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# The Effect of Melatonin on Pediatric Drug-Resistant Epilepsy; a Randomized Double Blind Clinical Trial

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## *Abstract*

### *Background*

About 15 to 40% of children with seizures are refractory to standard anti-epileptic drugs and for such patients, other treatments such as surgery and the ketogenic diet can reduce seizure frequency. Melatonin is a natural pineal gland hormone. The use of melatonin for controlling pediatric seizures is still controversial. This study aimed to evaluate the effect of melatonin on seizures, parent's satisfaction, sleep, and behavior in children with drug-resistant epilepsy.

***Materials and Methods:*** In a pilot crossover study, children with drug-resistant epilepsy, who referred to the epileptic clinic of Ghaem Hospital, were randomly assigned to receive treatment with melatonin or a placebo for 4 weeks followed by a one-day washout period. Then patients who started with melatonin were switched to the placebo. Melatonin was administered 30 minutes before bedtime at a dose of 10 mg /m2 in 3mg tablets.

### *Results*

Twenty patients, of which 11 (55%) were male, were enrolled into the study. The range and mean age of patients were 2 to 13 years and 7.28 ± 3.46 years, respectively. The mean number of diurnal seizures in the study group during placebo treatment was 11.05 and during melatonin treatment was 6.25, which was statistically significant (P=0.021). However, the reduction of the mean duration of diurnal seizures in the study groups was not statistically significant (P=0.386). There was no correlation between decreasing in number or duration of seizures with melatonin plasma levels. Drowsiness was the only side effect of melatonin, which occurred in three patients.

### *Conclusion*

Melatonin has probable beneficial effects on some epileptic patients with unclear mechanisms. Physicians can use it in selected epileptic children to improve seizures.

***Key Words:*** Children, Intractable seizure, Melatonin.

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## 1- INTRODUCTION

About 15 to 40% of children with seizures are refractory to standard anti-epileptic drugs (2-5). These patients have an increased mortality rate, estimated at 1.37 per 100 person-years (6). However, patients who become seizure free have no increased mortality rate in comparison to the normal population (7). Before marking a seizure as intractable epilepsy, one must rule out metabolic disorders such as pyridoxine deficiency or biotin disorders (8, 9). Alternative treatments for these patients such as surgery, vagal nerve stimulation, the ketogenic diet, intravenous immune globulin and herbal medicine can reduce seizure frequency (10-12).

Almost all of the melatonin formed in mammals is synthesized within the pineal gland from the essential amino acid tryptophan (13, 14). Based on this, the following studies have shown that suppression of melatonin after pinealectomy surgery could increase brain damage by kainic acid-induced seizures in rats, and so a neuroprotective role of melatonin was suggested (15). Studies have shown that the melatonin level is reduced at the interictal period in patients with refractory epilepsy or febrile seizures (16-18), and there is a lowered level of melatonin in these children in comparison with those without seizures. The first clinical use of melatonin for seizures was motivated by Anton Tay in 1974, who found that melatonin reduces the amplitude of the electrical electroencephalographic (EEG) (19). Coppola et al. investigated melatonin in wake-up disorders in children and found that melatonin can improve wake-sleep disorders such as time to fall asleep (20). Thus, the effect of melatonin treatment in seizures is still controversial and the studies have different models with different melatonin doses and routes of administration (21). In addition, exogenous melatonin has been investigated as a treatment for a number of medical and surgical diseases and only mild adverse effects, such as dizziness, headache, nausea, and sleepiness have been reported. No studies have indicated that exogenous melatonin could induce any serious adverse effects (22). This is the first of such a study done on Iranian drug-resistant epileptic children to evaluate the effect of melatonin on seizures, parental satisfaction, sleep, and behavior in children.

## 2- MATERIALS AND METHODS

### 2-1. Study Design

Due to difficulty in matching between the study groups because of vast distribution and possibility of confounding variables and the small sample size, we have designed a cross-over double blind placebo controlled pilot study for our intervention. Thus, each patient received both placebo and melatonin with a washout period between them and served as his or her own control. All participating patients or their legal guardians reviewed the study protocol and signed informed consent forms. The Research and Legal Committee of the Medical Center of the Mashhad University of Medical Sciences, Iran approved the study protocol.

### 2-2. Patient selection

Patients were selected from the tertiary referral center of the Children's Epilepsy Clinic of Ghaem Hospital of the Mashhad University of Medical Sciences. Inclusion criteria were: pediatric age range between 1 to 15 years, failure of at least two different antiepileptic drugs to control seizures [intractable epilepsy according to definition of the International League against Epilepsy (23)], not changing the drugs for at least one month prior to the study, and four seizures or more within the four weeks prior to the initiation of the study.

Exclusion criteria were: seizures with treatable etiology, history of neurodegenerative disorders syndromes, cardiovascular anomalies, liver and kidney dysfunction, blindness, history of pseudo seizures, seizures with very rapid or large numbers, and variety of seizures uncountable by parents, history of status or severe progressive seizure attacks and incompliance (irregular use of prescribed tablets, unreliable parents for recording events onto related forms). We classified the seizure into three types: partial, generalized and myoclonic according to the International League against Epilepsy Classification (24). We selected 32 patients to be candidates for our study; however, 12 patients could not complete their intervention, so our final samples were 20 patients. Exclusion reasons were: in three patients (two with the placebo regimen and one with melatonin) status epilepticus occurred, three patients on the melatonin regimen experienced drowsiness, and finally incompliance was observed in six other patients.

## 2-3. Intervention

Patients were randomly assigned to receive treatment with melatonin or the placebo for four weeks (first period of intervention). Randomization was undertaken by the pharmacist and the study physicians and patients were blind to the assignments. After a one-day washout period, patients who started initially with melatonin were switched to the placebo for an additional four weeks and in reverse order for the placebo group (second period of intervention). Thus, each patient served as his or her own control. Melatonin was administered at a dose of 10 mg/m2 in 3 mg tablets manufactured by Nature Made Company (the United States of America). The placebo tablets were the same shape, color, and taste as the melatonin tablets. Patients took the tablets daily and 30 minutes before bedtime in addition to their regular antiepileptic drugs.

## 2-4. Outcome

During the assessment of each period, the patients were visited weekly, the parents were asked to complete four weekly diaries specifically designed as follows: (1) seizures table, documenting the frequency of seizures, and duration of every seizure that occurred; except in myoclonic seizures. (2) Parents' sleep satisfaction and behavior table with parameters is as follows: daytime sleepiness, difficulty in falling asleep and waking up, agitation and concentration levels, parents' drug satisfaction, and any side effects. We measured plasma levels of melatonin and antiepileptic drugs before and after melatonin administration, and sampling was taken

one hour before using antiepileptic drugs (usually at 7 AM). The melatonin plasma levels were measured using the Melatonin ELISA (RE54021) kit.

### 2-5. Statistical analysis

Statistical data were analyzed by the Wilcoxon test using SPSS 16 software. $P < 0.05$ was considered statistically significant and power: 75%. For qualitative response assessment, more than 50% reduction in seizure number and duration was set as responding to treatment.

## 3- RESULTS

### 3-1. Patients' characteristics

In this randomized, double blind, placebo controlled, pilot study, the investigators examined the effect of melatonin on seizures, sleep, and behavior satisfaction in 20 patients; 11 (55%) patients were male. The range and mean (standard deviation SD]) age of patients were 2 to 13 years and 7.28 ± 3.46 years, respectively. Our groups were statistically equal in demographic parameters (**Table.1**)

### 3-2. Response to intervention

The mean number of seizures in the total melatonin intervention group decreased from 12.5 ± 10.67 to 6.25 ± 7.68 (50% reduction). In the total placebo intervention group the mean number of seizures decreased from 12.5 ± 10.67 to 11.05 ± 11.09 (11% reduction). The mean duration of seizures, except for the myoclonic form, in the melatonin intervention group decreased from 41.00 ± 36.5 to 29.90 ± 39.9 (27% reduction). The mean duration of seizures, except for the myoclonic form, in the placebo intervention group decreased from 41.00 ± 36.5 to 35.60 ± 39.7 (13% reduction). The mean number of seizures at the end of the placebo treatment was 11.05±11.09 and for melatonin treatment was 6.25±7.68. This difference was statistically significant (P = 0.02) (**Figure.1**).

The mean duration of seizures, except for the myoclonic form, in the end of the placebo treatment was 35.60 ± 39.7 and for melatonin treatment were 29.90 ± 39.9. This difference was not statistically significant (P= 0.14) (**Figure.2**). If we agree seizure number reduction beyond 50% as responsive to treatment, we have 55% respond with melatonin trail versus 36% in placebo trail that difference was statistically significant (P=0.002). Results showed that two (10%) children with intractable seizures achieved complete seizure freedom with the melatonin trial. Parent satisfaction with melatonin versus the placebo was acceptable (P=0.06), although mood and sleep effects were not significant. With the exception of three patients who suffered from drowsiness, we had no obvious melatonin side effects.

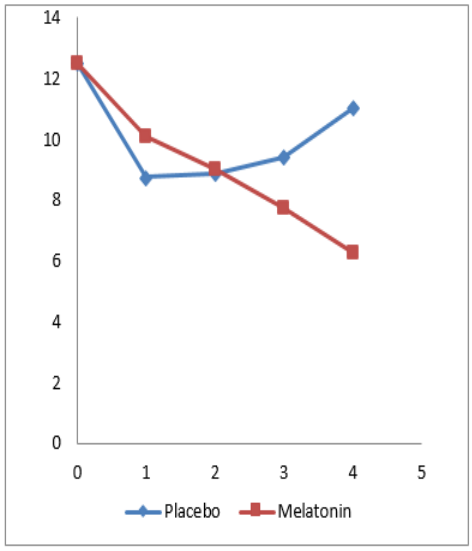
Mean plasma melatonin level after the intake of melatonin increased, but was not significant (P=0.6). There was not any correlation between melatonin plasma levels and decreasing in seizure number and duration after melatonin administration (P = 0.64, P= 0.22, respectively). Only the mean carbamazepine level increased significantly (P=0.05) after melatonin treatment. There was no significant difference between plasma levels of other anti-epileptic drugs, before and after the treatment (P>0.05). The weekly trend of seizure mean numbers

in melatonin and placebo groups and their P- value each week for two periods are shown without significant difference (**Figure.3**). With repeated measures, there was a significant difference in the trend of changes in seizure number decline in the two melatonin intervention groups in the first and second period respectively (P=0.03 and P=0.02). With repeated measurements, there was a significant difference in the trend of changes in total seizure number decline in the melatonin intervention group (P=0.002), but it was not significant in the placebo group (P=0.07) (**Figure.1**). Also, there was no significant relation between response to melatonin administration and gender, age, age of first seizure, duration of going to sleep, mood, developmental disturbances, and seizure forms (P>0.05). All children with normal development responded to melatonin.

**Table-1**: Distribution difference of these qualities' parameters was not statistically significant

| Descriptive statistics of some clinical features of patients | | | | | |
|---|---|---|---|---|---|
| Variables | | First Placebo | First Melatonin | Total | P-value |
| Gender | Male | 6 | 5 | 11 | 1.00 |
| | Female | 4 | 5 | 9 | |
| Delivery type | NVD | 7 | 9 | 16 | 0.582 |
| | C.S | 3 | 1 | 4 | |
| Delivery risk factor | Yes | 4 | 2 | 6 | 0.628 |
| | No | 6 | 8 | 14 | |
| Family history of seizure | Yea | 1 | 4 | 5 | 0.303 |
| | No | 9 | 6 | 15 | |
| Relativity of parents | Yes | 7 | 5 | 12 | 0.650 |
| | No | 3 | 5 | 8 | |
| Seizure forms | Generalized | 1 | 4 | 5 | 0.285 |
| | Focal | 2 | 3 | 5 | |
| | Myoclonic | 4 | 6 | 10 | |
| Age of First Seizure | <1 year | 5 | 8 | 13 | 0.424 |
| | 1-2 year | 1 | 0 | 1 | |
| | 2-3 year | 2 | 0 | 2 | |
| | 3-4 year | 1 | 1 | 2 | |
| | 4-5 year | 1 | 0 | 1 | |
| | <5 year | 0 | 1 | 1 | |
| Developmental defect | Yes | 7 | 9 | 16 | 0.58 |
| | No | 1 | 3 | 4 | |

NVD: Natural vaginal delivery; CS: caesarean section.

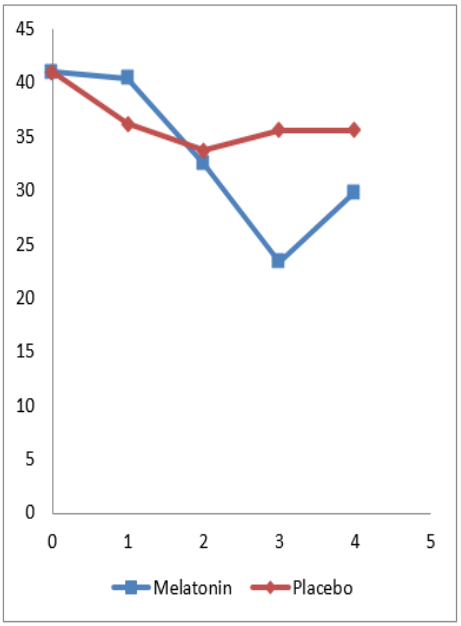



| Weeks | Mean |
|---|---|
| Base seizure. Daily Number | 12.50 |
| Melatonin.W1 | 10.10 |
| Mw2 | 9.00 |
| Mw3 | 7.75 |
| M.w.4 | 6.25 |
| Placebo.w1 | 8.75 |
| P.w2 | 8.85 |
| P.w3 | 9.40 |
| P.w4 | 11.05 |

(50%Reduction)

(11%Reduction)

**Fig.1:** Trend of changes in seizures number decline in melatonin and placebo intervention groups.

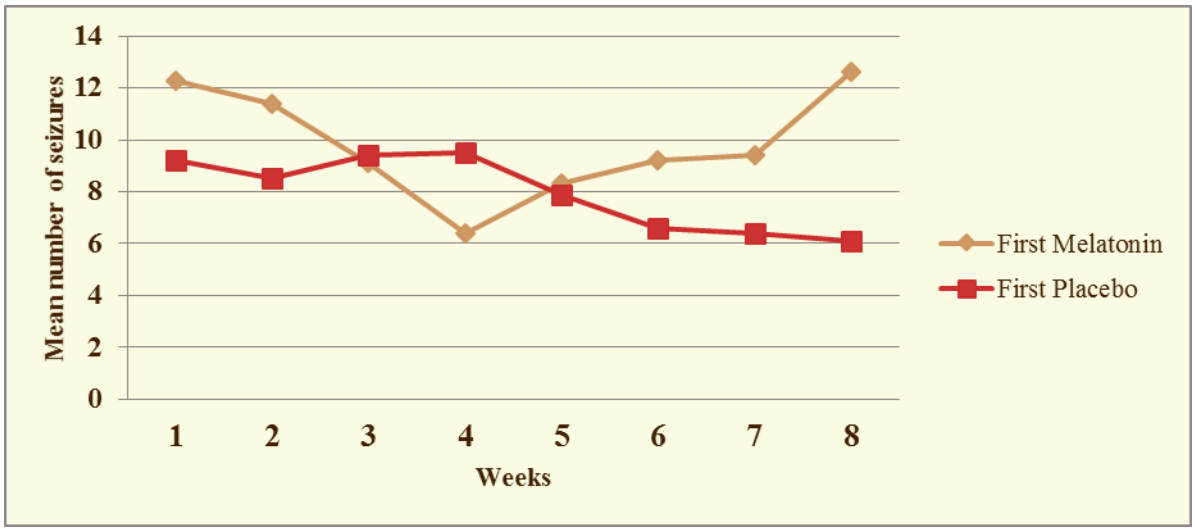



| Weeks | Mean |
|---|---|
| Seizure. Duration(s) | 41.00 |
| Melatonin.W1 | 40.40 |
| M.W2 | 32.50 |
| M.W3 | 23.30 |
| M.W4 | 29.90 |
| Placebo.W1 | 36.20 |
| P.W2 | 33.70 |
| P.W3 | 35.60 |
| P.W4 | 35.60 |

(27%Reduction)

(13% Reduction)

**Fig.2**: Trend of changes in seizures duration decline in melatonin and placebo intervention groups.




| Time | 1st period | Mean seizure number | P-value | Time | 2nd period | Mean seizure number | P-value |
|---|---|---|---|---|---|---|---|
| Week.1 | M | 12.30 | 0.627 | W5 | P | 8.30 | 0.980 |
| | P | 9.20 | | | M | 7.90 | |
| Week.2 | M | 11.40 | 0.786 | W6 | P | 9.20 | 0.630 |
| | P | 8.50 | | | M | 6.60 | |
| Week.3 | M | 9.10 | 0.60 | W7 | P | 9.40 | 0. 571 |
| | P | 9.40 | | | M | 6.40 | |
| Week.4 | M | 6.40 | 0.255 | W8 | P | 12.60 | 0.219 |
| | P | 9.50 | | | M | 6.10 | |

**Fig.3**: Trend of mean seizure frequencies of each week in melatonin and placebo groups.

## 4- DISCUSSION

In this double blind study, the mean number of seizures and also treatment response (more than 50% reduction in seizure number) between the melatonin and placebo groups was statistically significant. This means that melatonin maybe has effect on the number of seizures. A study by Saracz et al. has reported on two children with epilepsy who were prescribed melatonin as add-on therapy. The number of convulsions reduced clinically and the EEG record showed suppression of seizure activity in both children (25). Molina-Carballo et al. presented an infant with intractable epilepsy treated with high dose melatonin and observed a good response after one month (26). Goldberg-Stern et al. published a study similar to ours with 10 samples, but without checking melatonin and other antiepileptic levels. Seizure numbers decreased significantly with melatonin (27). In our study, the four children with normal development (100%) responded to melatonin; whereas, only

seven (43.8%) of the 16 patients with neurodevelopmental delay were melatonin responders. Therefore, we suggest that melatonin may have anticonvulsant effect in children with refractory seizures. However, it was limited by a small sample size and by a short period of follow-up, which may increase the possibility of chance findings. Another problem in our study relates to the short washout period, so after melatonin treatment, in spite of its short half-life of about an hour, circadian rhythms probably do not reverse completely to the pretreatment level. Therefore, melatonin may influence the seizure frequency in the placebo treatment with a slow reverse of seizure numbers after the 4-week placebo intervention (**Figure.1**).

## 5. CONCLUSION

We conclude that melatonin has probable beneficial effects on some seizure patients. Because of the low side effects and safety of melatonin, the treatment can be prescribed in short trials and discontinued in nonresponsive patients. However, further prospective double-blind studies are needed in larger cohorts to determine whether melatonin has an independent or nonspecific (via its beneficial sleep mechanism) effect on seizures in patients with intractable epilepsy.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENTS

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