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Original Article

Comparison Between Efficacy of Melatonin and Diazepam for Prevention of Recurrent Simple Febrile Seizures: A Randomized Clinical Trial

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ABSTRACT

Objectives: We evaluated the efficacy and safety of oral melatonin compared with oral diazepam for prevention of recurrent simple febrile seizures.
Methods: This prospective randomized clinical trial included 60 children aged six to 50 months with recurrent simple febrile seizures who attended the pediatric neurology clinic in Tanta University Hospital. Children were randomly allocated into two groups: the first group (30 children) received oral melatonin 0.3 mg/kg/8 hours, whereas the other group (30 children) received oral diazepam 1 mg/kg/day divided into three doses. Both melatonin and diazepam were given only during the febrile illness, started at the onset of the fever for 48 to 72 hours. Patients were followed up for six months. The primary outcome was recurrence of febrile seizures and the secondary outcome was occurrence of adverse effect related to melatonin or diazepam.
Results: The recurrence rate of febrile seizures was 17% (5/30) in the melatonin group and 37% (11/30) in the diazepam group. There was no significant difference between the two groups ($P = 0.08$) (95% confidence interval −0.025 to 0.42). Both melatonin and diazepam have significantly reduced recurrence of febrile seizures ($P < 0.001$). Adverse effects were reported in 13.3% and 23.3% of the children taking melatonin and diazepam, respectively. No serious side effects were reported with melatonin use. Sedation and dizziness were the main side effects reported in children receiving oral diazepam.
Conclusions: Our data suggest that melatonin, administered at the onset of a febrile illness, may effectively reduce the likelihood of recurrent simple febrile seizures. No serious side effects were encountered.

Introduction

Febrile seizures are the most prevalent form of seizures in infants and toddlers, occurring in around 4% of children aged less than five years. Febrile seizures are defined as convulsions associated with a temperature of 38°C or more, in the absence of central nervous system infection or other etiologies for seizures, which occur in children beyond age one month and up to five years who had no previous history of afebrile seizures.[1,2]

Although febrile seizures have a good prognosis, recurrence of seizures can occur in around 35% of affected children. Intermittent diazepam or clobazam during the febrile illnesses and chronic antiepileptic drug (AED) treatment with valproic acid or phenobarbital are considered effective for prevention of recurrence of febrile seizures.[3–7] However, the adverse effects of long-term use of AEDs outweigh the benefit of prevention of febrile seizures and the side effects of intermittent diazepam or clobazam can be intolerable for some children.[7,8]

There is a need for better tolerated prophylactic treatment for prevention of febrile seizure recurrence in children with recurrent febrile seizures. Melatonin is commonly used for treatment of insomnia, but an anticonvulsant action of melatonin was reported in both animal and human studies. Melatonin exerts anticonvulsant effects in experimental seizure models of hyperthermia as well.[9–11]

However, the anticonvulsant effects of melatonin in children with febrile seizures have not been previously evaluated. In this

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study, we tested the hypothesis that melatonin would prevent recurrence of febrile seizures because of its anticonvulsant effect. We evaluated the efficacy and tolerability of intermittent oral melatonin versus oral diazepam for prophylaxis of febrile seizures in children with recurrent simple febrile seizures.

Methods

Participants

We enrolled 60 children with simple febrile seizures recruited from the Pediatric Neurology Outpatient Clinic of Tanta University Hospital between April 2017 and August 2018. The study was approved by ethics committee of Faculty of Medicine, Tanta University, and a written informed consent was provided by the parents of all children.

Eligibility criteria

Inclusion criteria: children aged six to 60 months, who had recurrent simple febrile seizures. Simple febrile seizures are defined as generalized tonic-clonic seizures lasting less than 15 minutes and without recurrence during the same febrile illness in a neurologically normal child.[2] Children diagnosed with a simple febrile seizure who were followed up in the pediatric neurology clinic were included in the study if they developed recurrence of seizures during the febrile illnesses. The number of febrile seizures the children experienced before enrollment in the study was recorded in their medical records.

Exclusion criteria: complex febrile seizures (prolonged, focal, or recurrent in the same febrile illness),[2] previous afebrile seizures, developmental delay or abnormal neurological examination, positive family history of epilepsy, epileptiform activity in electroencephalograph (EEG), and use of AEDs.

At the time of enrollment in the study, all children were subjected to a detailed clinical evaluation, complete physical and neurological examination including assessment of development and EEG. EEG was recorded in the EEG laboratory in Pediatric Neurology Unit, Tanta University Hospital. Recordings were reviewed and reported by A.H.D and A.K.A.

Trial design

Parallel group randomized clinical trial comparing two drugs: melatonin and diazepam. The study was registered in clinicaltrials.gov with registration number NCT03631901.

Randomization and blinding

Children who met the eligibility criteria were randomized to either of the study groups by a computer-generated random sequence in 1:1 ratio. Concealment of the random allocation sequence was performed by sequentially numbered sealed opaque envelopes. After meeting the inclusion criteria and signing the written consent, the sealed opaque envelope was opened and the patient was allocated into the respective group.

One group received intermittent oral melatonin 1 mg/kg/day divided every eight hours. The other group received intermittent oral diazepam 0.3 mg/kg/8 hours. Both drugs were given only during the febrile illnesses, started at the beginning of fever and discontinued within 48 to 72 hours.

The treating physicians, the outcome assessors, parents, and those who performed the statistical analysis were not aware of the allocation sequence. The pharmacist was aware of the prophylactic treatment given during febrile illnesses, and he was responsible for calculating the dose and providing melatonin and diazepam. A suspension of diazepam in a concentration of 2 mg/5 mL and a suspension of melatonin in a concentration of 1 mg/1 mL were prepared by the pharmacist and used in the study.

Parents were instructed to measure their children's body temperature at the beginning of any illness and to start giving prophylactic treatment if temperature was $\geq$37.5°C. They were also instructed to give paracetamol in a dose of 15 mg/kg every six hours to control the fever.

Outcome measures

The primary outcome was recurrence of seizures during febrile illness and the secondary outcome was occurrence of any side effect during treatment with melatonin or diazepam in the studied children. Parents were asked to use a diary to record the occurrence of febrile illnesses and seizures, in addition to the duration of seizures and any side effects during intake of melatonin or diazepam. The treating physicians and the outcome assessors recorded the follow-up data in a worksheet for each child.

Patients were prospectively followed up for six months for recurrence of febrile seizures and occurrence of any side effects. Follow-up was accomplished through monthly telephone contact and every other month clinic visits to get the feedback data, to assess compliance, and to provide study drugs. Moreover, all parents were asked to return the empty used package of drugs during the follow-up visits to ascertain their compliance to treatment.

Sample size

Sample size calculation was performed before patient recruitment. A total sample size of 52 patients was needed to detect a difference of 40% in the frequency of recurrence of febrile seizures and to achieve a power of 80% with type I error probability of 5%.

Statistical analysis

Statistical presentation and analysis of the data were conducted using Statistical Package for Social Sciences V19. Continuous data were presented as the mean ± S.D., whereas categorical data were presented as number and percentage. Comparison between the two groups was performed using unpaired t test for continuous data and χ^2 test for categorical data. The marginal homogeneity test was used for comparing frequency of recurrence of febrile seizures and paired t test for comparing the number of febrile illnesses before and after treatment within melatonin or diazepam group. P value was considered significant if <0.05.

Results

Eighty-six children with simple febrile seizures were assessed for eligibility but only 66 patients were enrolled in the study and were randomly allocated to either melatonin or diazepam group in 1:1 ratio. Three children in the melatonin group discontinued intermittent therapy because they developed recurrent seizures; one of them developed afebrile seizures and long-term valproate was started. Meanwhile, two children in the diazepam group discontinued intermittent therapy because they developed intolerable sedation and dizziness and one child was noncompliant to

treatment. Among 66 children enrolled in the clinical trial, 60 children (90.9%) completed the study (Figure).

The melatonin group included 15 males and 15 females, and the diazepam group included 18 males and 12 females. There was no statistically significant difference in the mean age or sex between the two groups. Family history of febrile seizures was positive in 28 patients (46.67% of the studied children). There was no statistically significant difference in risk factors for recurrence of febrile seizures in children who received melatonin compared with those who received diazepam (Table 1).

During the six month follow-up period, the studied children had 131 febrile illnesses with temperature greater than 38.5°C. There was no reported significant difference in the mean number of febrile illnesses between the two studied groups. The recurrence rate of febrile seizures was reduced to 16.67% in children during melatonin therapy and 36.67% in those receiving diazepam therapy. Although the recurrence rate of febrile seizures was lower in children treated with melatonin compared with those treated with diazepam, the difference was insignificant ($P = 0.08$) (95% confidence interval −0.025 to 0.42).

Prophylactic treatment with melatonin causes a 45% lower relative risk of recurrence of febrile seizures (95% confidence interval 0.18 to 1.15) compared with diazepam. There was a significant difference in the frequency of seizures before and after treatment in both groups ($P < 0.001$), but no statistically significant difference between two groups after treatment ($P = 0.18$) (Table 2).

Upper respiratory tract infection was the most common cause of febrile illnesses in both groups. There was no statistically significant difference in the causes of febrile illness between the two groups ($P = 0.78$) (Table 3).

Adverse effects were reported in 13.3% of the studied children during intake of melatonin and in 23.3% of those who received diazepam (Table 4). There was no statistically significant difference between the two groups as regard the occurrence of side effects of the studied drugs ($P = 0.15$).

Discussion

The preventive effect of intermittent oral or rectal diazepam, administered during febrile illness, against recurrence of simple febrile seizures has been established in many placebo-controlled studies.[3,4,12,13] In addition, some comparative clinical trials have demonstrated similar or lower efficacy of diazepam when compared with intermittent intake of other benzodiazepines such

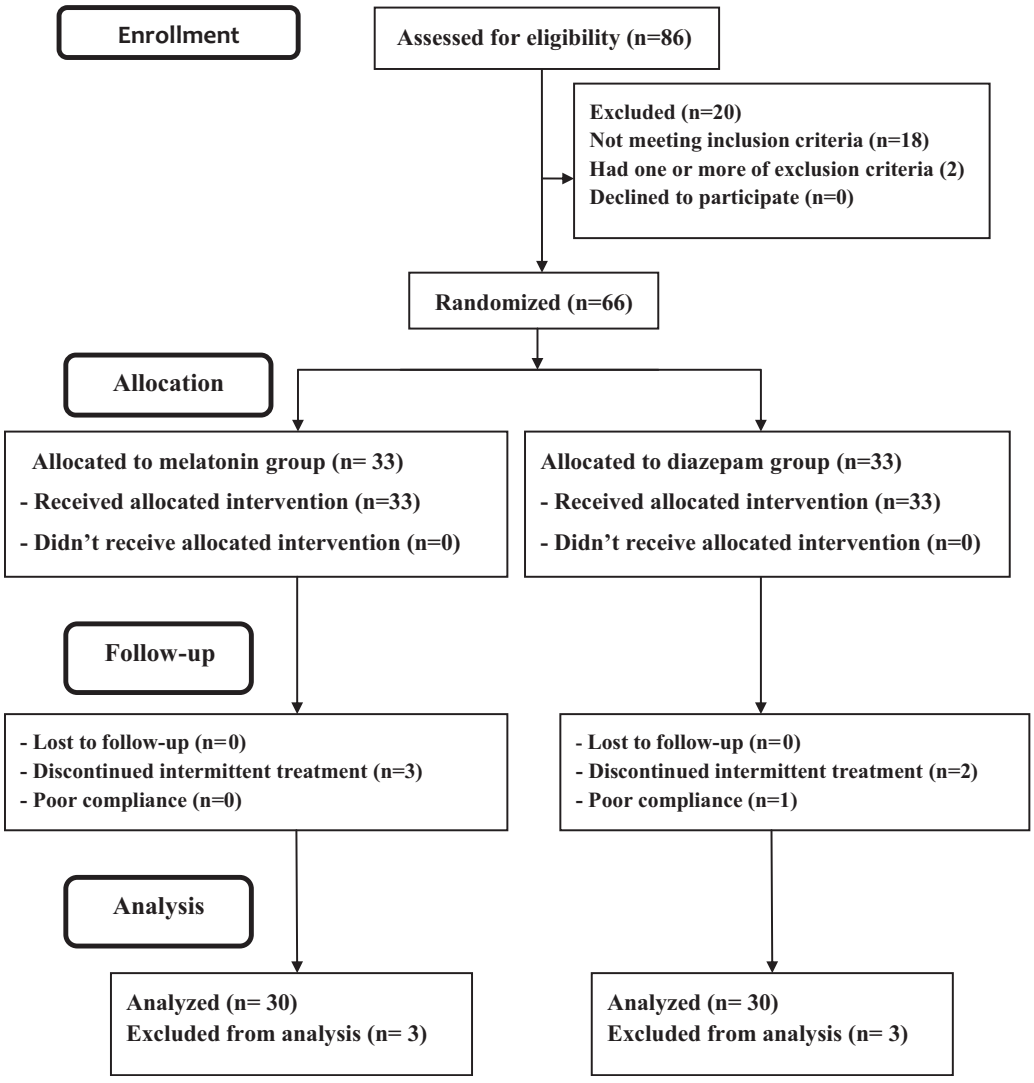

FIGURE. Participant flow diagram of a clinical trial comparing intermittent melatonin and intermittent diazepam for prophylaxis of recurrent febrile seizures.

TABLE 1.
Clinical Characteristics of the Studied Children

Clinical Characteristic	Melatonin Group (n = 30)	Diazepam Group (n = 30)	*P* Value	95% CI
Age (years)			0.48	−0.74 to 0.17
Range	1-4.25	1-4		
Mean ± S.D.	2.04 ± 0.85	2.33 ± 0.88		
Sex			0.44	−0.25 to 0.1
Male: N (%)	15 (50)	18 (60)		
Risk factors for recurrence of febrile seizures in the studied children				
Family history of febrile seizures				
Positive: N (%)	15 (50)	13 (43.33)	0.6	−0.2 to 0.3
Age of onset <12 months: N (%)	27 (60)	25 (83.3)	0.45	−0.24 to 0.11
Low grade fever*: N (%)	3 (10)	4 (13.3)	0.69	−0.20 to 0.14

Abbreviation:
CI = Confidence interval
* A body temperature of 37.5°C to 38.3°C.

as clobazam or clonazepam.[14–16] In other randomized controlled trials, intermittent diazepam was compared with long-term intake of AEDs such as phenobarbital and was reported to be equally effective.[5] Diazepam can reduce the risk of recurrence of febrile seizures if given in the first three days of the febrile illness.[3–5,12–16]

However, melatonin was never tried before as a prophylactic treatment against recurrence of febrile seizures. This is the first study evaluating the use of melatonin for the prevention of the recurrence of simple febrile seizures in children. The efficacy of oral melatonin was compared with oral diazepam for prevention of recurrence of simple febrile seizures.

Our data suggest that both oral melatonin and diazepam are effective in decreasing the frequency of simple febrile seizures compared with the frequency of seizures before treatment. Moreover, the efficacy of oral melatonin compared with oral diazepam for the prevention of the recurrence of simple febrile seizures in children was comparable with no serious side effects recorded for either drug.

Regulation of circadian rhythms represents the main function of melatonin. In addition, the anticonvulsant and antioxidant effects of melatonin were also previously studied. Melatonin produces its anticonvulsant action through modulation of the neuronal electrical activity as it enhances the inhibitory neurotransmitter gamma-aminobutyric acid and reduces glutamate, which is a powerful excitatory neurotransmitter, with subsequent inhibition of neuronal excitation. Moreover, melatonin inhibits the production of nitric oxide, which is considered a proconvulsant, through inhibition of nitric oxide synthase activity.[10,17–19]

Previous studies reported lower levels of serum melatonin in children with epilepsy or complex febrile seizures.[11,20] Similarly, Bazil et al.[21] reported lower melatonin levels in children with epilepsy compared with control subjects with an increase in melatonin levels after seizures. These findings suggested that melatonin could play a role in the treatment of epilepsy and febrile seizures. In contrast, Mahyar et al.[22] found no significant differences in serum melatonin levels between children with febrile seizures, epileptic children, and normal control children.

Some clinical trials have reported a beneficial effect of melatonin as an add-on treatment in refractory epilepsy. However, more randomized controlled trials are needed to confirm these findings before melatonin can be used to control seizures in epileptic children.[10,23]

The main principles of management of febrile seizures are reassurance of parents, confirming the benign nature of the febrile seizures, and health education to parents providing them with information about first aid management if seizures occurred. There is consensus in all guidelines that intermittent diazepam is the utmost accepted prophylactic treatment for prevention of recurrence of febrile seizures.[7,8,12,24] However, intermittent diazepam prophylaxis is not routinely recommended in all children with febrile seizures except in the history of febrile status epilepticus or recurrent febrile seizures with risk factors for

TABLE 2.
Recurrence Rate of Febrile Seizures in the Studied Children Before and After Prophylactic Treatment

Recurrence: N (%)	Melatonin Group (n = 30)			Diazepam Group (n = 30)			*P* Value	95% CI
	Before	After	P1	Before	After	P2		
No	0	25 (83.3)	<0.001*	0	19 (63.3)	<0.001*	0.18	−0.04 to 0.22
Once	21 (70)	4 (13.3)		23 (76.7)	7 (23.3)			
Twice	8 (26.7)	1 (3.3)		6 (20)	4 (13.3)			
Three or more	1 (3.3)	0		1 (3.3)	0			
Febrile illness			0.66			0.64	0.74	−0.71 to 0.51
Range †	1-5	1-5		1-5	1-5			
Mean ± S.D.	2.3 ± 1.1	2.1 ± 1.2		2.1 ± 1.1	2.2 ± 1.1			

Abbreviation:
CI = Confidence interval
P1: *P* value comparing before and after treatment within melatonin group using the marginal homogeneity test for frequency of recurrence of febrile seizures and paired *t* test for the number of febrile illnesses.
P2: *P* value comparing before and after treatment within diazepam group using the marginal homogeneity test for frequency of recurrence of febrile seizures and paired *t* test for the number of febrile illnesses.
P: *P* value comparing the results after treatment between melatonin and diazepam groups using Pearson-χ^2 test for frequency of recurrence of febrile seizures and unpaired *t* test for the number of febrile illnesses.
* Significant *P* value.
† Febrile illness with temperature >38.5°C was recorded.

TABLE 3.
Causes of Fever and Seizure Duration in the Studied Children

Cause of fever	Melatonin Group	Diazepam Group	*P* Value
Upper respiratory tract infection	40%	46.7%	0.78
Gastroenteritis	20%	13.3%	
Viral exanthems	16.7%	10%	
Lower respiratory tract infection	3.3%	10%	
Urinary tract infection	6.7%	3.3%	
Undefined cause	13.3%	16.7%	
Seizure duration			0.84
<5 minutes	83.3%	86.7%	
≥5 minutes	16.7%	13.3%	

recurrence. Family anxiety should be also considered an indication for intermittent prophylactic diazepam. Long-term AEDs are not recommended in treatment of febrile seizures except in prolonged or recurrent febrile seizures not responding to intermittent diazepam.[8,12,24]

On the other hand, the American Academy of Pediatrics guidelines do not recommend prophylactic treatment of children with simple febrile seizures with either continuous AEDs or intermittent diazepam, even in recurrent febrile seizures. Exceptionally, intermittent oral diazepam is recommend as a prophylactic treatment to prevent recurrence of febrile seizures in children with anxious caregivers.[7]

Previous studies have reported that the main risk factors for recurrence of febrile seizures are an age of onset of febrile seizures at less than one year, family history of epilepsy or febrile seizures, repeated febrile illnesses and febrile seizures occurring at temperature less than 38.5°C. Recurrence of febrile seizures occurs in approximately one third of children with febrile seizures. However, the risk of recurrence is increased to 50% or more in children with one or more risk factors.[25,26]

Both groups of the studied children had risk factors for recurrence of febrile seizures and there was no statistically significant difference between the two groups. The first attack of febrile seizures occurred at age less than one year in 60% and 83% of the children treated with melatonin and diazepam, respectively. In addition, 50% of children who received melatonin and 43% of those who received diazepam had positive family history of febrile seizures. Temperature ≤38.3°C at the onset of the febrile seizure was reported in 10% of the melatonin group and 13% of the diazepam group.

Upper respiratory tract infection, gastroenteritis, and viral exanthems were the most common causes of febrile illnesses in both studied groups. Similarly, previous studies have reported viral infections, particularly viral exanthems and upper respiratory tract infection as the most common infections associated with febrile seizures.[27]

All the five children who experienced recurrence of febrile seizures during prophylactic treatment with melatonin had seizures lasting less than five minutes, whereas only one child in the diazepam group had seizure duration of more than five minutes. Febrile status epilepticus can occur in about 5% of children with febrile seizures.[2] Some previous studies have reported an association between the duration of febrile seizures, the occurrence of multiple febrile seizures, and later development of epilepsy.[28]

Moreover, febrile seizures may represent the initial manifestation of some epilepsy syndromes, such as genetic epilepsy with febrile seizures plus, in which febrile seizures persist beyond six years of age, or afebrile generalized seizures occur.[29] Identifying genetic epilepsy with febrile seizures plus in children with febrile seizures is essential for appropriate management, as intermittent prophylactic treatment is inadequate and long-term treatment with AEDs is mandatory to control seizures and prevent recurrence. Among 66 children enrolled in this clinical trial, one child developed afebrile seizures during the follow-up, intermittent melatonin was then discontinued in this child and long-term valproate was started to control seizures.

The study revealed no major side effects in either group. Minor adverse effects of melatonin were reported in only four (13.3%) individuals (three with vomiting and one with diarrhea) whereas adverse effects of diazepam were reported in seven (23.3%) patients (sedation in three, dizziness and ataxia in two, and irritability and vomiting in one each). Consistent with our results, no severe side effects are reported with long-term or intermittent intake of melatonin therapy.[30] Ataxia and sedation were the most reported adverse effects during intermittent oral diazepam prophylaxis.[4,12]

The lack of placebo control group could be a limitation of the present study, but we compared the frequency of recurrence of febrile seizures between the children who received intermittent melatonin and those who received intermittent diazepam; the effectiveness of diazepam in reducing rate of recurrence of febrile seizures was proved in the previous studies.[3-5,12-16] In addition, all children with simple febrile seizures included in this study had developed two or more attacks of febrile seizures during the first six months of follow-up before melatonin or diazepam intake and those who did not develop recurrence of seizures during the febrile illnesses were excluded. Thus frequency of febrile seizures during prophylactic treatment with melatonin or diazepam was compared with the frequency of febrile seizures in the six months before treatment.

The short duration of follow-up could be a limitation of the study, but all the studied children had experienced one or more febrile illnesses during the six months of follow-up. Moreover, 50% to 60% of recurrences of febrile seizures occur during the first year after the first febrile seizure and the incidence of recurrence decreases thereafter. Further studies with larger sample size and longer duration of follow-up are required.

The study has low risk of selection bias as randomization and adequate allocation concealment were performed. The studied children were randomly allocated to either melatonin or diazepam and neither the physician nor the parents knew to which group the child had been allocated. In addition, the study was a double-blind study, both parents of participants and outcome assessors were not aware of the prophylactic treatment used during febrile illnesses; thus there is a low risk of performance and detection bias.

TABLE 4.
The Main Complaints in the Studied Children During Treatment With Melatonin and Diazepam

Side Effects	Melatonin Group, N (%)	Diazepam Group, N (%)	*P* Value	95% CI
No side effects	26 (86.67)	23 (76.67)	0.15	−0.68 to 2.05
Sedation*	0	3 (10)		
Ataxia/dizziness*	0	2 (6.67)		
Irritability*	0	1 (3.33)		
Vomiting	3 (10)	1 (3.33)		
Diarrhea	1 (3.33)	0		

Abbreviation:
CI = Confidence interval
* Mostly because of side effects of melatonin and diazepam in the studied children.

Conclusions

Melatonin, given at the onset of a febrile illness, may effectively reduce the likelihood of recurrent simple febrile seizures. Melatonin was well tolerated in the studied children.

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