https://doi.org/10.29309/TPMJ/2026.33.09.10433 www.theprofesional.com

ORIGINAL ARTICLE

Efficacy of melatonin as an adjunct to first-line therapy in epileptic patients.

Safiullah[1], Sadia Riaz[2]

ABSTRACT… Objective: To determine the efficacy of melatonin as an adjunct to first-line antiepileptic therapy in reducing seizure severity, seizure frequency, and electroencephalographic (EEG) abnormalities in pediatric patients with generalized epilepsy. **Study Design:** Quasi-experimental Comparative study. **Setting:** Department of Pediatrics, Pakistan Institute of Medical Sciences (PIMS), Islamabad. **Period:** July 2025 to Dec 2025. **Methods:** A total of 60 children aged 2–12 years with generalized epilepsy and suboptimal seizure control despite first-line antiepileptic therapy were enrolled using consecutive sampling. Patients were allocated into two groups: the treatment group (n=30) received melatonin as an adjunct to first-line therapy, while the control group (n=30) received placebo with first-line therapy. Melatonin was administered at bedtime for 12 weeks (1 mg for children <5 years and 2 mg for ≥5 years). Seizure severity was assessed using the Chalfont-National Hospital Seizure Severity Scale (NHS-3), while seizure frequency over a three-month period and EEG findings were recorded at baseline and follow-up. Data were analyzed using SPSS version 25.0, and a p-value of less than 0.05 was considered statistically significant. **Results:** The two groups showed no significant differences in baseline demographic and clinical characteristics. At 12 weeks, seizure severity scores were significantly reduced in the melatonin group compared to the placebo group (10.7 ± 2.4 vs. 17.9 ± 4.3; $p < 0.001$), with a mean reduction of 7.9 ± 3.1 versus 1.5 ± 1.6, respectively. Seizure frequency also showed a significant reduction in the melatonin group compared to placebo (mean reduction: 3.1 ± 1.1 vs. 0.4 ± 0.9; $p < 0.001$). 50% of patients in the melatonin group showed significant EEG normalizationin contrast to 26% in the placebo group ($p = .03$). **Conclusion:** Adjunctive use of melatonin with first-line antiepileptic therapy results in significant improvement in seizure severity, seizure frequency, and EEG findings in pediatric patients with generalized epilepsy, supporting its safety and effectiveness as an additional treatment option in children with inadequate seizure control.

Key words: Adjunct Therapy, Chalfont-NHS-3 Scale, EEG, Epilepsy, Melatonin, Pediatric Seizures.

Article Citation: Safiullah, Riaz S. Efficacy of melatonin as an adjunct to first-line therapy in epileptic patients. Professional Med J 2026; 33(09):1687-1692. https://doi.org/10.29309/TPMJ/2026.33.09.10433

INTRODUCTION

Epilepsy is a chronic and disabling neurological disorder characterized by recurrent unprovoked seizures and represents a major public health concern worldwide. It affects approximately 70 million individuals globally and accounts for nearly 1% of the total global disease burden, with about 80% of cases occurring in developing countries.[1,2] In Pakistan, active epilepsy is estimated to prevalent between 0.5% and 1.0%of population.[3] Beyond its clinical manifestations, epilepsy imposes substantial social, psychological, and economic challenges on patients, their families, and the community, highlighting the need for effective management strategies to reduce its overall burden.[4]

The cornerstone of epilepsy management is achieving optimal seizure management using a well-received anti-seizure medication (ASM).[5] Despite the availability of effective ASMs, nearly one-third of patients continue to experience uncontrolled seizures, indicating limited success of current therapeutic approaches.[6] In such cases, monotherapy often proves insufficient, necessitating the use of polytherapy. However, combination therapy is frequently associated with increased adverse effects and comorbidities, including mood disturbances, behavioral problems, cognitive impairment, psychosis, attention deficits, and sleep disorders.[7,8] Additionally, about 30% of patients experience significant adverse effects from ASMs, leading to poor treatment adherence and suboptimal seizure control.[6,9]

1. MBBS, PGR Peads Medicine, PIMS, Islamabad.
2. MBBS, FCPS, Professor Peads Medicine, PIMS, Islamabad.

Correspondence Address:
Dr. Safiullah
Department of Peads Medicine, PIMS, Islamabad.
do351776@gmail.com

Article received on:
04/02/2026
Accepted for publication:
11/04/2026

Melatonin is an endogenous pineal gland hormone in a circadian pattern, with peak levels during nighttime. It has demonstrated anticonvulsant and neuroprotective properties in various experimental models of generalized epilepsy.[10] Clinical studies have also reported beneficial effects of melatonin in reducing seizure frequency and severity. Maghbooli et al. reported a major reduction in seizure severity scores and seizure frequency in patients receiving melatonin compared to placebo, along with partial resolution of electroencephalographic abnormalities.[6] Similar findings have been reported in other trials, showing a statistically significant reduction in seizure frequency and Chalfont-NHS3 scores in patients treated with melatonin as an adjunct therapy.[10] These findings indicate a potential therapeutic role of melatonin in epilepsy management. However, most available evidence is derived from studies conducted in adult populations.

The rationale for the present study is based on the need to explore effective and safe adjunctive treatment options for pediatric patients with refractory generalized epilepsy in the local population. Despite first-line therapy, a considerable proportion of children continue to experience inadequate seizure control. Given the favorable safety profile and potential anticonvulsant effects of melatonin, its role as an adjunct to standard therapy warrants further investigation in children. Moreover, the limited data available on pediatric populations and the absence of local studies emphasize the importance of this research. This study aims to evaluate the efficacy of melatonin as an adjunct to first-line therapy in pediatric epileptic patients, with the goal of improving seizure control and overall quality of life.

METHODS

This quasi-experimental comparative study was held in the Department of Pediatrics, Pakistan Institute of Medical Sciences (PIMS), Islamabad, for a period of six months from July 2025 to December 2025, after approval from the Institutional Review Board (F-S-2/2024/(ERRC)DIMS/14-4-24). A total of 60 pediatric patients were enrolled using consecutive sampling. The required sample size was estimated with the WHO sample size calculator, considering a 5% significance level and a statistical power of 90%, based on a reported mean reduction in seizure severity score (Chalfont-NHS-3) of 32.33 ± 9.24 in the melatonin group and 5.58 ± 14.28 in the placebo group.[6] Thirty patients were included in each group, with seizure severity taken as the primary outcome variable, while seizure frequency and EEG findings were secondary outcomes.

Children aged 2–12 years of either gender, diagnosed with generalized epilepsy according to ILAE-2017 criteria and receiving first-line antiepileptic therapy, were included if they had suboptimal seizure control, defined as at least one seizure recurrence within the preceding three months despite maximum tolerated doses. Patients with structural brain lesions, neurosurgical history, central nervous system infections, focal, febrile or absence seizures, traumatic brain injury, hypoxic ischemic encephalopathy, metabolic or electrolyte disturbances, or those seizure-free for the last eight weeks were excluded.

After obtaining informed consent from parents or guardians and assent where applicable, baseline demographic and clinical data were recorded on a predesigned proforma. Participants were distributed into two groups using block allocation. The treatment group received first-line antiepileptic therapy (sodium valproate) along with melatonin at bedtime for 12 weeks (1 mg for children <5 years and 2 mg for ≥5 years), while the control group received first-line therapy with a placebo identical in appearance, containing dicalcium phosphate and similar excipients.

Seizure severity was assessed at baseline and at 12-week follow-up using the Chalfont- NHS-3 score, consisting of eight components with a maximum score of 27. Seizure frequency was determined through caregiver interviews by recording the number of seizure episodes over a three-month period. EEG was performed using a Nihon Kohden EEG-1260 machine with an 18–20 lead, 30-minute recording, and findings were categorized as normal or abnormal; abnormal EEG included background slowing or epileptiform discharges such as spike waves, sharp waves, spike-and-wave complexes, or polyspikes.

Data were analyzed using SPSS version 25.0. Qualitative variables were expressed as frequencies with percentages, while quantitative variables were presented as mean ± standard deviation. Independent sample t-test was applied for comparison of quantitative variables and Chi-square test for qualitative variables. Effect modifiers including age, gender, family history, and duration of epilepsy were controlled through stratification followed by post-stratification application of appropriate tests. A p-value less than 0.05 was taken as statistically significant.

RESULTS

In total 60 pediatric patients diagnosed with generalized epilepsy were included in the study, with 30 patients allocated to the melatonin group and 30 to the placebo group. The mean age of participants was 5.7 ± 2.9 years in the melatonin group and 6.3 ± 3.1 years in the placebo group. The age difference was not significant between two groups. Male patients constituted 56.7% of the melatonin group and 53.3% of the placebo group (p = 0.79). There were no statistically significant differences between the two groups with respect to age at seizure onset, duration of epilepsy, baseline seizure severity scores, seizure frequency, or EEG abnormalities, indicating comparability at baseline (Table-I).

Seizure severity assessed by the ChalfontNHS-3 score showed no significant difference between the two groups at baseline (18.6 ± 2.7 vs. 18.9 ± 2.9; p = 0.76). During the 12 weeks follow-up period, the mean seizure severity score was significantly lower in the melatonin group verses the placebo group (10.7 ± 2.4 vs. 17.9 ± 4.3; p < 0.001). The mean reduction in Chalfont-NHS-3 score was significantly higher in the melatonin group (7.9 ± 3.1) as compared to the placebo group (1.5 ± 1.6), with a p-value of <0.001. This corresponded to a percentage reduction of 40.5% in the melatonin group in contrast to 9.2% in the group without melatonin group (Table-II).

At baseline, seizure frequency over a three-month period was comparable between the melatonin and placebo groups (6.3 ± 2.1 vs. 6.1 ± 1.9; p = 0.68). After 12 weeks of treatment, seizure frequency was significantly reduced in the melatonin group (3.2 ± 1.9) compared to the placebo group (5.7 ± 2.2; p = 0.002). The mean reduction in seizure frequency was 3.1 ± 1.1 episodes in the melatonin group, whereas only 0.4 ± 0.9 episodes were observed in the placebo group (p < 0.001). The reduction in seizure count was 38.7% in the melatonin group in contrast to 6.7% in the placebo group (Table-III).

Electroencephalographic findings were comparable at baseline, with abnormal EEGs observed in 76.6% of patients in the melatonin group and 83.3% in the placebo group (p = 0.75). At 12-week follow-up, normalization of EEG recordings was observed in 50% of patients in the melatonin group compared to 26.0% in the placebo group, and this difference was statistically significant (p = 0.03). (Table-IV)

In our study, seizure severity was significantly reduced in the melatonin group as compared to placebo group. This improvement translated into a 40.5% reduction from baseline, highlighting seizure severity as the significant responsive outcome to melatonin therapy. Along with seizure frequency, seizure severity was also observed to reduced

TABLE-I

Baseline characteristics of study participants (N=60)

Variable	Melatonin Group (n = 30)	Placebo Group (n = 30)	P-Value
Age (years), mean ± SD	5.7 ± 2.9	6.3 ± 3.1	0.72
Male, n (%)	17 (56.7)	16 (53.3)	0.79
Female, n (%)	13 (43.3)	14 (46.7)	
Age at seizure onset (months), mean ± SD	21.4 ± 8.6	21.0 ± 9.6	0.84
Duration of epilepsy (months), mean ± SD	36.8 ± 13.2	34.9 ± 15.8	0.65
Baseline Chalfont-NHS-3 score, mean ± SD	18.6 ± 3.9	18.9± 3.8	0.76
Seizure frequency (per 3 months), mean ± SD	6.1 ± 2.1	6.0 ± 1.9	0.68
Abnormal EEG, n (%)	24 (80.0)	23 (76.7)	0.75

significantly in melanin group. This pattern is consistent with previous reports in which seizure severity, duration, or clinical impact improved; however, in our study extent of seizure severity and frequency reduction was approximately similar whereas, other reports other variables including severity improved better than seizure count.

TABLE-II

Chalfont-NHS-3 based seizure score severity among study group (N=60)

Parameter	Melatonin Group (Mean ± SD)	Placebo Group (Mean ± SD)	P-Value
Baseline score	18.6 ± 2.7	18.9 ± 2.9	0.76
Score at 12 weeks	10.7 ± 2.4	17.9 ± 4.3	<0.001
Mean reduction	7.9 ± 3.1	1.5 ± 1.6	<0.001
% reduction from baseline	40.5%	9.2%	—

TABLE-III

Seizure frequency at 3 months follow up (N=60)

Parameter	Melatonin Group (Mean ± SD)	Placebo Group (Mean ± SD)	P-Value
Baseline	6.1± 2.1	6.0 ± 1.9	0.68
After 12 weeks	3.2 ± 1.9	5.7 ± 2.2	0.002
Mean reduction	2.9 ± 1.1	0.3 ± 0.9	<0.001
% reduction	38.7%	6.7%	—

TABLE-IV

Comparison of EEG recording at study time points (N=60)

EEG Status	Melatonin Group n (%)	Placebo Group n (%)	P-Value
Baseline			
Normal	7 (23.0)	5(16)	0.75
Abnormal	23 (76.6)	25 (83.3)	
After 12 weeks			
Normal	15 (50)	8 (26.0)	0.03
Abnormal	15 (50)	21 (70.0)	

Several earlier studies have explored the anticonvulsant effects of melatonin in pediatric epilepsy, though most were limited by small sample sizes or secondary seizure outcomes. Goldberg-Stern et al. reported a major reduction in frequency of seizures in a double-blind placebo-controlled crossover study; however, their study included only 12 patients, with a follow-up duration of three weeks.[11] Similarly, Peled and other authors observed improvement in seizure frequency in younger participants with epilepsy treated with melatonin over three months, but the study involved only six participants.[12] Jain et al. reported favorable outcomes in seizure frequency; however, their cohort did not include children with refractory epilepsy, limiting comparability with the present study.[13]

Other randomized controlled trials evaluating melatonin primarily targeted sleep disorders rather than seizure outcomes. Hancock et al. and Coppola et al. documented no significant change in seizure count, possibly due to heterogeneous study populations, inclusion of seizure-free participants, or seizure frequency not being a primary endpoint.[14,15] Ameta-analysis from 2016 also concluded that evidence was insufficient to establish a definitive role for melatonin in seizure reduction, largely due to methodological limitations and inconsistent outcome measures across studies.[16]

Similarly, adult studies have shown pronounced anticonvulsant effects of melatonin. Verma et al. demonstrated a significant reduction in seizure frequency in adults with epilepsy melatonin treatment in addition to valproate.[10] These findings align with the present study and support generally accepted hypothesis that melatonin exerts antiepileptic effects when used as adjunctive therapy.

The anticonvulsant properties of melatonin are believed to be mediated through its action on MT1 and MT2 receptors, leading to inhibition of neuronal excitability.[17] Melatonin also enhances gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, modulates calcium channels, and stabilizes neuronal membrane potentials. Experimental animal models have further confirmed its anticonvulsant and neuroprotective properties.[18] These mechanisms likely contribute to the observed reduction in seizure severity and improved EEG findings in the present study.

EEG normalization was significantly greater in the melatonin group in contrast to other study group, portraying a potential beneficial effect on underlying epileptiform activity. Although EEG changes were

not the primary outcome, this finding strengthens the evidence for melatonin's neurophysiological impact. Similar EEG improvements have been inconsistently reported in previous pediatric studies, possibly due to shorter follow-up durations or lack of standardized EEG assessment.[19]

Although not reported but Melatonin was well tolerated in our study. Only minor adverse effects were reported, including transient vomiting and daytime sleepiness, none of which required discontinuation of therapy. These findings go hands in hands with established safety profile of melatonin reported in earlier pediatric and adult studies.[20] Given the absence of serious adverse events, melatonin can be claimed as suitable as an adjunctive treatment in children.

Despite its strengths, the present study has certain limitations, including a relatively small sample size and a short follow-up period of 12 weeks. Drug serum levels were not monitored, and EEG follow-up was limited to a single post-treatment assessment. Additionally, sleep quality, which may influence seizure control, was not formally assessed. These limitations should be addressed in future studies by incorporating larger sample sizes, extended follow-up periods, and a wider range of outcome measures.

CONCLUSION

Precisely speaking, our study demonstrates that melatonin, when used as an adjunct to first-line antiepileptic therapy, significantly reduces seizure severity and improves seizure control in pediatric patients with generalized epilepsy, with a favorable safety profile. Melatonin may therefore be considered a useful adjunctive option in children with inadequate seizure control on standard therapy. Further large-scale randomized controlled trials are recommended to confirm these findings and to explore the long-term benefits and optimal dosing strategies of melatonin in pediatric epilepsy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Safiullah:** Writing, data collection, analysis.
2	**Sadia Riaz:** Proof reading.