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EFFICACY OF MELATONIN VERSUS DIAZEPAM INTERVENTION IN REOCCURRENCE OF SIMPLE AND COMPLEX SEIZURE

Mubasher Rasheed[*1], Afshal Ali[2], Musawar Rasheed[3], Farah Ahmad[4], Hassan Danish[5]

*[*1]PGR, Social Security Hospital Multan Chungi, Lahore*
[2]Registrar, Fatima Memorial Hospital, Lahore
[3]Medical Officer, Arif Memorial Hospital, Lahore
[4]Program Director, MCPH-HCSM, College of Physicians & Surgeons Pakistan, Karachi
[5]Mentor, MCPH-HCSM, College of Physician & Surgeons Pakistan, Karachi

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Corresponding Author: *
Mubasher Rasheed

Abstract

Objective: *The objective of this study was to determine the efficacy of melatonin vs diazepam in the prevention of reoccurrence of simple and complex seizure*

Study Design: *A hospital based randomized controlled study.*

Place and Duration: *The study was conducted in Social Security hospital Shahdara, Lahore within a duration of six months.*

Methods: *Children of age 6 months to 5 years, male or female of any age, patients with history of at least one febrile Seizure, Normal neurological examination and Presenting with high grade fever (≥100°F) were included in this study group. Total 148 subjects were included in this study. The patients were divided into two groups. In group A, patients were given oral melatonin 0.33mg/kg dose every 8 h for 2 days while in group B, patients were given oral melatonin 0.3mg/kg every 8 h for 2 days. After treatment the recurrence of Febrile seizures was noted in both groups.*

Data was analysed by using SPSS Statistic version 27. Mean and standard deviation were calculated for quantitative variables while frequency and percentages were reported for qualitative variables. Chi-square/fisher exact test was applied to determine association between variables. P-value less than 0.05 was considered as significant.

Results: *The mean age of the patients was 31.41±16.22 months, 69(46.62%) patients were males at 48 hours. In oral melatonin the Febrile seizure were noted in 14(18.9%) patients while in oral diazepam group the Febrile seizures were noted in 5(6.8%) patients (p- value=0.027).*

Conclusion: : *This study concluded that the oral melatonin is more effective and significantly better than oral diazepam in preventing recurrence of febrile seizures in children presenting with fever.*

INTRODUCTION

Febrile seizure or febrile convulsion is associated with a high-grade fever without any underlying CNS infection, metabolic imbalance, or history of seizure without fever. Febrile seizures occur in children with age ranging between six months and five years and has a fever higher than 100.4°F (38°C) [1]. The duration of most seizures last for less than 5 minutes within an hour of the seizure episode and the child

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in entirely normal [1, 2].There are two types of febrile seizures: simple febrile seizures & complex febrile seizures. Simple febrile seizures (a tonic-clonic seizure of less than 15 minutes in a 24-hour period) occur in an otherwise healthy child. However, the differentiating features of complex febrile seizures may include localized seizures, duration longer than 15 minutes, or multiple seizure events within 24 hours. 80% of all febrile seizures in children are simple febrile seizures [3, 5, 6]The diagnostic criteria entail absence of CNS infections, metabolic disturbances and prior afebrile seizure. Extensive blood testing, CNS imagining, or an EEG is generally not recommended [3,5,7,8].

The prevalence of febrile seizures ranges between two to five percent exists in children less than 5 years of age [4]. They affect males predominantly [5]. The chance of recurrence following a single febrile seizure is 15-70%.[4] There is an approximate chance of experiencing another seizure in the following 2 years after a febrile seizure is 36% and the risk is inversely related to the age of the children [5].

Most preponderant cause of febrile seizures is viral illnesses. Febrile convulsions have a tendency of familial disposition. The risk of febrile seizures in siblings of a patient of febrile seizure is 10%. It is enhanced to 50% with a positive parental history of febrile seizures as well [15]. Some other causes include a previous family history of febrile seizures, fever (mostly high grade), motor mental delays, perinatal illness requiring hospitalization, daycare attendance. There is a two-fold increased risk of febrile seizures in children of mothers who consumed alcohol or smoked during pregnancy [9].

There are no long-term adverse outcomes of febrile seizures i.e., intellectual abilities and behavior remain normal. However, these children carry a higher risk of developing epilepsy than general populace. A study has showed that risk is 2% at 5 years, 4.5% at 10 years, 5.5% at 15 years and 7% at 25 years [10,11,12].

Febrile seizures carry a good prognosis but the high probability of recurrence adds to anxiety and concern of families' following the first seizure episode. Children with high risk of recurrent febrile seizures may be treated with intermittent prophylaxis [13].

The management of febrile seizure comprises of reducing fever through conduction or sponging of the patient, identifying and treating the cause or focus of fever and managing the seizures with anti-seizure therapy in appropriate dosage. The prophylaxis is extenuated with a relatively rate of recurrence (30-50%) and parent's anxiety [14].

Benzodiazepines can be given intermittently through oral, rectal or sublingual route for prophylaxis of febrile seizures. Diazepam is one of the most commonly implied therapeutic agents to prevent recurrence of febrile seizures, however it has adverse effects like drowsiness, ataxia and sedation. Given these facts, melatonin can be used as anti-seizure medication. The adverse effects of melatonin are non-serious like headache, mild sedation, if taken for short period [16,17,18].

Methods and Materials

A Randomized controlled trial was done in Pediatric Medicine Department Social Security Hospital Shahdara, Lahore. It is six months study after getting synopsis approved from 08-01-2019 to 08-07-2019. Sample size of 148 patients (74 patients in each diazepam and melatonin group) was estimated by using 95% confidence level and 10% absolute precision with expected percentage of melatonin group as 5% and diazepam group as 17.5%.

$$\mathbf{n= Z^2_{1-\alpha/2}[P_1(1-P_1)+P_2(1-P_2)] / d^2}$$

$Z^2\ 1-\alpha/2$ = Confidence Level 95% = 1.96

P_{1-} Population Proportion 1= 5%

P_2= Population Proportion 2=17.5%

d= Absolute Precision 10%

Probability random sampling technique was used. Children of age 6 months to 5 years, male or female of any age, patients with history of at least one febrile Seizure, Normal neurological examination and Presenting with high grade fever (≥100°F) were included in this study group. Children with any ongoing CNS infection, history of Afebrile Seizures, neurological abnormalities, Progressive Neurological Diseases (motor neuron disease, multiple sclerosis, muscular dystrophy, multiple system atrophy, Huntington's disease, Parkinson's disease, progressive supranuclear palsy, spinocerebellar ataxias, Epilepsy and On anticonvulsant therapy were excluded from this study design. Patients enrolled in study were admitted in ward of hospital for 48 hours to monitor the patient after administration of trial drug. Researcher provided the drugs to the patients

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enrolled and told them accurate dosage and usage of drugs to have better compliance and at hand availability of the drugs. Then randomly divided into two groups by using lottery method. In group A, patients were given oral diazepam 0.33mg/kg dose every 8 h for 48 hours while in group B, patients were given oral melatonin 0.3mg/kg every 8 h for 48 hours. The medicines were administered only for the first 48 hours of the febrile illness and then discontinued. Standard treatment (anti-pyretic and antibiotics) for resolution of fever was given as per hospital protocol. All parents were trained about using antipyretics and body sponge to keep the intervention similar in both groups. Parents were also trained about recording and reporting the frequency of febrile seizures recurrences. During these 48 hours, children were monitored for febrile seizures and side effects of each drug. All this information was recorded through Performa. The data was entered and analysed through SPSS version 26.0. Continuous variables like age, weight and duration of fever was presented by calculating mean and standard deviation. Categorical variables like gender and febrile seizures were presented by calculating frequency and percentage. Comparison of frequency of recurrence of febrile seizure between two groups was done by applying Chi-square test. P-value ≤0.05 was considered as significant.

Results

In this study total 148 patients were enrolled. The median age of the patients was 30±28 months with minimum and maximum ages of 6 & 60 months respectively. In oral diazepam group the mean age of the patients was 29.92±15.92 months while in oral melatonin group the mean age of the patients was 32.89±16.48 months. Statistically there is insignificant difference was found between the study groups and age. i.e. p-value=0.266. Out of 148 patients, 69(46.62%) patients were males whereas 79(53.38%) patients were females. **Fig 1.**

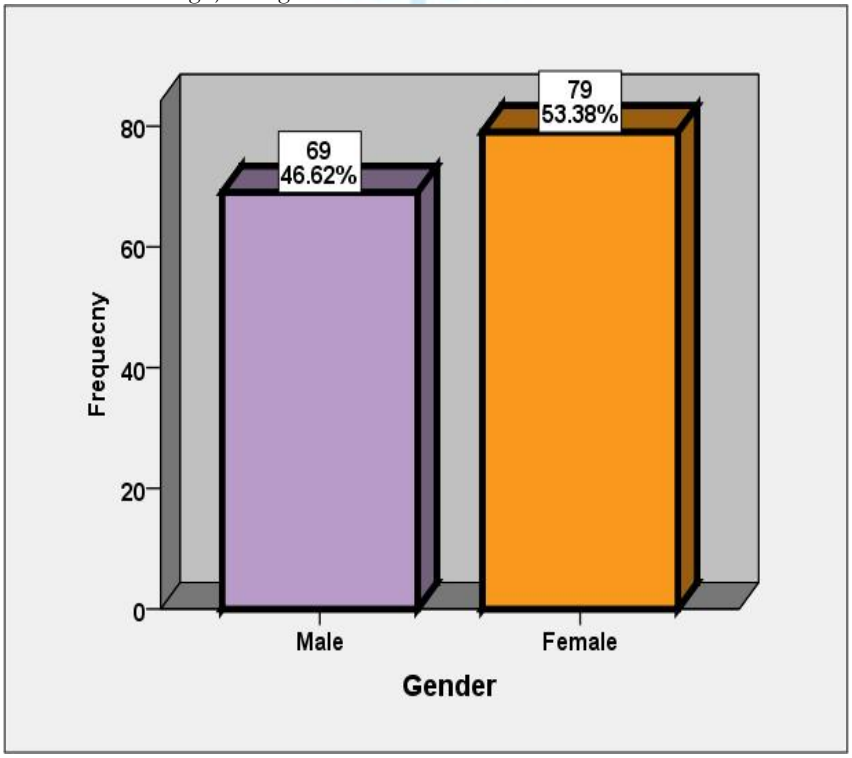

Figure - 1

In oral diazepam group 35(47.3%) patients were male while in oral melatonin group 34 (45.9%) patients were males. Similarly, oral diazepam group 39 (52.7%) patients were females while in oral melatonin group 40(54.1%) patients were females. Statistically there is insignificant difference was found between the study groups and gender. i.e. p-value=0.869. **Table 1**

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Table – 1: Comparison of gender in both groups

(n=148)

		Study Groups		Total	p-value
		Oral diazepam	Oral melatonin		
Gender	Male	35	34	69	0.869
		47.3%	45.9%	46.6%	
	Female	39	40	79	
		52.7%	54.1%	53.4%	
Total		74	74	148	
		100.0%	100.0%	100.0%	

At 24 hours, in oral diazepam group the febrile seizure was noted in 37(50%) patients and in oral melatonin group the febrile seizure was noted in 24(32.4%) patients. This difference was statistically significant. (p-value=0.030). **Table 2**

Table – 2: Comparison of febrile seizure at 24 hours in both groups

(n=148)

Febrile Seizure		Study Groups		Total	p-value
		Oral diazepam	Oral melatonin		
After 24 hours	Yes	37	24	61	0.030
		50.0%	32.4%	41.2%	
	No	37	50	87	
		50.0%	67.6%	58.8%	
Total		74	74	148	
		100.0%	100.0%	100.0%	

At 48 hours, in oral diazepam the febrile seizure was noted in 14(18.9%) patients while in oral melatonin group the febrile seizure was noted in 5(6.8%) patients. At 72 hours a statistically significant difference was identified between the study groups and febrile seizure (p-value=0.027). **Table 3**

Table – 3: comparison of febrile seizure at 72th hour in both groups

(n=148)

Febrile Seizure		Study Groups		Total	p-value
		Oral diazepam	Oral melatonin		
After 48 hours	Yes	14	5	19	0.027
		18.9%	6.8%	12.8%	
	No	60	69	129	
		81.1%	93.2%	87.2%	
Total		74	74	148	
		100.0%	100.0%	100.0%	

Discussion

Febrile seizure is a seizure associated with fever without any evidence of intracranial infection or electrolytic disorder. Its treatment includes anticonvulsant medicines administered for preventing recurrence. Febrile seizures are the most common types of seizure with a prevalence on 3 to 4 percent. They are age dependent and are rare before 9 months and after 5 years of age [19, 20].

In our study in oral diazepam group the mean age of the patients was 29.92±15.92 months while in oral melatonin group the mean age of the patients was 32.89±16.48 months (p-value=0.266). In oral diazepam the 35(47.3%) patients were males while in

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oral melatonin group 34 (45.9%) patients were males. This study has close resemblance with a study by S.Amouian et al [20] . He reported in his study that the mean age was 21.05±10.10 months and 21.96±10.74 months in diazepam and melatonin groups, respectively and 21.49±10.39 in total population. There were 62 males and 56 females in the population.

Another research by Mohammad Sami Barghoout et al [21] conducted a study with enlisting 30 patients in each melatonin and diazepam group. Melatonin group included 15 males and 15 females and the diazepam group included 18 males and 12 females. The study revealed that recurrence rate of febrile seizures was significantly reduced in both groups ($p<0.001$) however no statistically significant difference between two groups. Adverse effects were 13.3 % in melatonin group and 23.3% in diazepam group [14].

Another study has shown that the recurrence of febrile seizures was 8.7 % with melatonin as compared to 36.6% in control group that is statistically significant (p value 0.015). Adverse effects recorded were drowsiness, headache, vomiting, dizziness. However, no statistical significance in regard to side effects was noted between two groups [22]. In their study the median follow up duration was 6 months.

In their study Martin Offringa et al[23] deducted that intermittent diazepam and continuous phenobarbital therapy resulted in reduced recurrence of febrile seizure in children. Adverse effects were identified in only 30% of cases. This study was followed up more than 48 hours.

One study by Abolfazl Mahyar et al demonstrated in their study findings that Melatonin does not play any significant role in simple or complex febrile seizures. 111 patients having ages between 6 and 60 months were included in their study. Difference between age, sex, body weight. Head circumference was not statistically significant between control and experimental groups. On the other hand, Leyla Aydin conducted an experimental study on rats and found out that melatonin exerts anti-convulsant effect when given prior to hyperthermia induced seizures. Therefore, this drug can be used in prophylaxis of febrile seizures [24].

In order to evaluate and validate findings of our study, it is proposed that in future researched should be conducted with a relatively larger sample size and those studies should be conducted at different healthcare centers.

Conclusion

This study deducted that the oral melatonin is more efficacious and significantly better than oral diazepam in obviating recurrence of simple febrile seizures among children presenting with fever.

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