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Original Research Article

Intermittent clobazam therapy and febrile seizure recurrence – A follow up study

Cyril Ignatious Rozario[1], Sunil Daniel[1,*], Anzy N Saleem[1]

[1] *Dept. of Pediatrics, Govt. T.D.Medical College Hospital, Alappuzha, Kerala, India*

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ABSTRACT

Objectives: To identify the proportion of children on intermittent clobazam therapy developing febrile seizure recurrence and to assess the risk factors of febrile seizure recurrence in children.
Design: Descriptive follow up study.
Study setting: Children between 6 months to 5 years admitted in Govt.TDMCH for seizures associated with fever.
Materials and Methods: Children presenting with acute febrile seizures are started on intermittent clobazam therapy. The risk factors were assessed and study group is followed up for a period of one year. Data were analyzed using computer software SPSS. Data are expressed in its frequency and percentage as well as mean and standard deviation. To elucidate the associations and comparisons between different parameters, Chi square($X^{2)}$ test was used as non-parametric test.
Results: Out of the 80 children followed up 28 children developed recurrence. Those who took clobazam had considerable reduction in recurrence (8.3% in clobazam group compared to 56.8% in those who were not on intermittent clobazam therapy. Complex febrile seizures (Odds ratio of 16.5 and p value <.01) and history of febrile seizures in the first degree relatives (Odds ratio of 3.81 and p value of <.01) had increased chance of recurrence.
Conclusion: Intermittent clobazam therapy has definite role in preventing febrile seizure recurrence. The risk factors for considering intermittent prophylaxis from this study are family history of febrile seizure and complex febrile seizure.

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1. Introduction

Febrile seizures are seizures that occur between the age of 6 and 60 months with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures.[1] These are the most common type of seizure in children. They may recur frequently.

In 1976, Nelson and Ellenberg[2] using data from the National Collaborative Perinatal Project, further defined febrile seizures as being either simple or complex. A simple febrile seizure is a primary generalized, usually tonic-clonic attack associated with fever, lasting for a maximum of 15 minutes, and not recurrent within a 24 hour period.[1] The median age of onset of febrile seizure is 18 months,[3] and half of children present between 12 and 30 months.[4] A complex febrile seizure is more prolonged (>15 min.), is focal, and/ or recurs within 24 hour. Febrile status epilepticus is a febrile seizure lasting longer than 30 minutes. Some use the term febrile seizure plus for those with recurrent febrile seizures within 24 hour.

Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% infants younger than 1 year old at febrile seizure onset.[1] The major risk factors associated with recurrence are age <1 year, duration of fever prior to seizure less than 24 hours and temperature of 100.4–102. 2°F. The

* *Corresponding author*.
E-mail address: sunildaniel1971@gmail.com (S. Daniel).

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minor risk factors include family history of febrile seizures, family history of epilepsy, complex febrile seizure, daycare attendance, male gender and low serum sodium at the time of presentation.[1]

In general, antiepileptic therapy, continuous or intermittent is not recommended for children with 1 or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and chances of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If seizure lasts for longer than 5 minutes, acute treatment with diazepam, lorazepam, or midazolam is needed.[1] The decision of not treating febrile seizure implies in the risk of seizure recurrence during febrile episodes. Even if these seizures are rarely responsible for neurological sequelae, they are a cause of stress for the family.

Prevention of the febrile seizure is highly desirable since seizure is upsetting to both parents and children. Clobazam, a 1,5-benzodiazepine, is completely absorbed 1 to 4 hours after oral administration, has a mean half-life of 18hours, and has less sedative and behavioral effects than diazepam. Some studies have compared clobazam against placebo as prophylaxis for febrile convulsion and there are a few studies comparing diazepam with clobazam in this regard.

In February 2017 the Cochrane database of system reviews, has updated the prophylactic management of febrile seizures in children. Intermittent clobazam compared to placebo at six months resulted in a recurrence rate of 36% (95% CI 0.20 to 0.64) an effect found against an extremely high (83.3%) recurrence rate in controls, which is a result that needs replication. They concluded that recurrence rates for children with febrile seizures for intermittent diazepam and continuous phenobarbitone, with adverse effects in up to 30%. Apparent benefit for clobazam treatment needs to be replicated to be judged reliable.[5]

The objectives of our study was to identify the proportion of children on intermittent clobazam therapy developing febrile seizure recurrence and to study the association of risk factors of febrile seizure recurrence.

2. Materials and Methods

The study was a descriptive follow up study from December 2015 to May 2017. Children admitted with seizure associated with fever, aged 6 months to 60 months were included in the study. 100 cases were enrolled in the study by consecutive sampling during the period of 6 months, and they were followed up for 1 year. Children with proven central nervous system (CNS) infection, CNS malformation, progressive neurological disease, proven chromosomal anomalies, developmental delay and on any other anticonvulsant were excluded.

The study variables are age in months, gender, type of seizure, intermittent clobazam therapy, temperature at presentation, fever seizure interval, hemoglobin (Hb) level, mean corpuscular volume (MCV), serum sodium, family history and day care attendance.

After getting informed consent from parents a detailed history was noted and clinical examination done. Sample was collected for a period of 6 months. Relevant details were collected in a proforma. All the children presenting with acute febrile seizures are started on intermittent clobazam therapy (0.75mg/kg/day in 2 divided doses for 3 days) and study group was followed up for a period of one year. The risk factors were studied and follow up was done through phone call every month for a period of one year to get details regarding fever, seizure following fever and drug intake. The parents were given the investigators contact number to inform any episodes of febrile seizure during the period.

2.1. Statistical analysis

Quantitative data was analyzed using mean, median, and standard deviation. Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS). Data were expressed in its frequency and percentage as well as mean and standard deviation. To elucidate the associations and comparisons between different parameters, Chi square (X^2) test was used as non-parametric test. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant.

3. Observations and Results

Out of the 100 children enrolled in the study 14 were lost to follow up and 6 were started on other antiepileptics and hence excluded from the study. 80 children were followed up for a period of one year. Among this 46 were boys and 34 were girls with a mean age of occurrence 1.5± 0.7. The mean duration of fever seizure interval was observed as 6.5± 6.9 hours and the mean temperature at presentation was 101.1 ± 1°F. Family history of febrile seizure was there for 32 children and 4 had family history of epilepsy

Among the study group 59 had simple febrile seizure, 17 had complex febrile seizure and 4 had status seizure at admission. 61% of children had low Hemoglobin (<11) and 36% had low mean corpuscular volume. Out of the 80 cases who were followed up for a period of one year 28 had febrile seizure recurrence, with 2 having febrile status and 4 with complex seizure.

Statistically significant association was not observed for age at presentation, gender, fever seizure interval, family history of epilepsy, day care attendance, hemoglobin level, MCV, serum sodium level, temperature at presentation and recurrence.

There was a significant association between family history of febrile seizure and recurrence with an Odds ratio of 3.81 and p value of < 0.01 [Table 1]. Those presenting with atypical febrile seizure during first episode had increased chance of recurrence with an Odds ratio of

Table 1: Associationof recurrence with F/H/O Epilepsy

	No		Yes		X^2	P
	Count	Percent	Count	Percent		
No	50	65.8	26	34.2		
					0.42	0.519
Yes	2	50.0	2	50.0		

Table 2: Association of recurrence with type of Seizure

Type of Seizure	Recurrence				Odds (95% CI)
	No		Yes		
	Count	Percent	Count	Percent	
Simple	46	78.0	13	22.0	1
Complex	3	17.6	14	82.4	16.51 (4.11 – 66.33)
Status	3	75.0	1	25.0	1.18 (0.11 – 12.31)

X^2 = 21.29**, p = 0.000

Table 3: Association of recurrence with prophylaxis

Prophylaxis	Recurrence				Odds (95% CI)
	No		Yes		
	Count	Percent	Count	Percent	
No	19	43.2	25	56.8	14.47 (3.85 – 54.39)
Yes	33	91.7	3	8.3	1

X^2 = 20.46**, p = 0.000

16.5 and p value <0.01[Table 2].

Out of the 80 children, 36 children took intermittent clobazam therapy as advised. Among them only 3 children developed febrile seizure during the one year follow up period. Out of the 44 children who had not taken prophylaxis 25 developed febrile seizure recurrence. This was observed to be statistically significant with an Odds ratio of 14.47 and p value of <0.01 [Table 3].

4. Discussion

Prophylactic treatment for febrile seizure recurrence has been criticized by several authors on the ground that febrile seizures have a benign outcome, and that antiepileptic drugs have short and long term adverse effects especially for the lower age group. There have been multiple studies regarding the use of intermittent clobazam therapy in preventing recurrence of febrile seizure.

According to Offringa et al and Wairuru et al the median age of presentation of febrile seizure is 18 months and half of the children presents between 12 and 30 months.[3,4] In our study also the mean age of presentation was observed to be 1.5 ± 0.7. The male female ratio of occurrence from the study is 1.3:1. This means that there is a definite male predominance of febrile seizure detected in our study. Various other studies have also observed an increased risk of febrile seizure with male gender.[6–8]

Kjeldsen et al have noticed that those presenting with febrile seizure, 24% will have a family history of febrile seizure and 4% will have family history of epilepsy.[9] However in our study a slightly greater percentage was noticed to have family history of febrile seizures (40%) and 5% had family history of epilepsy.

It was observed from our study that the percentage of recurrence of febrile seizure is 24.5 – 45.5% with an average of 35%. According to many studies.[10–12] the chances of recurrence within a one year period was observed as 30-40% which is comparable to our observation.

There are many studies on the efficacy of various antiepileptics and comparative studies of diazepam and clobazam. Most of the studies have reached a conclusion that clobazam is safe and effective in preventing febrile seizure recurrence. However meta-analysis of these trials had failed to show a benefit from intermittent prophylaxis.[13] But the latest meta-analysis in Fbruary 2017, based on the Cochrane database of system reviews, have concluded that the apparent benefit for clobazam treatment needs to be replicated to be judged reliable.[5]

We observed that out of 36 children who took intermittent clobazam therapy as advised, only 3 had a recurrence during the one year follow up study. Out of the 44 children who had not taken prophylaxis even though advised, 25 developed a recurrence of febrile seizure. This was observed to be statistically significant with an Odds ratio of 14.47 and p value of <0.01 in determining that intermittent clobazam therapy is effective in preventing the recurrence of febrile seizure. This result is comparable to the study conducted by Winsley Rose et al determining efficacy

of clobazam in preventing febrile seizure recurrence.[14] Bajaj et al, Aslam et al, Manreza et al have reached similar conclusion.[15–17]

The risk factors that were studied include age of onset of first febrile seizure episode, gender, temperature at presentation, fever seizure interval, type of seizure, family history of febrile seizure, family history of epilepsy, those attending day care, serum sodium, hemoglobin level and mean corpuscular volume.

Out of the 28 recurrences 17 had a family history of febrile seizure giving a statistically significant association with a p value <0.01. Family history in first degree relative was considered in the study. Berg et al, Pavlidou et al had observed the increased risk of recurrence with family history.[10,18]

Those with complex febrile seizure during first episode was observed to have an increased recurrence risk with an Odds ratio of 16.51 (p value of <0.01). Berg et al observed that a complex febrile seizure will not increase the recurrence risk. This is in contrast to various other studies including our study, from which a significant association was derived.[11,18,19]

Other risk factors that were studied were observed to have no significant association with recurrence. However a positive correlation was observed for male gender, those attending day care, low hemoglobin, low MCV and children less than 12 months age.

Iron deficiency is associated with an increased risk of febrile seizures.[1] It was observed that, those who presented with first episode febrile seizure 61% had low Hb and only 45% had low MCV. Even thougha positive correlation was observed for low Hb and low MCV with recurrence, it was not statistically significant.

5. Conclusion

Intermittent clobazam therapy has definite role in preventing febrile seizure recurrence. Those with family history of febrile seizure and those children presenting with first episode complex febrile seizure has increased risk of recurrence. The risk factors for considering intermittent prophylaxis from this study are family history of febrile seizure and complex febrile seizure.

6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

7. Source of Funding

None.

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Author biography

Cyril Ignatious Rozario, Additional Professor,

Sunil Daniel, Associate Professor https://orcid.org/0000-0002-6969-7534

Anzy N Saleem, Senior Resident

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