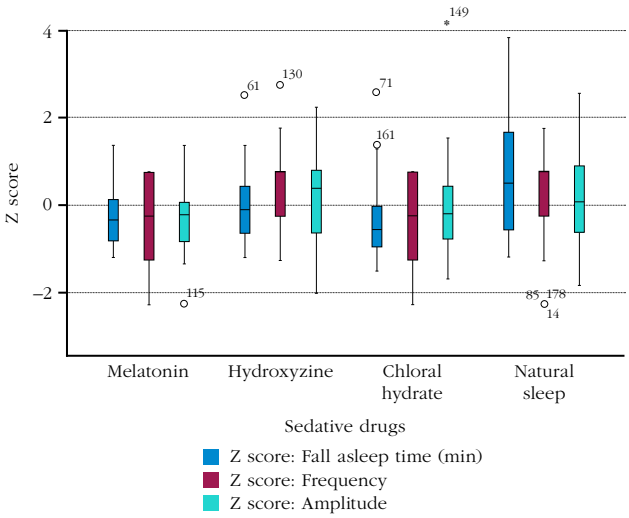

Figure 4. Sleep pattern measurements according to sedative substance groups.

with no statistically significant result. There were no patients in Stage II or III in the melatonin and hydroxyzine groups. The frequency values differed significantly among the groups; they were significantly higher in the hydroxyzine group (5, 4.5–5 Hz) than in the melatonin group (4.5, 4–5; p = 0.001). Although the amplitude value was higher in the hydroxyzine group, there was no significant difference among the groups (p = 0.053). The comparative values of measurements related to sleep patterns are presented in Figure 4.

A multicategory (multinomial) logistic regression model was established to determine the diagnostic factors affecting the melatonin, hydroxyzine, and chloral hydrate groups by taking the natural sleep group as a reference for the patient groups that were administered sedative substances. Sex, age, weight, vertex sharp waves, excessive fast activity, K-complexes, and the duration of falling asleep were added to the model as independent variables. The features that significantly contributed to the model were determined using the forward selection method. The model's goodness-of-fit values were found significant (-2LL = 442.09; chi-square = 29.93 [p < 0.001], Nagelkerke R^2 = 0.351). Melatonin was found to have significant effects on K-complex presence (odds ratio [OR] = 3.60), excessive fast activity presence (OR = 6.81), and the duration of falling asleep (OR = 1.07). The presence of vertex sharp waves (OR = 6.41), K-complexes (OR = 7.34), and excessive fast activity (OR = 7.93) and the duration of falling asleep (OR = 1.06) were determined as significant factors in the hydroxyzine group. Similar to the melatonin group, K-complex presence (OR = 5.13), excessive fast activity presence (OR = 9.08), and the duration of falling asleep (OR = 1.10) were found to have a significant effect in the chloral hydrate group. Demographic characteristics such as sex, age, and weight had no significant effects (Table 3).

TABLE 3
Factors affecting sedative substances

	Beta	p	OR	95% CI
Melatonin				
K-complex	1.281	0.030*	3.600	1.134–11.422
Excessive fast act	1.919	0.012*	6.813	1.515–30.643
Falling asleep duration	–0.074	<0.001*	1.076	1.034–1.120
Vertex sharp	0.193	0.806	1.213	1.515–30.643
Hydroxyzine				
K-complex	1.993	0.006*	7.341	1.754–30.728
Excessive fast act	2.071	0.007*	7.937	1.744–36.122
Falling asleep duration	–0.067	0.001*	1.069	1.029–1.111
Vertex sharp	–1.858	0.021*	6.411	1.317–31.216
Chloral hydrate				
K-complex	1.636	0.008*	5.136	1.522–17.333
Excessive fast act	2.206	0.004*	9.083	1.997–41.322
Falling asleep duration	–0.098	<0.001*	1.103	1.054–1.153
Vertex sharp	–0.117	0.885	0.889	0.181–4.370

OR, odds ratio; CI, confidence interval; * p<0.05; The natural sleep is the reference category.

DISCUSSION

The selection of an appropriate sedative agent is a critical aspect of pediatric neurodiagnostic procedures, particularly EEG recordings, where both patient comfort and the integrity of the EEG signal must be carefully preserved. Although many sedative drugs are used during pediatric examinations, the mechanism of action of the sedative drug used during EEG recording is crucial, as many sedative drugs affecting the central nervous system can suppress brain waves and prevent the detection of some anomalies by causing background activity changes.[2,11] This study contributes valuable insights into the efficacy and safety profiles of commonly used sedative agents during EEG procedures in pediatric patients. Understanding the specific EEG patterns associated with each sedative agent can aid clinicians in selecting the most appropriate sedative based on clinical priorities such as seizure detection, sleep onset latency, and patient safety. These findings build upon and extend previous research by offering comparative data from a sizable pediatric population, highlighting distinct differences in EEG outcomes among the sedative groups. The present study has the potential to serve as a foundation for further investigation into individualized sedation protocols in pediatric neurophysiology. The results indicate that the choice of sedative not only influences the ease of EEG acquisition but may also affect the diagnostic yield, particularly in the identification of epileptic discharges or sleep-related patterns such as vertex sharp waves, K-complexes, or excessive fast activity. The protocol used in this study could be translated into routine clinical practice, particularly in settings where natural sleep is not feasible.

There is evidence that some sedative drugs have negative impacts in terms of a long half-life, high sedation failure, and undesirable side effects (e.g., respiratory depression, hypoxia, bradycardia, and suppression of epileptiform activity in children).[39-42] The sedative drug administered to children should have a rapid onset, sufficient duration, minimal side effects, and be cost-effective.[2] However, there is evidence that more research is needed to determine the safest and most effective sedative drug for EEG recordings.[11-17]

When the study groups were compared in terms of required sedation for transition to sleep and provision of sedation during EEG measurement, it was determined that chloral hydrate was less successful than melatonin and hydroxyzine; however, it achieved adequate sedation in a shorter time (from the administration of the drug to EEG measurement). Melatonin was found to be more successful in providing sedation during EEG measurement compared to the other drugs, but it achieved adequate sedation later than chloral hydrate. The sedation failure of melatonin was at the same level as that of hydroxyzine and at a better level in terms of achieving adequate sedation compared to chloral hydrate and natural sleep (Figures 2, 3; Table 1). Previous studies[2,43-45] reported that chloral hydrate reached adequate sedation in a shorter time compared to a group of sedative drugs (oral dexmedetomidine, oral hydroxyzine hydrochloride, oral promethazine, oral clonidine, and rectal midazolam) and provided sufficient sedation for neurodiagnostic procedures compared to another group of sedative drugs (intravenous phenobarbital, intranasal midazolam, and intranasal dexmedetomidine). In studies that compared chloral hydrate and hydroxyzine, sedation failure was reported to be higher in the hydroxyzine group.[23,46] However, other studies noted that intranasal dexmedetomidine[47] and intranasal fentanyl[48] were more successful in sedation compared to oral chloral hydrate. A meta-analysis study[49] reported that triclofos, which is an active metabolite of chloral hydrate, was more successful in providing the necessary sedation during transition to sleep and in EEG measurement compared to melatonin. Another study[50] found that when melatonin was used in combination with sleep deprivation, it was effective in providing and sustaining sedation. These findings demonstrate both the merits and limitations of the studied sedative drugs. While chloral hydrate shows strength in rapid onset, its side effect profile, particularly nausea and vomiting observed in our study, limits its broader clinical applicability. Melatonin, although slower to act, appears more favorable in terms of safety and sustained sedation, supporting its growing role in pediatric EEG sedation protocols. As shown, studies report different results in terms of providing sedation and achieving the necessary sedation using the same drugs. It is believed that these differences result from both the heterogeneous nature of the studies and the physical conditions in the clinic (e.g., noise, light, and child's preparation for the procedure), as well as other factors, such as the drug administration methods, the sedative drug dosages administered, and whether sleep deprivation was applied before the procedure. Therefore, these factors should be considered when administering

sedative drugs to children. Our study supports the view that standardizing sedation procedures, including environmental factors and preprocedural preparation, is critical for achieving consistent results. This highlights a key challenge in this field: the need for uniform, evidence-based guidelines that optimize both clinical efficacy and diagnostic accuracy.

When the sedative drugs used in this study (chloral hydrate, melatonin, and hydroxyzine) were evaluated in terms of their side effect profiles and their effects on EEG, it was determined that there was no oxygen desaturation in any of the sedative drugs, side effects such as nausea and vomiting were observed only in the chloral hydrate group, and the four intervention types showed no differences in detecting epileptiform anomalies. When EEG properties were examined, it was found that sleep spindles had a high and similar presence in all groups and that K-complexes were at a moderate and similar level in all groups. Vertex sharp waves were observed more frequently in the melatonin and the chloral hydrate groups. Excessive fast activity had the highest presence in the chloral hydrate group, closely followed by the melatonin and the hydroxyzine groups; however, their presence was significantly lower in the natural sleep group. Although frequency values were significantly different among the groups, the frequency value of the hydroxyzine group was significantly higher than those of the other groups. While the amplitude value was higher in the hydroxyzine group, there were no significant differences among the groups (Tables 2, 3; Figure 4). Similar results were found in a previous study,[16] which reported no significant difference between chloral hydrate and hydroxyzine in determining epileptiform anomalies. Another study[51] noted that abnormal epileptiform discharges were observed more in children who were administered chloral hydrate for sedation compared to those who received oral midazolam. In a study that investigated the effect of melatonin and chloral hydrate on sleep EEG in children, melatonin was found to be reliable and at least as effective as chloral hydrate.[52] The same study reported results similar to those of the present study, and it was determined that drug-related side effects were noted in the children assigned to the chloral hydrate group, while such side effects were not observed in the melatonin group. An interesting finding of our study was the increased frequency of vertex sharp waves in the melatonin and chloral hydrate groups, which may reflect their deeper modulation of cortical activity. Conversely, the highest detection of excessive fast activity in the chloral hydrate group points to its stronger central nervous system depressant effect. These EEG pattern differences are significant because they can influence diagnostic interpretations and should, therefore, be taken into account when selecting sedatives for EEG. During EEG measurement in children, administering sedative drugs that do not affect EEG activity while providing adequate sedation is an important issue in terms of making an accurate diagnosis and starting the proper treatment. Thus, high-quality research is needed to determine the most effective sedative drugs to be used during EEG measurement in children.

This study had some limitations. Electroencephalogram recordings of the majority of children in the sample group due to suspicion of epilepsy could not provide definitive information about the effectiveness of the sedative drugs used in the study in making the diagnosis. In addition, since the number of patients with a high variety of symptoms in this group was observed and the number of patients was low, all cases were grouped as suspected epilepsy (e.g., headache and syncope). Furthermore, the results may not be generalizable to children with special diagnoses, such as severe mental retardation and autism. Additionally, this study excluded patients who could not fall asleep or those who experienced side effects, lacked long-term follow-up, and focused on only a few commonly used agents. Nevertheless, the strengths of the study, namely its prospective design, clinically relevant comparisons, and robust statistical analysis, enhance its translational potential. Future research should explore the mechanisms behind these observed EEG differences and investigate additional sedative options or combinations. Ultimately, the goal is to develop personalized sedation protocols that optimize diagnostic accuracy while ensuring safety and comfort in pediatric patients undergoing EEG.

In conclusion, health professionals working in the field of pediatrics (e.g., nurse, physician, and EEG technician) have important roles in the planning and implementation of neurodiagnostic procedures. This randomized controlled trial evaluated the efficacy and safety profiles of three sedative agents (chloral hydrate, hydroxyzine, and melatonin) used to induce sleep prior to EEG in children in comparison to natural sleep. The results demonstrated that all three agents were effective in facilitating sleep onset and providing

adequate sedation for EEG recording, although with varying onset times and side effect profiles. Chloral hydrate induced sleep more rapidly but was associated with a higher incidence of adverse effects, such as nausea and vomiting. Melatonin and hydroxyzine showed better tolerability and fewer side effects, with melatonin providing more stable EEG conditions. Importantly, none of the agents significantly interfered with the identification of epileptiform discharges, and all preserved key EEG characteristics such as sleep spindles and K-complexes. Given these findings, melatonin and hydroxyzine may offer safer alternatives to chloral hydrate for EEG preparation in pediatric patients. However, clinical settings, patient profiles, and logistical considerations should guide the choice of sedative agent. Further large-scale prospective studies are warranted to refine sedation strategies and optimize EEG quality in children.

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