Original Article

Melatonin and Intravenous Midazolam Administered Orally in Drug Induced Sleep Electroencephalography of Children: Randomized Clinical Trial of Efficacy

Razieh Fallah MD[1], Yaser Yadegari MD[1], Shekofah Behdad MD[2], Sedighah Akhavan Karbasi MD•[1]

Abstract

Background: Electroencephalography (EEG) is a useful diagnostic tool in the diagnosis of seizure and differentiating it from seizure-like attacks. Cooperation and immobility of the patient is crucial and in children who do not naturally sleep, pharmacological agents and procedural sedation should be used for sleep inducement. The purpose of this study was to compare efficacy and safety of melatonin and intravenous solution of midazolam administered orally in sedation induction for EEG of children.

Methods: In a parallel single-blinded randomized clinical trial, sixty 1 – 8 year old children who were referred to EEG Unit of Shahid Sadoughi Hospital, Yazd, Iran from September 2011 to March 2012 were evaluated. The Children were randomly assigned into two groups to receive orally 0.3 mg/kg melatonin or 0.75 mg/kg ampoule of midazolam.

The primary outcome was efficacy in adequate sedation (Ramsay sedation score of four) and recording of EEG. Secondary outcome was clinical side effects.

Results: Nineteen girls (31.7%) and 41 boys (68.3%) with the mean age of 2.8 ± 1.8 years were evaluated. Adequate sedation and recording of EEG was achieved in 36.7% of midazolam group and in 73.3% of melatonin group, (p = 0.004).

Transient agitation was seen in 6.6% of midazolam group. No significant difference was observed from the viewpoint of side effects frequency between the two drugs, (p = 0.15).

Conclusion: Melatonin is a safe and an effective drug in sedation induction for EEG in children.

Keywords: Children, electroencephalography, melatonin, oral Midazolam, sedation

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Introduction

A seizure is one of the most common problems in pediatric neurology which occurs in 4 – 10 percent of children in the first 16 years of their life. [1]

A detailed and reliable account of the event by an eyewitness is the most important part of the diagnostic evaluation, but it may not often be available. Electroencephalography (EEG) is recommended in the evaluation of a child with the first seizure presentation and it is a useful diagnostic tool in the diagnosis of seizure and differentiating it from seizure-like attacks.[1]

EEG needs the cooperation and immobility of the patient and in all children, despite the age, recording during natural sleep is preferred to drug- induced one. In almost no case, sedation is really necessary, but, in children who do not naturally sleep, pharmacological agents and procedural sedation should be used to induce it.[2]

Different sedation regimens may be used in children for sedation induction.[2,3]

Chloral hydrate is a sedative-hypnotic drug which has been used for sedation of children for electroencephalography from many years ago.[4,5] However, there are concerns about its long action duration, obstruction of airway and depression in respiration, desaturation of oxygen , sedative effects consistency and its potential for carcinogenicity.[6]

Melatonin is an indoleamine, which is mainly produced in the pineal gland. It is an efficient sedative, hypnotic, analgesic, anti-inflammatory and antioxidative.[7] Melatonin is a useful oral natural-sleep agent, the main role of this hormone is modulation of the circadian rhythm of sleep.[7,8]

Midazolam is a water-soluble benzodiazepine which can be used in different routes (oral, intravenous, intramuscular, rectal, sublingual, aerosolized buccal and intranasal) for sedation induction in children.[9–11] Oral midazolam is a non-parenteral route that does not cause pain of injection and it is used in dosages of 0.5 – 1 mg/kg in pediatric sedation induction but it may be associated with paradoxical reactions and dysphoria in children.[12]

Efficacy and safety of ampoule of midazolam that administered orally in dose of 0.75 mg/kg as a premedication was shown by other studies.[13,14]

The purpose of this study was to compare efficacy and safety of injectable midazolam given orally and melatonin in children sedation induction for sleep EEG in Yazd, Iran.

Authors' affiliations: [1]Department of Pediatrics, Children Growth Disorders Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [2]Department of Anesthesia and Intensive Care, Research Center of Pain, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

•Corresponding author and reprints: Sedighah Akhavan Karbasi MD, Department of Pediatrics, Growth Disorders of Children Research Center , Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Address: Sina Blvd, Shahid Ghandi Blvd, Yazd, I.R. of Iran . Tel: +983518224000, Fax: +983518224100, E-mail: sakarbasi@yahoo.com.

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Materials/patients and methods

We followed a randomized, single–blind study that was conducted on the referred children to the EEG unit of Shahid Sadoughi Hospital, Yazd, Iran from September 2011 to March 2012. Sample size was assessed to be 30 children in each group based on Z formula and a confidence interval of 95% with 80% power to detect a 20% difference in efficacy between the two drugs with type one error (alpha) of 0.05. Eligible participants were children aged 1 – 8 years, who were referred to EEG unit for recoding of EEG and didn't naturally sleep and immobilize. These children were in American Society of Anesthesiology (ASA) class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease: mild asthma, controlled diabetes mellitus).[15]

Exclusion criteria included the presence of gastritis or any other severe systemic diseases, severe systemic reaction, head injury and receiving a sedative hypnotic agent within the past 48 hours.

The trial used computer generated equal simple randomization by random numbers and allocation ratio was 1:1 for the two groups.

Randomization and blinding were done by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors and data analysts were all kept blinded to the allocation. However, patients and allocated EEG staff to the intervention group were aware of the allocated arm.

The drug was delivered by EEG staff, and primary and secondary outcomes were assessed by the resident of a researcher who was not informed of the drug group assignment.

The children were randomized to receive either single dose of 0.75 mg/kg intravenous solution of midazolam administered by the oral route (product of Aburaihan Pharmaceutical Co, Iran and ampoule of 5 mg in 1 milliliter) which was diluted in water as placebo (Group I) or 0.3 mg/kg of melatonin (product of Nature made Pharmaceutical Co, USA as a 3 mg tablet) dissolved in water as placebo (Group II).

In both groups, before entering to electroencephalography room, the drugs were administered orally,

The ramsay sedation scale was used for assessment of sedation level[16] and score of four was considered as adequately sedated. The primary outcomes were efficacy in adequate sedation and completing of EEG recording.

Secondary outcomes were clinical side effects, serious adverse events (hypotension, hypoxia and cyanosis, severe vomiting, intractable irritability and agitation, apnea, laryngospasm, and bradycardia), time from administration of the drug to adequate sedation, caregiver's satisfaction on a likert scale of 1 – 5 by asking from them (five for completely satisfied, four for satisfied, three for partially satisfied, two for partially unsatisfied and one for completely unsatisfied),[17] and total stay time in EEG unit.

Respiratory depression requiring assisted ventilation, oxygen saturation of less than 90%, or a 25% or greater decrease in presedation mean arterial blood pressure were considered as serious side effects.

Failure to achieve adequate sedation (patient awakened or moved, interfered with the recording of EEG, inadequate sedation and need to administer of another sedative drug) and procedure abortion due to serious adverse events, were considered as failure of sedation regimen.

The developmental status of the patient was assessed by a pediatric neurologist based on Denver II Developmental screening test.

The data were analyzed using SPSS: 15 statistical software. Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared by independent T-test. Kaplan–Meier survival analysis was used to calculate probability of adequate sedation during the observation period.

Differences were considered significant at P values of less than 0.05.

Informed consent was taken from patients' parents before the administration of the drugs and the study has been approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. This study is registered in Iranian clinical trials with registration number: IRCT 201107182639N5.

Results

The design and conduct of this trial was straightforward, and we did not have any losses to follow-up or exclusions.

Nineteen girls (31.7%) and 41 boys (68.3%) with mean age of 2.8 ± 1.8 years were evaluated.

Comparison of some characteristics of the children is shown in Table 1, which indicates that no statistically significant differences were seen from the viewpoints of mean of age and mean of weight of children, sex distribution, developmental status, age group and recorded EEG results in both groups.

Adequate sedation (Ramsay sedation score of four) and success in EEG recording was achieved in 11 children (36.7%) in oral midazolam (95% confidence interval: 19.45% to 53.95%) and in 22 children (73.3%) in melatonin (95% confidence interval: 57.47% to 89.13%) groups, respectively. Statistical analysis showed that melatonin was a more effective drug in the sedation induction (P-value = 0.004).

The probability of being adequately sedated vs. time after taking the drugs by Kaplan–Meier plots is shown in Figure 1 which indicates that the Ramsay sedation score of four was obtained in all children who achieved adequate sedation 40 minutes after taking the drugs.

Table 2 shows the comparison mean of some variables and indi-

Table 1. Comparison of some characteristics of children in both groups

Data		Melatonin	Oral Midazolam	P-Value
Age in year (mean ± SD)		2.76 ± 1.25	2.75 ± 1.35	0.9
Weight in kg (mean ± SD)		11.78 ± 6.13	11.45 ± 5.44	0.3
Sex	Female	11	8	0.4
	Male	19	22	
Developmental status	Normal	17	19	0.5
	Delay	13	11	
Age group	< 2 years	14	12	0.6
	≥ 2 years	16	18	
Abnormal epileptic discharges in recorded EEG	Yes	10	6	0.6
	No	12	5	

Table 2. Comparison of mean of some variables in the two groups

Data	Melatonin Mean ± SD	Oral Midazolam Mean ± SD	P-value
Acquired Ramsay sedation score	4.33 ± 1.15	3.13 ± 1.59	0.001
Time from drug administration to adequately sedated (in minutes)	24.1 ± 9.6	18.63 ± 10.51	0.1
Time after taking the drug to completing EEG recording (in minutes)	37.72 ± 10.43	34.09 ± 14.63	0.4
Caregiver's satisfaction scale	3.57 ±1.36	2.53 ± 1.38	0.005
Total stay time in EEG unit (in minutes)	54.32 ± 12.93	53.18 ± 17.5	0.8

Table 3. Comparison of success in EEG recording in both groups based on developmental status and age group

Data			Yes (N %)	No (N %)	P-value
Developmental Status	Normal	Melatonin	11 (65%)	6 (35%)	0.1
		Midazolam	7 (37%)	12 (63%)	
	Delay	Melatonin	11 (85%)	2 (15%)	0.01
		Midazolam	4(36%)	7 (67%)	
Age group	< 2 years	Melatonin	9 (64%)	5 (36%)	0.01
		Midazolam	2 (17%)	10 (83%)	
	≥ 2 years	Melatonin	13 (81%)	3 (19%)	0.06
		Midazolam	9 (50%)	9 (50%)	

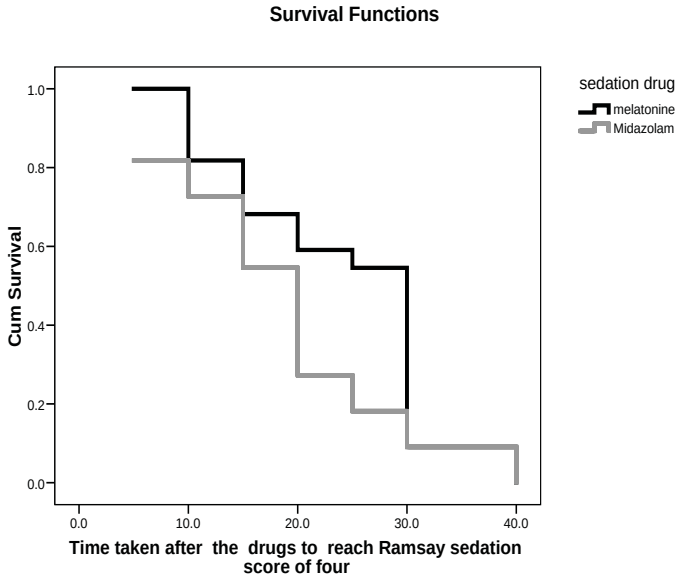

Figure 1. Probability of being adequately sedated vs time after taking of the drugs by Kaplan–Meier plots

cates that in melatonin group, higher Ramsay sedation score was obtained and child's parents were more satisfied.

Comparison of success in EEG recording in both groups based on the developmental status and age group is presented in Table 3, which indicates that its frequency in children with developmental delay is more in melatonin group than in midazolam group (85% vs. 36%) and the frequency with melatonin sedation is more than in midazolam (64% vs. 17%) and the results show that melatonin is a better sedative and more effective drug than midazolam in sedation induction in kids who have developmental delay and in less than two year old children.

No serious adverse events were seen in the two groups. Clinical side effects were not seen in melatonin group, but transient agitation occurred in 6.6% (N = 2) of oral midazolam group. No statistically significant differences were seen from the viewpoint of safety between the two drugs (*P*-value = 0.1).

Discussion

Various drugs have been used for procedural sedation in children. In the present study, efficacy and safety of oral midazolam and melatonin were compared. Melatonin does not change the quality of recording EEG in epileptic children or in those who suspected to have epilepsy.[18] Effect of the drugs on the quality of recorded EEG quality was not assessed in the present study. However, frequency of significant epileptic discharges in recorded EEG was not statistically different in melatonin and midazolam groups. Results of this study showed that melatonin was more

effective than oral midazolm in sedation induction for EEG recoding in children who did not naturally sleep. In four studies, efficacy of oral midazolam and melatonin as a premedicant in children, were compared.[19–22]

In Saudi Arabia study, efficacy of melatonin or midazolam in different dosage (0.1, 0.25 or 0.5 mg/kg) was equal in reducing of anxiety, but melatonin was associated with a lower incidence of postoperative excitement and a lower incidence of sleep disturbance in two weeks after the operation.[19]

In a study in Turkey, oral melatonin, dexmedetomidine, and midazolam were equally effective in decreasing of agitation in children after sevoflurane anesthesia.[20]

According to another study in Turkey, efficacy of melatonin, midazolam or placebo was equal in sedation of anxious children undergoing dental treatments.[21]

In Kain, et al. study, midazolam was more effective than melatonin in decreasing of pediatric anxiety, but children who took melatonin developed less emergence of delirium.[22]

In the present study, melatonin was effective in induction of sleep for EEG recoding which is in agreement with another Iranian study[23] and two other studies.[24,25]

In this study, the procedure was done successfully with melatonin sedation in 73.3% of children. However, in other studies success rate varied between 55% and 87%.[20,21,24–27] Possible explanations for these discrepancies are difference in age, drug dosage, race, sample size, type of procedure, drug administration time, the drug usage as a premedication before anesthesia or sleep deprivation before the drug use in some of researches.

In the present study, 73.3% of children slept 24.1 ± 9.6 minutes after taking melatonin and it is similar to 25 ± 7.9 minutes of a study in Paris.[27]

In this research, Kaplan–Meier plots showed that adequate sedation (Ramsay sedation score of four) in all children who were sedated with oral midazolam or melatonin, appeared up to 40 minutes after taking the drugs. It indicates if the child does not sleep after 40 minutes of administration of oral midazolam or melatonin, these sedative drugs would not be effective and other sedative regimens should be used.

According to Wassmer, et al. the sleep onset effect of oral melatonin appears 30 – 35 minutes after it has been taken[24] and it is in compliance with result of the present study therefore, it is conclusive that administration of melatonin in 30 minutes before the procedure may be more effective.

In this study , successful EEG recording was obtained in 45.8% (11 of 24) of children with developmental delay by administration of melatonin which was more effective in sleep induction of children with developmental delay and it is in agreement with Eisermann, et al. study which showed that in children with harsh behavior problems, melatonin was an acceptable effective drug in sleep induction for EEG recording.[27]

In the present study, both drugs were safe and no serious clinical adverse event was seen in the two groups. Safety of melatonin has also been reported in other researches.[7,8,19,20,24,27]

In this study, EEG was recorded successfully in 36.7% of children whom were sedated by 0.75 mg/kg oral midazolam. In other studies, success rate with oral midazolam sedation varied between 54 % and 95.9%.[28–32] The lowest efficacy of oral midazolam in sedation induction of children was seen in present study. However, effectiveness of oral midazolam in a dose of 1 mg/kg in conscious sedation of Iranian children was reported in two other studies.[31,32] But, ineffectiveness of oral midazolam in sedation of children was reported in other studies.[33,34]

Possible explanations for these discrepancies are differences in age, drug dosage, and race, usage as a premedication before anesthesia and child temperament factors. Finley, et al. suggested that there might be a contraindication between high levels of impulsivity and midazolam premedication in children.[35]

Onset time of oral midazolam sedation can be reduced by using a mixture of intravenous midazolam and antacid which is given orally.[36]

Therefore, further boluses of oral midazolam, its maximum dose, its combination with other sedative drugs, use of it as a premedication before anesthesia or mixed with antacid or orange juice may be more effective in sedation induction of Iranian children.

In the present study, adequate sedation and sleep was achieved 18.6 ± 10.5 minutes after taken midazolam orally. This result is in agreement with Cox, et al. conclusion which says that administration of oral midazolam 20 – 30 minutes preoperatively, may be effective in reducing of separation anxiety in children.[37]

In present study, transient paradoxical agitation as the only side-effect of oral midazolam occurred in 6.6 % of children. In a study in London, diplopia and agitation were the most side effects of oral midazolam.[38] The safety of midazolam sedation is in agreement with other studies.[29,31,32,37,39]

Limitations of this study were its small sample size and short duration of follow up. Therefore, it is suggested that further studies will need to be undertaken with larger sample sizes, longer follow up periods and different dosages of the drugs.

In conclusion, results of the present study showed that melatonin is a safe and an effective drug in sedation induction for EEG in children. However, the drug should be administered thirty minutes before the procedure.

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