European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 02, 2023

Original Research Article

Role Of Vitamin E Supplementation in Treatment Resistant Epilepsy in Children in The Age Group of 1-12 Years

Dr. Muhammed Shabeer P[1]*, Dr. Prabha Khaire More[2], Dr. Prashant Srinivas Patil[3],

[1]*Assistant professor, Department of pediatrics, Government medical college, Aurangabad. Maharashtra , India Email: mohdshabeerp@gmail.com

[2]Professor and head of department , Department of pediatrics, Government medical college, Aurangabad. Maharashtra , India Mail: pwmore1968@gmail.com

[3]Ex Professor and head of department , Department of pediatrics, Government medical college, Aurangabad. Maharashtra, India Mail: Dr prashantpatil@yahoo.com

***Corresponding Author:- Dr. Muhammed Shabeer P**

*Assistant professor, Department of pediatrics, Government medical college, Aurangabad. Maharashtra , India Email: mohdshabeerp@gmail.com

ABSTRACT

Background: A seizure is a transient occurrence of signs and or symptoms from abnormal excessive or synchronous neuronal activity in the brain. The commonly used treatment for epilepsy is antiepileptic drugs; there is an increased oxidative stress in epilepsy patients, this study was to look for effectiveness of vitamin E in children with treatment resistant epilepsy in the form of improvement in frequency, duration of seizure, number of hospitalization, and EEG change.

Subject and Methods: Randomized control trail conducted in 32 children with treatment resistant epilepsy, with supplementation of vitamin E in upper limit of RDA and placebo in addition to antiepileptic drugs after randomization and allocation for 6 months' duration with prior recording history related to seizure prior to 6 months of trail. Patient kept on follow up with number of seizures, number hospitalization, duration each seizure occurred, changes in antiepileptic drugs made, an EEG after 6 months of intervention.

Result: Reduction in seizure frequency, number of hospitalization and duration of seizures occurred in both group, significant difference was observed in number of Impending status seizure episode ($p=0.037$), there is no significant positive changes in observed.

Conclusion: Supplementation of vitamin E as per the upper limit of RDA is effective in reducing the number of impending status seizure, hence the severity of epilepsy in treatment-resistant epileptic patients of the pediatric age group.

Keywords: Epilepsy, Vitamin E, EEG, Children

INTRODUCTION

Epilepsy is disorder which is characterized by a tendency to generate seizures and its neurobiological, cognitive, psychological, and social consequences. Clinically diagnosis of epilepsy requires the happening of at least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate a long-term predisposition to develop recurrence. It is a highly prevalent important neurological disease in the world. Epidemiologically at least 50 million people worldwide are affected by the disease and nearly 100

million people have experienced a seizure at least once in their lives. In children, approximately 4-10% of children experience at least 1 seizure (febrile or afebrile) in the 1st 16 years of life. The overall lifetime incidence of epilepsy is 3% and more than fifty percent of the cases start in childhood. The annual prevalence is 0.5-1 %. [1,2]

The most commonly used treatment for epilepsy is antiepileptic drugs including Valproate sodium, Phenobarbitone, Carbamazepine, Phenytoin, currently and Levetiracetam. A combination of drugs is used to treat resistant cases of epilepsy. Choosing any of these drugs depends on the type of seizure and the involved part of the brain. One of the functions of these drugs is through the impact on the course of oxidative stress.[3,4] Antiepileptic drugs are known to produce oxidative free radicals, produce oxidative stress. Oxidative stress involved in many neurodegenerative disorders such as epilepsy.[5,6,7] Aguir et al explained an increase in oxidative stress in epilepsy and have stated that free radicals act as a pathogen in the disease.[8] So oxidative stress will be there in epilepsy patients as a cause of disease or it develops during the course of treatment due to antiepileptic drugs.
Vitamin E (α-tocopherol) is lipophilic alcohol and its food source is the root of wheat and vegetable oils. The most important part of this substance is the α part because it forms 90% of the tocopherol composition of animal tissues. Many physiological functions have been considered for this substance including stabilization of membrane, acting as an enzyme inhibitor and the multiplier of the effect of Vitamin A2. Vitamin E has the ability to prevent the negative effects of lipid peroxidation in the brain tissue because it can absorb free radicals of oxygen. Many studies have shown the effect of Vitamin E on the treatment of epilepsy. In these studies vitamin E was used as adjunctive therapy in the treatment of epilepsy in children, whose seizures were not well controlled, resulting in significant improvement. It has no serious side effects and risk of toxicity. But higher doses can cause nausea, diarrhea, stomach cramps, fatigue, and weakness, headache, rash, and bruising and bleeding. This causes the substance to be considered in the treatment of epilepsy.

In 1989 Ogunmekan et al conducted a study in children with epilepsy, and it was found that adding Vitamin E to AEDs reduces their seizures. [9] In another study conducted by Kovalenko et al, it was found that adding Vitamin E to antiepileptic reduces plasma levels of lipid peroxidation and decreases the frequency of seizures in these patients.[10]

A study by Mehvari et al in 2016 observed that Vitamin E reduces the seizure in epileptic patients on anti-epileptic therapy by decreased in positive change in EEG findings. Vitamin E is a natural antioxidant free of major side effects and it can easily be used by patients as adjunctive therapy.[11] Due to the above-mentioned reasons and because of a high prevalence of epilepsy in Indian population as well as in the world, which cause injuries to the social, occupational, and other fields of life, research into finding ways to help the treatment of this disease is a big step towards helping these patients.[12] This study kept the objective to study the effectiveness of vitamin E in reducing seizure episodes, hospitalization and duration of seizures, and changes in EEG in treatment-resistant epilepsy patients of age group 1-12 years. Hypotheses set aside as Vitamin E reduces the episode of seizure, hospitalization and duration of seizures and look for EEG changes in children with treatment-resistant epilepsy.

MATERIAL AND METHODS

This is a randomized controlled clinical trial on pediatric patients with treatment resistant epilepsy treated by AEDs referred to a tertiary care hospital in western India. After approval from Institutional Ethical Committee, Children of the age group between 1 to 12 years who were fulfilling all inclusion and exclusion criteria were included in the study the sampling method was simple non-random, and the experiment and control groups were assigned randomly. Study period was January 2018 to September 2019.

Inclusion Criteria:

- Age 1 -12 years
- Diagnosis of treatment-resistant epilepsy:
  (a) Receiving any of at least two antiepileptic drugs for the past 6 months.
  (b) At least 3 seizures in the last 6 months
- The ability of care taker to record information needed during determined period.

Exclusion Criteria:

- Neuroimaging suggestive of a mass lesion
- Receiving vitamin E supplementation within 6 months of study
- Chronic Kidney and Liver diseases.

Moreover, the patients with lack of consent to continue with the study were excluded. The sample size calculated with Level of significance 5%, Power of 80%.A total of 38 patients allocated in the study after assessment. A total of 6 patients were excluded. 5 were not continuing drug and one patient developed side effects for vitamin E. Amongst a total of 32 patients, 15 patients were in the Vitamin E group and 17 patients in the control group.

Enrolled patients were randomized in group A and Group B. Allocation was done by simple randomization. Informed written consent was taken from the parents of the enrolled children for participation in the study. Data about detailed information of the enrolled patient in the form of biodata, clinical history, including antiepileptic drug, and last 6-month data of the number of seizures, semiology of seizure was noted as per Performa. The patient was clinically examined and signs noted. EEG, MRI were noted. Vitamin E was supplemented to group A within the upper limits of RDA,[13] (1 to 3 years: 200 Units daily 4 to 8 years: 400 Units daily 9 t0 13 years: 600 Units daily) while Group B, as control was received placebo, both groups were received medication for 6 months, subjects were kept under follow up by call back method monthly for 6 months, either by direct contact or telephonically. During the intervention, subjects were followed up and monitored monthly for 6 months for Number of seizure episode, Number of hospitalization, Change in type of seizure, duration of seizure as simple seizure and impending status, Change in antiepileptic drugs and dosage, Side effects of vitamin E like nausea, diarrhea, stomach cramps, fatigue, and weakness, headache, rash, and bruising and bleeding. Patients who refused to continue the study, with side effects of Vitamin E and deaths were excluded from the study. An EEG is reported after the completion of study period. Duration of seizure is divided in to two, based on the chance of being progress in to status epileptics. Duration less than 5 minutes (uncomplicated), duration more than 5 minutes (impending status) for GTCS, for focal seizure duration less than 10 min (uncomplicated) and duration more than 10 min is considered (Impending status).[14]

Clinical trial is registered with registration number CTRI/2018/08/015275.
Statistical Analysis: Data were statistically described using the Mann Whitney test and Fischer exact test. The level of significance was considered statistically significant with P- values of ≤ 0.05. All statistical calculations were done using computer programs Microsoft excel 2010(Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science Inc. Chicago, IL, USA) version 20.

RESULT:

Consort flow diagram shows profile of the study, of 38 allocated patients 6 patients were excluded from study 4 patients from vitamin E group, 2 from placebo group. Finally 32 patients completed the study and analyzed. One patient from case group excluded due to milder side effects of Vitamin E.

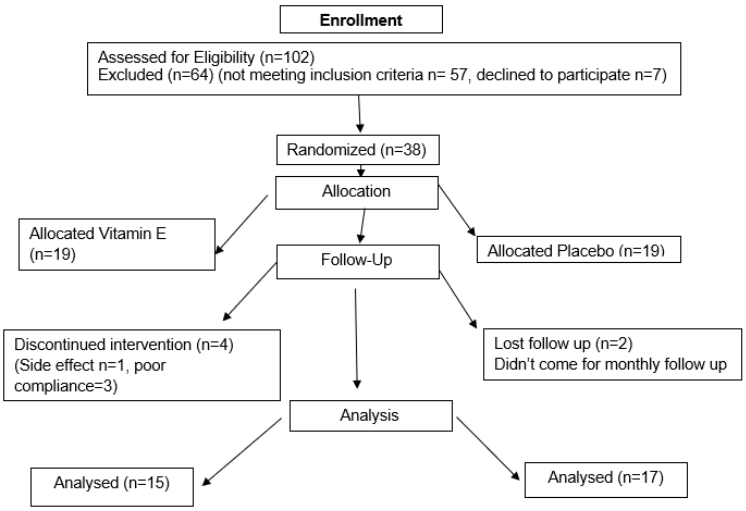

Table 1, the mean of age in studied patients were 4.6 years in Vitamin E group, 4.5 years in placebo group. Females were 40% in the vitamin E group and 41.2 % in the control group, the rest were males. Generalized seizures were the most common type, 86.7 % in the Vitamin E group and 76.5 % in the control group. Valproate and levetiracetam were most common combination of antiepileptic drugs in both the groups followed by valproate and phenytoin combination. No significant difference was noted between both groups for baseline characteristics.

Table 2 shows comparison of study parameters prior to 6 months of study and after 6 months. Reduction of seizure frequency occurs in both the Vitamin E group and in control. Mean was 11.07±8.991in the vitamin E group and 8.24±6.807in the control group 6 months prior to the study. Mean is 9.07±6.989 in the vitamin E group and 6.53±4.375in the control group during the study. This was not statistically significant (p value: 0.076).

The number of hospitalizations was reduced in both groups. Mean the number of hospitalization prior to the study was 3.27±1.907 in Vitamin E group and 2.94±1.512 in control group During 6 months of study observations of the mean number of hospitalization was 1.73±1.038 in Vitamin E group and 2.24±1.306 in control group. This was not significant (p value: 0.831).

The mean number of uncomplicated seizures was 5.93±2.158 in the Vitamin E group, and 4.82±1.623 in the control group. While comparing the data of 6 months prior to the study and during the study, both uncomplicated seizures and impending status were reduced in vitamin E as well as the control group. Data in uncomplicated seizures was not significant in vitamin E and control group, p-Value was 0.302. The Mean number of impending status seizures were 4.07±1.07 in vitamin E group and 2.71±0.71 in control group 6 months prior to the study while it was 0.47±0.53in Vitamin E group and 1.171±0.696 in control group during 6 months of study. There was a statistically significant reduction in the number of impending statuses during 6 months of study. P-Value was 0.037.
7 out of 15 patients had increased in the number of drugs or dosages in the vitamin E group, and 10 out of 17 patients had an increased number of drugs or dosages in the control group. It didn't show any statistical significance. (P-Value is 0.723).vitamin E toxicity features observed in one patient. There were no significant changes in EEG of patients after 6 months of study with P value 0.728.

ISSN 2515-8260 Volume 10, Issue 02, 2023

DISCUSSION & CONCLUSION

A seizure is signs and symptoms occurred due to abnormal excessive or synchronous electrical activity in the brain. In patients with epilepsy the deficiency of vitamin E has been reported, [15] but antiepileptic effect of vitamin E is contrary. This randomized controlled trial was aimed to study effectiveness of vitamin E on the seizure frequency, duration and EEG finding as add on therapy to antiepileptic drugs in treatment resistant epilepsy patients in children. The study was one of the rare pediatric studies based on the effect of Vitamin E on treatment-resistant epilepsy.

Our finding show that no significant change in frequency seizures, number of uncomplicated seizure, frequency of hospitalization, EEG finding in Vitamin E group compared to placebo both before and after supplementation of vitamin E, but there is a significant reduction in number impending status n.

In previous studies, Ogunmekan et al divided patients into responders and nonresponders, the patient having a seizure seizure is observed in vitamin E group than placebo group after 6 months of supplementatio frequency reduction >60% were considered responders and it show The proportion of responders in the vitamin E was significantly higher than that in the placebo group. Similarly **Mehvari et al** also found that Seizure frequency is reduced in Vitamin E group and which is significantly lower than placebo group. A cross over trail done by **Raju et al** [16] shows Seizure frequency was reduced during both the placebo and vitamin E phases of treatment. Seizure frequency was not significantly different between the vitamin E phase and the placebo phase (p=0.35). our study used duration of seizures, number hospitalization and EEG changes as measure of severity. Similar parameter as a measure of severity studied not studied previously. EEG changes was studied by Ogunmekan et al and mehvari et al, both show decrease in positive EEG changes after add on treatment of vitamin E. no changes in EEG is observed in our study.
The differences between our findings and some previous studies can explain by difference in combination antiepileptic therapy, age group, and the dosage and treatment duration Vitamin E varies across studies. Vitamin E has been used in a wide dose ranges from modest 100 IU/d or 200 IU/d to high doses such as 1200 IU/d in various experiments. There is varied opinion among researches on efficacy of Vitamin E and its exact pharmacological mechanism in epileptic patients.
Our study concluded that Supplementation of vitamin E in upper limit of RDA is effective in reducing the number of impending status seizure, hence the severity of epilepsy in treatment-resistant epileptic patients of the pediatric age group on antiepileptic therapy.

There are few limitations to our study; we did not limited inclusion criteria to restricted specific antiepileptic drug combination. The previous 6 months Vitamin E supplementations was considered as exclusion criteria, we supplemented the study group without knowing the pre-enrollment Vitamin E level of the patients. Since the prevalence of treatment-resistant epilepsy is less, the present study has less sample size. More studies with large sample size or multi centric trials are required for confirmation of results.

Conflict of interest: Nil

Source of support: Nil

ACKNOWLEDGEMENTS:

I would like to express my gratitude to my advisers and patients who given consent for participation, all others helped me to complete the study.

ISSN 2515-8260 Volume 10, Issue 02, 2023

REFERENCES

1. Amudhan S, Gururaj G, Satishchandra P. Epilepsy in India I: Epidemiology and public health. Annals of Indian Academy of Neurology. 2015 Jul; 18(3):263.

2. Gadgil P, Udani V. Pediatric epilepsy: the Indian experience. Journal of pediatric neurosciences. 2011 Oct; 6(Suppl1): S126.

3. Cárdenas-Rodríguez N, Coballase-Urrutia E, Rivera-Espinosa L,Romero-Toledo A, Sampieri III A, Ortega-Cuellar D, Montesinos-Correa H, Floriano-Sánchez E, Carmona-Aparicio L. Modulation of antioxidant enzymatic activities by certain antiepileptic drugs (valproic acid,oxcarbazepine, and topiramate): evidence in humans and experimental models. Oxidative medicine and cellular longevity. 2013;2013.

4. Nemade ST, Melinkeri RR. Effect of antiepileptic drugs on antioxidant status in epilepsy. Current Neurobiology. 2010;1(2):109-12.

5. Martinc B, Grabnar I, Vovk T. Antioxidants as a preventive treatment for epileptic process: a review of the current status. Current neuropharmacology. 2014 Dec 1;12(6):527-50.

6. Shin EJ, Jeong JH, Chung YH, Kim WK, Ko KH, Bach JH, Hong JS, Yoneda Y, Kim HC. Role of oxidative stress in epileptic seizures. Neurochemistry international. 2011 Aug 1;59(2):122-37.

7. Hamed SA, Abdellah MM, El-Melegy N. Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. Journal of pharmacological sciences. 2004;96(4):465-73.

8. Aguiar CC, Almeida AB, Araújo PV, Abreu RN, Chaves EM, Vale OC, Macêdo DS, Woods DJ, Fonteles MM, Vasconcelos SM. Oxidative stress and epilepsy: a literature review. Oxidative medicine and cellular longevity. 2012 Jul 14;2012.

9. Ogunmekan AO, Hwang PA. A Randomized, Double- Blind, PlaceboControlled, Clinical Trial of D- α- Tocopheryl Acetate (Vitamin E), as AddOn Therapy, for Epilepsy in Children. Epilepsia. 1989 Feb;30(1):84-9.

10. Kovalenko VM, Kryzhanovskiĭ GN, Kovalenko VS, Pronina IG, Nikushkin EV. Alpha-tocopherol in the complex treatment of several forms of epilepsy. Zhurnal nevropatologii i psikhiatrii imeni SS Korsakova (Moscow, Russia: 1952). 1984;84(6):892-7.

11. Mehvari J, Motlagh FG, Najafi M, Ghazvini MR, Naeini AA, Zare M. Effects of Vitamin E on seizure frequency, electroencephalogram findings, and oxidative stress status of refractory epileptic patients.Advanced biomedical research. 2016;5.

12. Mula M, Sander JW. Psychosocial aspects of epilepsy: a wider approach. BJPsych open. 2016 Jul;2(4):270-4.

13. Dietary reference intake, food and nutrition board, institute of medicine,National academics.

14. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015 Oct;56(10):1515-23.

15. Ogunmekan AO. Relationship between age and vitamin E level in epileptic and normal children. The American journal of clinical nutrition. 1979 Nov 1;32(11):2269-71.

16. Raju GB, Behari M, Prasad K, Ahuja GK. Randomized, Double- Blind, Placebo- Controlled, Clinical Trial of D- α- Tocopherol (Vitamin E) as Addon Therapy in Uncontrolled Epilepsy. Epilepsia. 1994 Mar;35(2):368-72.

TABLES AND FIGURES.

Table 1 Baseline characteristics

Baseline characteristics	Vitamin E Group (n)	Placebo Group (n)
Age		
Less than 5 year	6	7
1 to 10 year	9	10
Mean age	4.6 years	4.5 year
Sex		
Male	9	10
Female	6	7
Antiepileptic Drugs		
Valproate and levetiracetam	8	9
Valproate and Phenytoin	3	2
Other combination	4	6
Seizure Semiology		
Generalized	13	13
Focal	2	4

Table 2: Outcome parameter

	6 month prior to study	During 6 months of study
Number of seizure		
Vitamin E	11.07±8.991	9.07±6.989
Placebo	8.24±6.807	6.53±4.375
P Value	0.16	0.76
Number of hospitalization		
Vitamin E	3.27±1.907	1.73±1.038
Placebo	2.94±1.512	2.24±1.306
P Value	0.296	0.831
Number of uncomplicated seizures		
Vitamin E	9.67±2.42	5.93±2.158
Placebo	6.06±1.93	4.82±1.623
P Value	0.088	0.302
Number of impending status		
Vitamin E	4.07±1.07	0.47±0.53
Placebo	2.71±0.71	1.171±0.696
P Value	0.413	**0.037**

ISSN 2515-8260 Volume 10, Issue 02, 2023

EEG Finding			
Vitamin E	Normal	4	6
	Abnormal	11	9
Placebo	Normal	6	8
	Abnormal	11	9
P Value		0.728	

Figure 1: Mean number of seizures in each month of intervention