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Effect Of Melatonin as a Prophylaxis for Febrile Convulsion

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Abstract

Background and objective: The efficacy of melatonin for febrile seizure prevention has been demonstrated in various studies. Febrile seizures are common in children and can be a cause of significant concern for parents. Melatonin is a hormone that regulates sleep-wake cycles and has neuroprotective properties. This study evaluates the effectiveness of melatonin in preventing febrile seizures. We searched to determine whether melatonin can reduce the frequency and severity of febrile seizures compared to a placebo.

Methods:
A clinical trial study was conducted at Raparin Teaching Hospital from January to June 2023. Patients with febrile seizures were divided into two cohorts: 38 in the melatonin group and 39 in the control group. In the melatonin group melatonin administered every 8 hours for 48 to 72 hours during febrile episodes, while the control group received no medication. Both groups were followed up after six months.

Results: There were no significant differences in age, gender, seizure onset age, or number of attacks between both groups. They had similar fever histories over the past six months ($p = 0.672$). However, 34.8% of the control group had seizures after six months compared to 5% of the melatonin group ($p = 0.024$). In the melatonin group, 15% experienced dizziness, 5% had headaches, and 80% had no side effects.

Conclusions: We advise using melatonin to prevent recurring febrile seizures, avoiding the negative effects of other anticonvulsant drugs.

Keywords: Antiepileptic, Febrile seizure, Melatonin, Neuroprotective

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Introduction

Febrile seizures occur due to a rapid rise in body temperature, with fevers exceeding 38°C (100.4°F) and are not linked to other seizure-inducing factors such as CNS infections, electrolyte imbalances, drug withdrawal, trauma, hereditary predisposition, or existing epilepsy. These seizures most commonly affect children between 6 and 60 months of age.[1-4] The ratio of febrile seizure is nearly 2-4% between 6 months to 6 years.[5,6] A second recurrent febrile seizure occurs in about 35% of people with febrile seizures.[5] They are classified into simple and complex febrile seizures.[1-4] The history of FS treatment trials in the medical literature is lengthy.Scientists considered administering regular antiseizure medicine to children following their first FS in the late 1970s. Phenobarbital was used in the first randomized controlled trial (RCT) conducted by Camfield and colleagues in Canada to reduce febrile seizures. Given the side effects of antiseizure medications, there is a need for a more recent pharmacological treatment that is easily accessible and has fewer side effects and negative consequences than traditional antiseizure drugs. using melatonin to prevent febrile convulsions is based on data from prior clinical and animal research.[7,8] Furthermore, melatonin is used to reduce the frequency of seizures in children with epilepsy in conjunction with diazepam or phenobarbital.[7] Surprisingly, Guo and Yao reported that serum melatonin levels are reduced in children with complex febrile seizures and epilepsy.[9] One of the most adaptable molecules, melatonin affects many physiological processes, including circadian homeostasis, sleep, reproduction, and retinal neuromodulation. The pineal gland is the primary site of melatonin synthesis, and the suprachiasmatic nucleus is the organ that senses light-dark cycles in the environment. Every part of the body, including the skin, bone marrow, gastrointestinal tract, retina, and lymphocytes, produces melatonin. Through paracrine signaling, which also affect other physiological processes, like antidepressant, antiepileptic, cardiovascular disease, neuromodulation.[10] Excellent free radical scavenging abilities are responsible for melatonin's neuroprotective qualities. Melatonin operates through all three of the melatonin receptors, or MT1, MT2, and MT3. For instance, agonistic activity towards the MT2 receptor is linked to qualities that are neuroprotective, hypnotic, and anxiolytic.[11] In 2021, a study conducted in Wuhan, China, aimed to determine the effect of melatonin on febrile convulsion based on underlying molecular mechanisms. The study's findings revealed that the febrile seizure (Fc) group had significantly more apoptotic neurons than the control group; however, melatonin (MT) treatment significantly reduced the number of apoptotic neurons compared to the Fc group.[12] It has been claimed that kynurenic acid, a melatonin byproduct, has endogenous anticonvulsant properties, in a study examining the impact of high melatonin concentration on PC12 cells, the release of norepinephrine and melatonin's effect on excitatory postsynaptic potential in rat hippocampal slices were analyzed. Melatonin inhibits neurotransmitter release, likely by blocking voltage-sensitive Ca2+ channels. [13] The aim of this study is to assess the efficacy of melatonin in prevention of recurrence of simple and complex febrile seizure in pediatric age group (6month to 6 year).

Patients and methods

The study was a clinical trial study at Raparin Teaching Hospital from January to June 2023, involving only in-patients. Parents were informed about the study and melatonin’s side effects, with consent obtained from one parent per participant. Seventy-seven patients with febrile convulsions were included, divided into melatonin and control groups. Simple febrile

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seizures are short, generalized seizures under 15 minutes without recurrence within 24 hours, while complex seizures are prolonged or recurrent with potential neurological deficits. Patients with specific criteria were included, while those with abnormal neurological exams, EEG, CSF, delayed milestones, on prophylactic anti-seizure meds, or whose parents refused consent were excluded. Data collected included age, sex, seizure details, fever causes, family history, and neurological development. The melatonin group received 0.3 mg/kg/dose every 8 hours during febrile episodes, while the control group received only antipyretics. Both groups avoided other medications except acetaminophen and necessary antibiotics. Outcomes were measured by seizure recurrence over six months, comparing both groups. Adverse effects were reported by parents and monitored through follow-up visits or phone interviews, with instructions to report significant side effects like dizziness or headache to the hospital.38 parents were advised to give Melatonin to their children during febrile illness, and 39 parents were not advised to give any prophylaxis, 7 parents from who were advised to give melatonin did not answer our calls and didn't visit outpatient department for follow up so they were excluded from data analysis, and 7 patients didn't receive melatonin because some of them didn't get fever during this 6 months and 2 of them due to ignorance of the family, so what remained was 20 patients that got fever and received melatonin properly.39 patients were in the control group, 5 of them didn't come back for follow up and did not answer our calls, 11 of them did not get fever, so what remained are 23 patients that got fever and were included in data analysis.Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26). To compare the proportions of the two study groups, the Chi-square test of association was utilized. When more than 20% of the table cells had an expected frequency of less than 5, Fisher's exact test was applied. A p-value of ≤ 0.05 was considered statistically significant.This study was approved by Raparin teaching hospital ethics committee.

Result

The total number of children was 77. Their mean age (SD) was 26.1 (15.9) months, the median was 20 months, and the age range was 6-72 months. They were divided into two groups, the first group was composed of 38 children who received melatonin, and the second group (control) was composed of 39 children who didn't receive melatonin. More than one third (37.7%) of the children were aged 12-23 months, and only 15.6% were aged less than 12 months. No notable difference in the age distribution was found between the two groups (p = 0.688). More than half (58.4%) of the children were males, but there was no obvious difference between the groups (p = 0.923). More than two thirds (68.4%) of children of the melatonin group were living in urban areas, compared with 35.9% of the control group (p = 0.004), as presented in Table (1).

Table (1): Socio-demographic characteristics.

	Melatonin	Control	Total	
	No. %	No. %	No. %	P
Age (months)				
< 12	6 (15.8)	6 (15.4)	12 (15.6)	
12-23	12 (31.6)	17 (43.6)	29 (37.7)	
24-35	8 (21.1)	5 (12.8)	13 (16.9)	
≥ 36	12 (31.6)	11 (28.2)	23 (29.9)	0.688*
Gender				
Male	22 (57.9)	23 (59.0)	45 (58.4)	
Female	16 (42.1)	16 (41.0)	32 (41.6)	0.923*
Residency				
Urban	26 (68.4)	14 (35.9)	40 (51.9)	

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Rural	12 (31.6)	25 (64.1)	37 (48.1)	0.004*
Total	38 (100.0)	39 (100.0)	77 (100.0)	

*By Chi square test.

The majority (80.5%) of the children had one attack in the previous 24 hours, 11.7% had two attacks, and 7.8% had three attacks, but the groups showed no significant difference (p = 0.140). Only 11.7% of the children had a temperature exceeding 38.5 ℃, but no significant difference was detected between the two groups (p = 0.481). Regarding the duration between fever and the seizure, it was more than an hour among the majority (82.1%) of children of the control group, compared with 52.6% of children of the melatonin group (p = 0.015). The duration of the attack was less than 5 minutes among 49.4% of children, and there was no notable difference between the groups (p = 0.988). All the children had generalized type of seizure. The postictal phase was significantly shorter in the melatonin group, as it was less than five minutes in 52.6% of children of the melatonin group, compared with 23.1% of children of the control group (p = 0.028). The type of febrile seizure was simple febrile convulsion in 68.8% of children, but the difference was not significant (p = 0.289) between the groups Table (2).

Table (2): Details of current attack.

	Melatonin	Control	Total	
	No. %	No. %	No. %	P
No. of attacks last 24 hours				
One	29 (76.3)	33 (84.6)	62 (80.5)	
Two	7 (18.4)	2 (5.1)	9 (11.7)	
Three	2 (5.3)	4 (10.3)	6 (7.8)	0.140**
Temperature				
37.4-38.5	35 (92.1)	33 (84.6)	68 (88.3)	
> 38.5	3 (7.9)	6 (15.4)	9 (11.7)	0.481**
Duration between fever and seizure				
< 5 minutes	9 (23.7)	2 (5.1)	11 (14.3)	
5 minutes - 1 hour	9 (23.7)	5 (12.8)	14 (18.2)	
> 1 hour	20 (52.6)	32 (82.1)	52 (67.5)	0.015*
Duration of the attack				
< 5 minutes	19 (50.0)	19 (48.7)	38 (49.4)	
5-14 minutes	13 (34.2)	14 (35.9)	27 (35.1)	
≥ 15 minutes	6 (15.8)	6 (15.4)	12 (15.6)	0.988*
Type of seizure				
Generalized	38 (100.0)	39 (100.0)	77 (100.0)	N/A
Postictal phase				
< 5 minutes	20 (52.6)	9 (23.1)	29 (37.7)	
5-9 minutes	5 (13.2)	9 (23.1)	14 (18.2)	
≥ 10 minutes	13 (34.2)	21 (53.8)	34 (44.2)	0.028*
Type of febrile seizure				
Simple febrile convulsion	24 (63.2)	29 (74.4)	53 (68.8)	
Complex febrile convulsion	14 (36.8)	10 (25.6)	24 (31.2)	0.289*
Total	38 (100.0)	39 (100.0)	77 (100.0)	

*By Chi square test. **By Fisher's exact test. N/A: Not applicable.

The largest proportion of the whole sample (41.6%) had no family history of seizures, 24.7% had family history of first-degree relatives, 31.2% for second degree, and 2.6%

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for third degree, but there was no considerable difference between the groups (p = 0.234). Around two thirds (66.2%) of children of the whole sample had recent history of acute respiratory tract infection, and 29.9% had no such a history, but the difference was not substantial between groups (p = 0.531), as presented in Table (3).

Table (3): History of both groups' melatonin and control group regarding presence of family history of febrile seizure and history of recent infection.

	Melatonin	Control	Total	
	No. %	No. %	No. %	P*
Family history				
Negative	13 (34.2)	19 (48.7)	32 (41.6)	
First degree	13 (34.2)	6 (15.4)	19 (24.7)	
Second degree	11 (28.9)	13 (33.3)	24 (31.2)	
Third degree	1 (2.6)	1 (2.6)	2 (2.6)	0.234
History of recent infection				
None	13 (34.2)	10 (25.6)	23 (29.9)	
Acute respiratory tract infection	23 (60.5)	28 (71.8)	51 (66.2)	
Acute gastroenteritis	2 (5.3)	1 (2.6)	3 (3.9)	0.531
Total	38 (100.0)	39 (100.0)	77 (100.0)	

*By Fisher's exact test.

No significant variation was detected between the two groups regarding history of fever during the previous six months (p = 0.672). More than one third (34.8%) of the control group developed seizures after six months compared with only 5% of the melatonin group (p = 0.024), but no significant (p = 0.556) discrepancy was detected in the number of attacks Table (4).

Table (4): Follow up after 6 months.

	Melatonin	Control	Total	
	No.%	No. %	No. %	P
Fever during this 6 month				
None	8 (2.1)	11 (28.2)	19 (24.7)	
Yes	23 (60.5)	23 (59.0)	46 (59.7)	
Non-response	7 (18.4)	5 (12.8)	12 (15.6)	0.672*
Total	38 (100.0)	39 (100.0)	77 (100.0)	
Seizure during this 6 month				
None	19 (95.0)	15 (65.2)	34 (79.1)	
Yes (Convulsion)	1 (5.0)	8 (34.8)	9 (20.9)	0.024**
Total	20 (100.0)	23 (100.0)	43 (100.0)	
No. of attacks				
One	0 (0.0)	4 (50.0)	4 (44.4)	
Two	0 (0.0)	2 (25.0)	2 (22.2)	
Three	1 (100.0)	2 (25.0)	3 (33.3)	0.556**
Total	1 (100.0)	8 (100.0)	9 (100.00)	

*By Chi square test. **By Fisher's exact test.

Out of the twenty children who received melatonin, three (15%) developed dizziness,

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one (5%) developed headache, while the rest (80%) didn't develop any side effect Table (5).

Table (5): Melatonin intake and its side effects.

	No.	%
Melatonin		
Didn't receive	11	(28.9)
Received	20	(52.6)
No answer	7	(18.4)
Total	38	(100.0)
Side effects		
No side effect	16	(80.0)
Dizziness	3	(15.0)
Headache	1	(5.0)
Total	20	(100.0)

Discussion

Melatonin is a hormone produced by the pineal gland, regulated by the circadian rhythm, which follows a 24-hour cycle. Disruptions in this cycle can lead to disorders like depression, anxiety, and sleep deprivation. Research suggests that individuals with epilepsy or febrile seizures (FS) often have lower melatonin levels, with a reactive increase following seizures.[20] However, some studies indicate melatonin might have proconvulsant properties due to higher levels during increased seizure frequency.[9,16-18] A study reported by Mahyar found no association between serum melatonin levels and febrile seizures or epilepsy, suggesting melatonin might not play a significant role in these disorders. Conversely, Guo et al. reported lower melatonin levels in children with epilepsy or complex FS, suggesting exogenous melatonin could be beneficial.[9]A study reported by Tarcin 111 participants found lower basal melatonin levels in patients with epilepsy, Febrile seizure compared to controls.[14,15] At 2019 study compared melatonin and diazepam for febrile seizure prophylaxis, finding both equally effective. The recurrence rate in the melatonin group was 16.6%, but diazepam was not commonly recommended due to side effects.[5, 19] while recurrence rate of seizure in melatonin group in our study was only 5%.Another study by Assawabumrungkul included 23 patients in the melatonin group and 41 in the control group, 8.7% of patients had recurrent febrile seizure in melatonin group compared to 36.6% in the control group, which is statistically significant (p value 0.015). There was no statistically significant difference in adverse effects between the two groups.[20] which is more like the result of our research. Barghout's melatonin group was composed 60% of children under 12 months old and 50% of children with family history of febrile seizure, while Assawabumrungkul's study had children with 30% and 20%, correspondingly, while in our study only 15.6% patients age are less than 12 months, 58.5% of children their family history was positive in both groups.[5,20] There were only a few studies that evaluated melatonin efficacy in preventing a second recurrence of simple and complex febrile seizure this is why we did this study.In our study not all 77 patient got fever after 6 month which makes our sample size to lessen to only 46 (59.9%) patients that got fever after 6 month in both groups, But more than one third (34.8%) of the control group developed seizures after six months compared with only 5% of the melatonin group that got seizure after this 6 month, which makes our study to be statistically significant. Regarding side effects of melatonin our study reported dizziness (15%) and headache (5%). Melatonin adverse effects of vomiting, drowsiness and headache were reported in Barghout's study at a rate of 14.7%. [5] whereas in Assawabumrungkul's study these same symptoms were reported in the melatonin group at a rate of 34.8%.[20] Most parents noted positive results. The study had limitations, including a short 6-month follow-up, longer follow up duration needed to confirm the

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beneficial effect of melatonin and it is safety. In addition, there was missing data due to neglecting family 7 patient in melatonin group and 5 patients in control group did not come back for follow up and ignore our calls.

Conclusion

This study confirms the effectiveness and safety of short-term melatonin use in preventing recurring episodes of simple or complex febrile seizures in children. We advocate for melatonin as a preventative measure against recurrent febrile convulsions, to avoid the side effects associated with diazepam and other anticonvulsant medications previously used for this purpose.

Conflicts of interest

There are no conflicts of interest

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