Melatonin vs. Clobazam for Preventing Recurrent Simple Febrile Seizures: A Randomized Clinical Trial

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Abstract- Febrile seizures are the most common neurologic disorder in infants and young children. Febrile seizures generally have a good prognosis, but approximately one-third of patients may experience a second attack. This study was conducted to assess the effectiveness of melatonin in preventing the recurrence of subsequent seizures. In this prospective randomized clinical trial study, 60 children with febrile seizures were enrolled in two groups of 30. Clobazam was administered to the control group, while melatonin was given to the intervention group for prophylaxis. Over a 12-month telephone follow-up, the number of febrile illnesses and seizure attacks, as well as drug side effects, was recorded of the 60 children included in this study, 56.7% were boys. The mean age of the participants was 30.22±11.69 months. Seven patients experienced febrile seizures after receiving prophylactic medication, including three patients in the melatonin group and four in the clobazam group. This difference was not statistically significant (*P*=1.00). Additionally, only two patients in the control group experienced sleepiness. Melatonin may be effective in preventing recurrent febrile seizure episodes without any serious side effects. Iranian Registry of Clinical Trial (IRCT20221102056380N1).

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Introduction

Febrile seizures are the most common neurologic disorder in infants and young children, affecting approximately 2-4% of children aged 6 months to 5 years (1). Diagnostic criteria for febrile convulsions include convulsions occurring with a temperature above 38° C, age between 6 and 60 months, the absence of infection or inflammation in the central nervous system, the absence of acute systemic metabolic problems, and a lack of previous convulsions without fever (2,3). Most febrile seizures are classified as simple febrile seizures, characterized by generalized seizures lasting less than 15 minutes and not recurring within a 24-hour period. While febrile seizures generally have a favorable prognosis and do not result in any neurological sequelae, it is noteworthy that around 35% of febrile seizure patients may experience a second recurrent febrile seizure (4).

At present, the primary treatment for febrile seizures worldwide is reassurance. However, owing to the recurring nature of the condition and the associated risks of aspiration and injury to the child, the parents of children with febrile convulsions often experience worry and anxiety. This concern may warrant the consideration of prophylactic measures for children, particularly those with a higher risk of recurrence (5).

Currently used prophylactic medications such as clobazam, diazepam, valproic acid, and phenobarbital can

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be effective but are often limited by their side effects, including sedation, behavioral changes, and the potential for cognitive impairment, especially with long-term use (6-10). These adverse effects, coupled with the need for prolonged administration, highlight the necessity for alternative therapies that are both effective and better tolerated.

Melatonin, a hormone naturally produced by the pineal gland, has gained attention due to its neuroprotective, antioxidant, anti-inflammatory, and anticonvulsant properties (11,12). Unlike conventional antiepileptic drugs, melatonin is associated with a favorable safety profile and minimal adverse effects, making it a promising candidate for the prophylaxis of febrile seizures. Although several clinical studies have reported melatonin's anticonvulsive effects in epileptic patients, only a limited number have specifically assessed its efficacy in preventing recurrence of simple febrile seizures (13,14).

The primary aim of this study was to assess the effectiveness of melatonin in comparison to clobazam for preventing the recurrence of subsequent attacks of simple febrile seizures.

Materials and Methods

Study design

This study was a prospective randomized clinical trial. The study population comprised children aged 12-60 months who experienced a second simple febrile seizure and were referred to Bahrami Children's Hospital within a two-year period, spanning from October 2020 to October 2022.

The inclusion criteria for this study encompassed children aged twelve to sixty months who had a history of two simple febrile seizures and had not received any prophylactic treatment. The exclusion criteria for this study consisted of children with developmental delays, a central nervous system infection, or a positive family history of epilepsy. Additionally, patients who did not receive the drugs regularly or did not experience any febrile illness during the study were also excluded from the study.

Sample size

The sample size for each group, as determined by previous studies, was set at 30 (13,15,16).

Intervention

For this study, a checklist was prepared to record demographic data, including age, gender, the number of fever episodes (without seizures) and seizures, as well as any drug side effects. Initially, written informed consent was obtained from the parents of eligible children who expressed a desire to initiate medication for the prevention of febrile convulsions during subsequent febrile illnesses. The patients in the study were randomized into two groups alternately using a simple random method. One group received melatonin, while the other group received clobazam for prophylaxis. The treatment regimen involved administering the assigned medication during the first 48 hours of the next Febrile illness. Melatonin (manufactured by Razak Iran) was prescribed at a dose of 0.3 mg/kg every 8 hours. Clobazam (manufactured by Hakim Iran) was prescribed at the following dosages based on the child's weight: ≤5 kg: 1/4 of a tablet, 5-10 kg: 1/2 of a tablet, 10-15 kg: 3/4 of a tablet, and >15 kg one tablet every 12 hours. Over a 12-month period, parents were contacted via telephone for follow-up at 6 and 12 months after the initiation of the intervention. During these follow-up calls, data on the number of febrile illnesses and seizure attacks, as well as any drug-related side effects, including drowsiness, sleep disorders, imbalance, and vomiting, were recorded.

The primary outcome of the study involved assessing the drug's effectiveness in preventing the recurrence of subsequent attacks of simple febrile seizures. The secondary outcome of this study focused on evaluating the side effects associated with the drug.

In this study, prophylactic drug treatment was administered to the patients with their consent, without imposing any additional costs. The patients' data was confidential. This study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1399.168). It was also registered in the Iranian Registry of Clinical Trial (IRCT20221102056380N1).

Statistical analysis

The data was analyzed using the SPSS statistical software. Quantitative variables are reported as mean and standard deviation, while variables are reported as frequency and percentage. If the variables exhibited a normal distribution, the T-test was utilized for analysis; otherwise, non-parametric tests were applied. The relationship between qualitative variables was examined using the chi-square test or, when necessary, Fischer's exact test. *P* less than 0.05 were considered statistically significant.

Results

A total of 65 patients were initially included in the study. However, three patients were excluded for not accepting the study protocol, and two patients were excluded due to the impossibility of follow-up. Ultimately, the study enrolled a total of 60 eligible children who were randomly assigned to two groups of 30. Notably, all 60 enrolled patients successfully completed the study (Figure 1). Of the patients included in the study, 56.7% were male (n=34). The mean age of the patients was 30.22±11.69 months (range: 12-53 months). In terms of age and gender distribution, there was no statistically significant difference between the two groups (*P*=0.686 and *P*=1.00, respectively). The mean body temperature of the patients was 39.2˚ C in melatonin and 39.0˚ C in the clobazam group. The mean number of fever episodes was 3.50±1.61 times in the melatonin and 3.73±1.55 times in the clobazam group. After the treatment, febrile seizures occurred on average at 207.57±90.38 days, with the shortest interval being 65 days and the longest 326 days. In total, seven patients (11.7%) experienced febrile seizures after receiving prophylactic medication, including three patients were in the melatonin and four patients in the clobazam group. This difference was not statistically significant (*P*=1.00). Two patients (3.3%) in the clobazam group experienced sleepiness as a side effect of drug consumption. Detailed demographic characteristics of the patients are presented in Table 1.

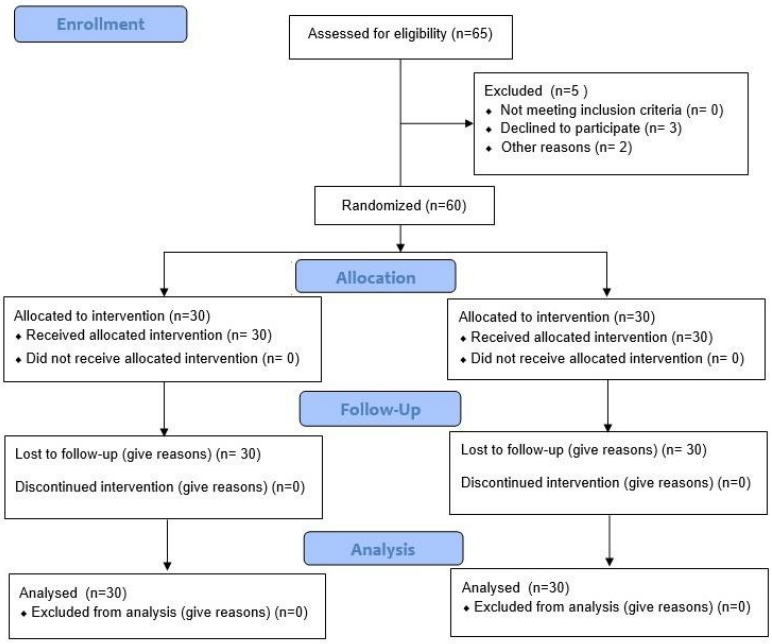

Figure 1. CONSORT Flow Chart of the patients

Table 1. Demographic characteristics of the studied patients (n=60)

Variables		Prophylactic agent		*P*
		Clobazam	Melatonin	
Age (Month)		30.83± 11.47	29.60± 12.06	0.686
Gender	**Male**	17 (56.7%)	17 (56.7%)	1.00
	Female	13 (43.3%)	13 (43.3%)	
Fever Degree		39.0	39.2	0.653
Fever episode number		3.73±1.55	3.50±1.61	0.570
Seizure After Prophylaxis		4 (13.3%)	3 (10.0%)	1.00
Seizure interval after prophylaxis (days)		173.25±80.492	253.33±96.381	0.283
Drugs side effect		2 (6.6%)	0 (0.0%)	0.492

Discussion

Febrile seizures are the most common disorder in children. While these seizures generally have a very good prognosis, the possibility of subsequent convulsions can leave many parents and families in a state of anxiety and worry for years after the first occurrence. Prophylaxis has, therefore, played a pivotal role in managing this

condition. According to the literature, daily phenobarbital has been the drug of choice for preventing febrile seizures for over two decades (17). Subsequent studies suggested intermittent diazepam as a prophylactic measure in febrile attacks (7). In the following years, safer drugs were introduced. One of these drugs is clobazam, which has demonstrated positive impacts with minimal side effects (9,15,16,18-20). Melatonin has also been reported as an anticonvulsant agent in patients with epilepsy (11,21). Some studies used melatonin in combination with diazepam or phenobarbital to reduce the frequency of seizures in epileptic children (11). Recently, melatonin has been added to the above drug list, although the studies in this area remain limited (13,14).

Several studies have confirmed the efficacy and safety of clobazam and melatonin in preventing the recurrence of febrile seizures. However, based on a review of the literature, no study has compared these two drugs. The present study was conducted with the aim of investigating the effectiveness of melatonin compared to clobazam for the prevention of febrile seizures. The results showed that both drugs were effective in preventing febrile seizures. No significant difference was found between the groups in terms of the time interval between the occurrence of febrile seizure and receiving prophylaxis and the degree of fever. On the other hand, no serious side effects were seen in any of the groups. However, about 3% of patients taking clobazam reported drowsiness, indicating no statistically significant difference between the two groups.

Currently, the mainstay of treatment for febrile seizures is reassurance (6).

A study by Assawabumrungkul *et al*., showed that melatonin is effective in preventing the recurrence of febrile seizures compared to the control group, which is consistent with the results of the present study (14). Similarly, no side effects were reported in the above study (14).

In 2019, Barghout *et al*., evaluated the efficacy and safety of oral melatonin compared with oral diazepam for the prevention of recurrent febrile seizures. They found that the recurrence rate of febrile seizures was 17% in the melatonin group and 37% in the diazepam group, indicating no significant difference between the two groups. Both melatonin and diazepam significantly reduced the recurrence of febrile seizures and no serious side effects were reported with the use of melatonin (13). These findings are similar to the results of the present study, suggesting that both drugs are effective in preventing febrile seizures without any complications.

The present study demonstrated no significant difference between clobazam and melatonin, with both effectively reducing febrile seizure recurrence when administered from the onset of fever. No serious adverse effects were reported for either drug. Given melatonin's favorable safety profile and minimal side effects, it represents a promising alternative to conventional prophylactic medications for preventing febrile seizures, particularly in settings where access to standard drugs may be limited. Additionally, having an alternative prophylactic option like melatonin is valuable for patients or families who may be reluctant or unable to use clobazam, thereby enhancing overall treatment flexibility and adherence. Further large-scale studies are warranted to confirm these findings and further define melatonin's role in clinical practice.

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