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Protocol

Effect of vitamin E as an add-on therapy on oxidative stress in patients with epilepsy: a randomized placebo-controlled trial

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ABSTRACT

Background: Epilepsy, a chronic neurological disorder, is often complicated by oxidative stress due to long-term antiepileptic drug (AED) use. While preclinical studies suggest vitamin E may mitigate oxidative damage, its clinical efficacy as adjunctive therapy in epilepsy remains underexplored.
Methods: This randomized, double-blind, placebo-controlled trial enrolled 60 adults with epilepsy on stable AED therapy at JIPMER, Puducherry (March 2022-March 2024). Participants were allocated to either vitamin E (400 mg/day) or placebo for two months. Primary outcomes included changes in oxidative stress biomarkers [total antioxidant capacity (TAC), catalase, glutathione (GSH), malondialdehyde (MDA)]. Secondary outcomes assessed EEG changes, seizure-free intervals, and metabolic syndrome incidence. Statistical analysis used ANOVA/Kruskal-Wallis for biomarkers and repeated-measures ANOVA for EEG.
Conclusions: This study aims to determine whether vitamin E supplementation reduces oxidative stress and improves clinical outcomes in epilepsy patients, potentially informing future antioxidant-based adjunctive therapies.
Trial registration: CTRI/2022/04/041902 (Clinical trials registry-India).

Keywords: Vitamin E, Epilepsy, Oxidative stress, Add-on therapy, Randomized controlled trial, Antioxidants

INTRODUCTION

Epilepsy is a major public health concern, affecting nearly 50 million individuals worldwide.[1] In India, the prevalence is 4.7 per 1000 population.[2] The long-term use of AEDs, while effective in seizure control, is associated with cognitive decline, metabolic syndrome, and increased oxidative stress.[3]

Oxidative stress plays a key role in epileptogenesis by inducing neuronal damage, excitotoxicity, and mitochondrial dysfunction.[4]

Preclinical research suggests that antioxidants like vitamin E can mitigate oxidative damage, potentially enhancing seizure control.[5]

Despite encouraging animal studies and preliminary human trials, there remains a lack of robust clinical evidence on the role of vitamin E in epilepsy. This trial aims to evaluate whether Vitamin E supplementation can reduce oxidative stress and improve clinical outcomes in epilepsy patients.

METHODS

Study design

This randomized, double-blind, placebo-controlled clinical trial was conducted at JIPMER, Puducherry, from June 2022 to May 2024. The study follows the SPIRIT guidelines and adheres to GCP standards.

Inclusion criteria

Adults ≥18 years old of either gender, diagnosed epilepsy on stable AED therapy for ≥6 months and willing to provide written informed consent were included.

Exclusion criteria

Patients with comorbid conditions (diabetes, liver/kidney disease, severe cardiovascular disease). previous vitamin E supplementation. patients with structural brain abnormalities (MRI-confirmed) were excluded.

Randomization and blinding

Randomization: Computer-generated sequence (1:1 allocation).

Blinding: Double-blind (both participants and investigators blinded).

Allocation concealment: Sequentially numbered opaque, sealed envelopes.

Intervention

Vitamin E group: 400 mg vitamin E capsule daily.

Placebo group: Identical placebo capsule.

Treatment duration: 2 months (adjunct to standard AED therapy).

Outcome measures

Primary outcomes

Changes in oxidative stress biomarkers: TAC, catalase activity, GSH levels and MDA levels.

Secondary outcomes

Seizure-free interval over 6 months, EEG changes between groups and incidence of metabolic syndrome.

Sample size calculation

Based on prior antioxidant therapy studies, the required sample size is 60 patients (including 10% attrition rate) to achieve 80% power (α=0.05).[6]

Data collection and statistical analysis

To evaluate the effect of vitamin E supplementation on oxidative stress in epilepsy patients, blood samples will be collected at two time points: baseline (Day 0) before intervention and post-treatment (Day 60) after two months of therapy. A 4 mL venous blood sample will be drawn from the antecubital vein using a sterile venipuncture technique and collected in EDTA tubes to prevent coagulation. The samples will be immediately placed on ice and transported to the department of pharmacology laboratory for processing. Plasma and serum will be separated by centrifugation at 3000 rpm for 15 minutes at 4°C and stored at -80°C until further analysis. The oxidative stress biomarkers assessed in this study include TAC, catalase activity, GSH levels, and MDA levels. TAC will be estimated using the ferric reducing antioxidant power (FRAP) assay, catalase activity will be measured through hydrogen peroxide decomposition analysis, GSH levels will be quantified using Ellman's reagent, and MDA, a key indicator of lipid peroxidation, will be determined by the thiobarbituric acid reactive substances (TBARS) assay. Each biochemical assay will be performed in triplicates to ensure accuracy and reproducibility.

In addition to biochemical assessments, EEG recording will be performed at baseline and after two months of intervention to assess neurophysiological changes. The EEG recording will take place in a quiet, temperature-controlled environment in the department of neurology, JIPMER using a 32-channel EEG system with electrodes placed according to the 10-20 international system. Each session will last 30 minutes, including 5 minutes of hyperventilation and photic stimulation to evaluate seizure susceptibility. The EEG signals will be analyzed by an experienced neurologist blinded to treatment allocation. The key EEG parameters analyzed will include interictal epileptiform discharges (IEDs), seizure activity, and background rhythm stability. A reduction in spike-wave discharges and an improvement in alpha-wave symmetry will be considered indicative of positive neuroprotective effects (Figure 1).

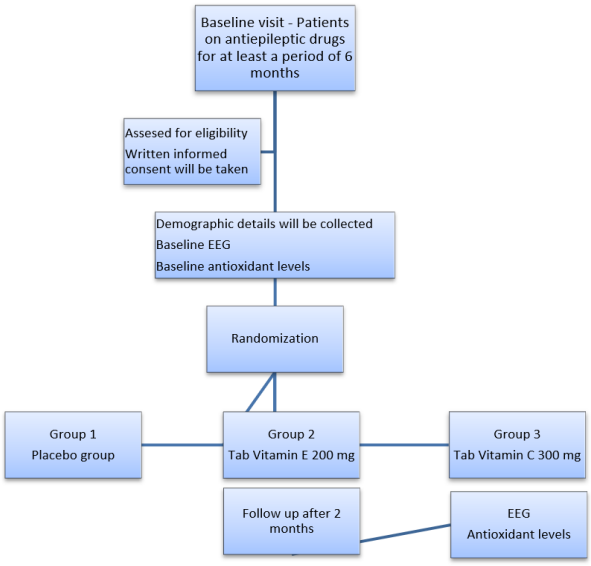

Figure 1: Procedure flowchart.

For statistical analysis, data will be entered into Microsoft excel and analyzed using SPSS v25.0. The

normality of continuous data will be assessed using the Kolmogorov-Smirnov test. For continuous variables such as oxidative stress biomarkers (TAC, catalase, GSH, and MDA levels), comparisons between the vitamin E and placebo groups will be performed using one-way analysis of variance (ANOVA) if data are normally distributed. If normality is not met, the Kruskal-Wallis test will be used as a non-parametric alternative. EEG parameters will be analyzed using repeated measures ANOVA, considering both treatment group effects and time effects (baseline vs. post-treatment). Categorical variables, such as incidence of metabolic syndrome and seizure-free intervals, will be compared between groups using Chi-square test. If the expected frequency in any cell is <5, Fisher's exact test will be applied. P<0.05 will be considered statistically significant for all analyses. Additionally, effect sizes will be reported using Cohen's D for continuous variables and Cramer's V for categorical outcomes (Table 1).

Table 1: Statistical analysis.

Data collected	Time points	Statistical test	Interpretation
Blood sample (Oxidative stress markers: TAC, catalase, GSH, MDA)	Baseline (Day 0) and post-treatment (Day 60)	ANOVA/ Kruskal-Wallis	Assess vitamin E's impact on oxidative stress
EEG (Seizure activity, IEDs, background rhythm)	Baseline and after 2 months	Repeated measures ANOVA	Detect neurophysiological changes
Seizure-free interval (%)	6 months follow-up	Chi-square test	Compare effectiveness of vitamin E
Incidence of metabolic syndrome	6 months follow-up	Chi-square/ Fisher's exact test	Assess metabolic effects of vitamin E

Ethical considerations

IEC approval: JIPMER institutional ethics committee (IEC Approval No: JIP/IEC/2022/03).

Trial registration: CTRI/2022/04/041902.

Confidentiality: Data secured following GCP.

DISCUSSION

Epilepsy treatment is limited by AED-induced oxidative stress, contributing to neuronal injury. Prior research suggests that vitamin E supplementation may reduce seizure burden by neutralizing free radicals.[7] This trial is among the first to rigorously evaluate Vitamin E as an adjunctive therapy in epilepsy. If successful, it could lead to evidence-based antioxidant therapy in epilepsy management. Further multi-center trials will be necessary to confirm these findings and establish clinical guidelines for antioxidant supplementation in epilepsy.

This protocol builds upon previous research investigating antioxidant therapies in epilepsy while addressing several methodological gaps. Unlike Najafi et al which focused solely on refractory epilepsy patients, our study includes a broader epilepsy population on stable AED regimens, potentially increasing clinical applicability.[5] While Sudha et al and Oliveira et al established the preclinical rationale for antioxidant therapy our protocol introduces more comprehensive outcome measures by combining oxidative stress biomarkers (TAC, MDA, GSH) with EEG monitoring and metabolic assessments-an approach not simultaneously employed in prior clinical trials.[4,7] The study design improves upon Ayyildiz et al by implementing a longer intervention period (2 months vs. acute dosing) and stricter blinding procedures.[6] Particular attention has been given to standardization challenges noted in previous work, including uniform sample processing (-80°C storage, triplicate assays) and EEG interpretation (blinded neurologist using 10-20 system). By incorporating these methodological refinements while adhering to SPIRIT guidelines, this protocol aims to generate higher-quality evidence regarding vitamin E's potential role in epilepsy management.

CONCLUSION

This rigorously designed randomized controlled trial protocol addresses critical gaps in understanding the potential role of vitamin E as adjunctive therapy for epilepsy management. By systematically evaluating both biochemical (oxidative stress markers) and clinical (seizure frequency, EEG changes) outcomes with standardized methodology, this study will provide high-quality evidence to determine whether antioxidant supplementation can mitigate AED-induced oxidative damage. The protocol advances upon previous research through its comprehensive outcome measures, strict blinding procedures, and adherence to SPIRIT guidelines. Results from this trial may establish a foundation for evidence-based recommendations regarding antioxidant use in epilepsy care, potentially offering a novel therapeutic approach to improve long-term patient outcomes beyond conventional seizure control.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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