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Original article

Efficacy of melatonin for febrile seizure prevention: A clinical trial study

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ABSTRACT

Background: Prophylactic treatment for recurrence of febrile seizure generally consists of intermittent administration of diazepam or clobazam, or long-term treatment with valproic acid or phenobarbital. However, the adverse effects outweigh the benefits. A newer, effective, more tolerable drug treatment is warranted.

Objective: To study melatonin efficacy in prevention of recurrence of one or more episodes of either simple or complex febrile seizure compared to a control group.

Methods: A quasi-experimental study in children who were diagnosed with febrile seizure in Bhumibol Adulyadej Hospital, between 6 months to 5 years old, divided into two groups, melatonin group and control group, depending upon parental convenience. Melatonin was given 0.3 mg/kg/dose every 8 hours for 48 to 72 hours during febrile illness to melatonin group if body temperature was more than 37.5 °C. Control group had no medicine. Patients were followed at 3 and 6 months.

Results: The study included 23 patients in the melatonin group and 41 in the control group. Mean age of diagnosed of febrile seizure onset was 17.3 and 21.6 months, respectively. In the melatonin group, 8.7% of patients had recurrent febrile seizure compared to 36.6% in the control group, which is statistically significant (*P-value* 0.015, RD −0.28(95%CI: −0.46 to −0.09)). There was no statistically significant difference in adverse effects between the two groups.

Conclusion: This study demonstrates the efficacy and safety of short-term melatonin use to prevent the recurrence of one or more episodes of either simple or complex-febrile seizure in children.

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1. Introduction

Febrile seizure is the most common etiology of seizure in children [1,2]. The prevalence of febrile seizure is approximately 2-4% in children between 6 months to 6 years old [1–4]. Most febrile seizure events are simple febrile seizure and occur only 1 time during the first 24 hours after fever onset. Despite the fact that febrile seizure has a good prognosis and does not have any neurological sequelae, approximately 35% of febrile seizure patients experience a second recurrent febrile seizure [1]. Only 2% of febrile seizure patients develop epilepsy. The risk factors for epilepsy after febrile seizure are epilepsy in family, neurological abnormalities and complex febrile seizure [5].

At the present, the principal treatment of febrile seizure worldwide is reassurance. However, at noticed above, one-third of the patients will develop second febrile seizure episode. Febrile seizure is not a benign condition, particularly upon recurrence. There are risks of aspiration and injury to the child. Rescue benzodiazepine given outside healthcare facilities is uncommon in Thailand. A meta-analysis showed antiseizure medications specifically diazepam and clobazam, are currently used as an intermittent febrile seizure prophylaxis with effectiveness [5]. Despite their effectiveness, antiseizure medications also have side effects, namely dizziness, sedation, ataxia and irritability which some patients cannot tolerate [5–8]. Given concerns over the side effects of antiseizure medications, a newer drug treatment which is effective and has lower side effects and is common available is warranted. Therefore, authors have selected melatonin for preventing febrile convulsion based on the evidence in previous animal and clinical studies. There are a few clinical studies reported melatonin as an anticonvulsive agent in epilepsy patients [9,10]. In addition, melatonin has been used in combination with diazepam or phenobarbital to decrease seizure frequency in epileptic children [9]. However, there was only one study that evaluated melatonin efficacy in preventing second recurrence of simple febrile seizure. The instant study evaluates melatonin efficacy in the prevention of

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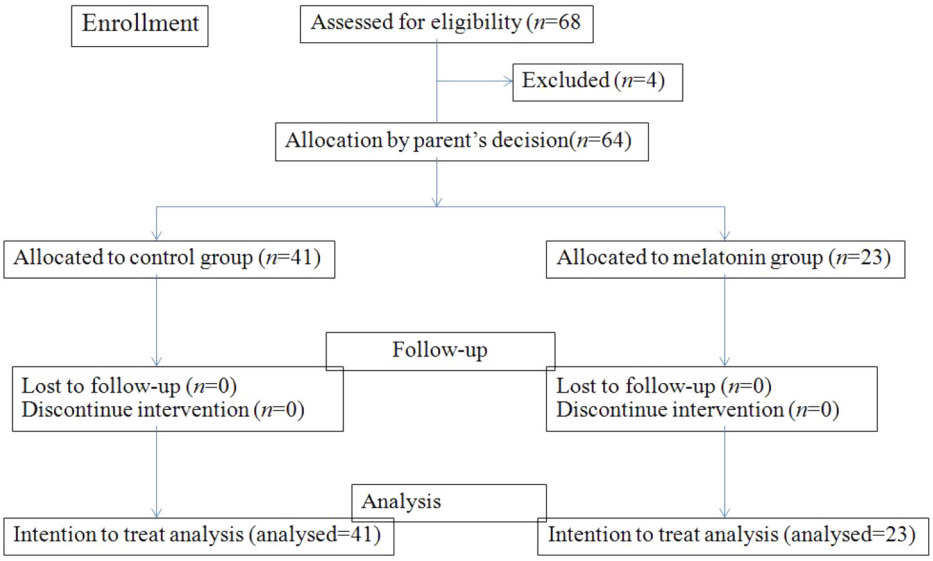

Fig. 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trial.

the recurrence of any episode of either simple or complex febrile seizure compared to a control group.

2. Methods

2.1. Study design

The present study was a quasi- experimental study and was conducted in a single center. The study was conducted following ethical guidelines from the institutional ethic committee of BAH. Informed consent was obtained from one parent of all participants.

2.2. Study population

Patients attended Bhumibol Adulyadej hospital (BAH), both from in-patient and out-patient departments, who were diagnosed with febrile seizure and enrollment was done considering the inclusion criteria. The recruitment was during the period from August, 2018 to October, 2020.

2.2.1. Inclusion criteria

All recruited patients were diagnosed with simple or complex febrile seizure in any number of episodes. The first diagnosed of febrile convulsion was made between 6 months and 5 years of age.

2.2.2. Exclusion criteria

Patients with abnormal neurological examination (e.g. focal neurological deficit), delayed milestone or previous abnormal EEG; patients who receiving antiseizure medication for febrile seizure prophylaxis; patients whose parents declined to give consent were excluded from the study.

2.3. Allocation

Recruited patients were divided into two groups: the melatonin group and the control group. Parents chose which group their child would be enrolled in.

2.4. Study procedure and data collection

Patient data, including age, sex, age at first febrile seizure onset, type of febrile seizure, duration of febrile seizure, fever degree at febrile seizure onset, family history of febrile seizure and epilepsy were collected from in-patient and out-patient department records. Subject patients were fully examined by pediatricians who recorded neurological signs and development, including gross motor, fine motor, social and language aspects.

In the melatonin group, patients who subsequently develop a fever were given melatonin (Circadin®) 0.3 mg/kg/dose every 8 hours for 48 to 72 hours during febrile illness as a febrile seizure intermittent prophylaxis. Parents were advised of how many Circadin® tablets to take when the fever was greater than 37.5 °C (Omron digital thermometer MC-246). Melatonin usage guidelines and febrile seizure event record forms were provided to the melatonin group. The control group received only the same thermometer and recurrent febrile seizure event record forms. Both groups were advised not to take any medication or food supplement other than acetaminophen syrup or other medicine prescribed by the BAH Pediatrics Unit. At 3 and 6 months after patients were included in the study, recurrent fever episodes and febrile seizure events were reviewed during out-patient visits or by telephone interview. (Fig. 1)

2.5. Study outcome measures

- Recurrent rate: The primary outcome measure of the study was the recurrent seizure rate. In the present study, recurrent febrile seizure was calculated by number of patients who had recurrent febrile seizures divided by total patients in that group. Every patient in our study had similar follow-up period at 6 months and we assumed every patient would be at similar risk during follow-up period. The other method to calculate recurrent febrile seizure is number of occurrence of febrile seizure divided by total number of febrile illness. This method has to do multiple logistic regressions. Therefore, this method is not chosen.

- The occurrence of adverse effect was reported based on self-reporting by the parents and by nondirective questioning in the follow-visit in OPD department or by telephone interview. Parents were given a form for recoding their observations of the effect of melatonin on their children. The severity of adverse events was evaluated by using WHO toxicity grading scale. The study drug was discontinued only if the patients developed Grade 3 or 4 adverse reactions.

Table 1
Demographic and clinical characteristics of the study population.

	Melatonin (n=23)	Control (n=41)	P-value	95%CI****
Sex*			0.43	0.24 to 1.86
Male	43.50(10)	53.70(22)		
Female	56.50(13)	46.30(19)		
Age at onset of FS** (month)***	17.30 ± 10.37	21.60 ± 10.34	0.51	−9.74 to 1.13
Number of febrile illnesses*	19 (82.6)	30 (73.2)	0.038	0.55 to 7.01
Degree of fever (Celsius)***	39.29 ± 0.60	39.62 ± 0.59	0.28	−0.78 to 0.61
Type of FS**			0.83	0.30 to 4.34
Simple*	19(82.61)	33(80.49)		
Complex*	4(17.39)	8(19.51)		
Number of FS**			0.74	0.21 to 2.67
First FS*	18(79.17)	34(82.93)		
Second FS*	5(20.83)	7(17.07)		
Seizure duration (minute)***	1.97 ± 1.15	2.35 ± 1.21	0.36	−1.07 to 0.19
Family history*				
FS**	6(26.08)	11(26.82)	0.94	0.30 to 3.07
Epilepsy	0(0)	0(0)		

* n(%)
** FS: febrile seizure(s)
*** Mean ± SD
**** CI: confidence interval

2.6. Definitions

Febrile seizure is divided into 2 groups: simple and complex. Simple febrile seizure is characterized by a generalized seizure less than 15 minutes long, seizure does not recur within 24 hours and there is neither focal neurological deficit nor Todd paralysis after seizure. Complex febrile seizure is a focal or prolonged seizure lasting more than 15 minutes or recurring within 24 hours or resulting in either focal neurological deficit or Todd paralysis.

2.7. Sample size

The research question was whether melatonin reducing the recurrent febrile seizure. The hypothesis was melatonin reducing the recurrent febrile seizure and no or mild adverse effect from melatonin. Sample size calculation were based on a 2-side x^2 test for detecting a different between 2 proportions, assuming a type 1 error of 0.05, with a sample size of 18 subjects receiving melatonin and 36 subjects in control group (ratio 1:2). The study had 80% power to detect a difference 40% in risk of recurrent febrile seizures.

2.8. Statistical analysis

Data analysis used IBM Statistical Package (SPSS) version 27. Continuous data were presented as the mean+/-S.D., whereas categorical data were presented as number and percentage. Comparison between the melatonin and control groups was performed using unpaired t test for continuous data and chi-square test for categorical data. Melatonin efficacy in febrile seizure prevention used intention to treat analysis. The melatonin group was compared to the control group by relative risk, significant at p-value < 0.05.

3. Results

Sixty-eight patients diagnosed with febrile convulsion were originally enrolled by eligibility criteria. Four were excluded because of their delayed development. Ultimately, the study enrolled 64 children, where 23 children were enrolled in the melatonin group and 41 in the control group, a ratio of 1:2. No subjects were lost during the follow-up period of this study because follow-up by telephone interview was used.

There were 10 male, 13 female and 22 male, 19 female subjects in the melatonin and control groups respectively (Table 1). The mean age of diagnosing febrile seizure onset was 17.3 months in the melatonin group and 21.6 months in the control group with no statistical significance between the two groups (p-value 0.51). Over 6-month follow-up period, febrile illnesses occurred 82.6% in the melatonin group and 73.2% in the control group with no statistical significance. None of the patients had 2 febrile illnesses. The mean fever degree in the melatonin and control groups was 39.29 °C and 39.62 °C, respectively, with no statistical significance between them (p-value 0.28). Both groups consisted of either simple or complex febrile convulsion with no statistically significant difference between the groups (p-value 0.83). Both groups had patients diagnosed with either first or second febrile seizure before they were included in the study, with no statistically significant difference between the groups (p-value 0.74). There was no statistical difference (p-value 0.36) between the mean seizure duration in the melatonin group (1.97 min) and the control group (2.35 min). Family history of febrile seizure was found in 26.08% and 26.82% in the melatonin and control groups, respectively, with no statistical significance (p-value 0.97). No family history of epilepsy was recorded in any of the patients in this study.

At 3- and 6-month follow-up, only 2 patients in the melatonin group had recurrent febrile seizure, compared to 15 patients in the control group (8.7% and 36.6% respectively) with a statistically significant difference (*P-value* 0.015, RD −0.28(95%CI: −0.46 to −0.09)), Table 2). In summary, prophylaxis treatment with melatonin causes a lower relative risk of recurrence of febrile seizure (RR 0.24(95%CI: 0.06 to 0.95)) compared to the control group. Both of these patients in melatonin group who had recurrent febrile seizure were diagnosed with second febrile seizure. They received melatonin when the fever was discovered. However, one had a seizure a half an hour after receiving melatonin, and the other had a seizure one hour after melatonin was given.

Adverse effects of melatonin were recorded. Adverse effects in the melatonin group compared to the control group were drowsiness (17.39% and 14.28%, p-value 14.28), dizziness (8.69% and

Table 2
Febrile seizure recurrent rate and adverse effects of melatonin.

	Melatonin (n=23)	Control (n=41)	*p*-value	RD** (95%CI)***
Recurrence*			0.015	0.24(0.06 to 0.95)
Yes	2 (8.7)	15(36.6)		
No	21 (91.3)	26(63.4)		
Adverse effect*				
Dizziness	2(8.69)	2(4.87)	0.54	
Drowsiness	4(17.39)	6(14.28)	0.77	
Vomiting	1(4.34)	0 (0)	0.17	
Headache	1(4.34)	3(7.31)	0.63	

* n(%)
** Risk difference
*** CI: confidence interval

4.87%, *p*-value 0.54), vomiting (4.34% and 0%, *p*-value 0.17) and headache (4.34% and 7.31, *p*-value 4.34). There was no statistically significant difference in adverse effects between the two groups (Table 2).

4. Discussion

Melatonin is a hormone found naturally in the body and has been reported as a neuroprotective, antioxidant, anti-inflammatory and anticonvulsive agent [9,11,12]. The relationship of melatonin and epilepsy even though not fully understood, has long been recognized [13]. The pharmacodynamics of anticonvulsant property of melatonin was demonstrated in induced hyperthermia in rats, by inhibition of excitatory neurotransmitter effect by decreasing GABA receptor activity [14,15]. In a recent study, the mechanism of both sleep and circadian rhythm in epilepsy was disrupted through clock genes, epigenetic regulator SIRT1 and gamma-aminobutyric acidergic (GABAergic) tonic inhibition [16]. It has been reported that basal melatonin levels were found to be lower in patients with epilepsy and/or febrile seizures compared with a healthy control group, and following the onset of seizure activity, the level of this hormone rises sharply in a reactive way [17–19]. In contrast, there were studies stating that melatonin has proconvulsant properties, because melatonin was found to be at higher levels during the hours with higher seizure frequency [20,21]. The pharmacokinetics of melatonin show the bioavailability ranged from 9-33%, in children, depending on age and feeding status [22].

Most of the literature found an association between decrease in clinical seizures and use of melatonin [23]. Melatonin has been used in combination with diazepam or phenobarbital to decrease seizure frequency in epileptic children [10]. Some pediatric clinical trials concluded that melatonin could be effective and safe for decreasing seizure frequency and severity in patients with epilepsy and has the potential to improve quality of life because of its beneficial effect on sleep, wide safety window, and the ability to cross the blood-brain barrier and neuroprotective due to antioxidant property [24–27]. However, there was only one study that evaluated melatonin efficacy in preventing a second recurrence of simple febrile seizure [1]. To our knowledge, melatonin efficacy for prevention of any recurrence of either simple or complex febrile seizure has not been investigated. Therefore, this article evaluates the efficacy of melatonin to prevent recurrence of one or more episodes of either simple or complex febrile seizure compared to a control group.

The etiology of febrile convulsion is likely multifactorial from viral illnesses, certain vaccinations, and genetic predisposition. These factors may affect a vulnerable, developing nervous system under the stress of a fever [8]. The strong independent predictors of recurrent febrile seizures are young age of onset, a history of febrile seizure in a first-degree relative, low degree of fever wile in the emergency department and brief duration between the onset of fever and the initial seizure [28]. According to the Barghout study, approximately 35% of febrile seizure patients experience a second recurrent febrile seizure [1]. Our recurrent febrile seizure rate in the control group was 36.6%, no difference from that reported in other studies.

The Barghout study compared melatonin efficacy with the use of diazepam as an intermittent prophylaxis for febrile seizure [1]. This study found both to be equally effective. However, diazepam was not routinely recommended as a prophylaxis for febrile seizure because of its adverse effects [1,29]. Our study also found melatonin was an effective febrile seizure preventative. Recurrent febrile seizure rate in the melatonin group in Barghout's study was 16.6% [1], whereas in the present study it was 8.7%. Barghout's melatonin group was composed 60% of children under 12 months old and 50% of children with family history of febrile seizure, while this current study had children with 30% and 20%, respectively. Having a subject population with a lower percentage of young age and family history of febrile seizure explains the lower recurrent febrile seizure rate in our study.

Melatonin adverse effects of vomiting, drowsiness and headache were reported in the literature at a rate of 14.7% [1], whereas in the present study these same symptoms were reported in the melatonin group at a rate of 34.8% and in the control group at a rate of 26.5%. The difference in the rate between the melatonin and the control groups was not statically significant. Therefore these adverse effects reported in the melatonin group cannot be solely attributed to melatonin.

When compared to intermittent diazepam and continuous phenobarbitone febrile seizure prophylaxis adverse effects, generally reported in the literature at a rate of 30% [29], total adverse effects of melatonin in this study are occurred at about the same rate (34.8%). Serious adverse effects of melatonin such as ataxia or hyperkinesia were not reported in this study.

Parents of the patients of the melatonin group reported satisfaction in using melatonin as febrile seizure prophylaxis. Many mentioned excellent results from the first dose. Their children became relaxed and rested well. These parents had had a hard time caring for their children when previous febrile seizure episodes occurred. Anecdotally they reported a reduction in their stress after using melatonin which they believed prevented further febrile seizures.

In the present study, there are certain limitations. First, the parents self-selected whether their children would be placed in the melatonin group or the control group. We suspect the parental choice was influenced by lack of knowledge about melatonin. This study will be only the second study to support the use of melatonin to prevent the recurrence of one or more episodes of either simple or complex febrile seizure. The second limitation was that the 6- month follow-up period was too short, but it was chosen because in the authors' clinical experience, febrile illness is likely to recur in young children within 6 months. In the present study, febrile incidents during follow-up period occurred only 76.6% of the time. A longer period of time would likely have resulted in more episodes in both groups which then would have been included in the study. In addition, there are insufficient data concerning the safety and efficacy of long-term melatonin use in children [30]. Further studies with longer follow-up period are needed to confirm the usefulness and safety of long-term melatonin use for preventing recurrent febrile seizure in children.

5. Conclusion

This study demonstrates the efficacy and safety of short-term melatonin use to prevent the recurrence of one or more episodes of either simple or complex febrile seizure in children. We recom-

mend the use of melatonin for preventing recurrent febrile convulsion especially in high-risk patients where caregivers have express concern about, or actually already seen, the adverse effects of diazepam in their children.

Ethical approval

This study was approved by Bhumibol Adulyadej Hospital Ethics Committee.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Declaration of competing interest

The authors declare that they have no known competing financial or personal relationships that could be viewed as influencing the work reported in this paper.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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