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Original Research Article

Lipid Profile Level in Patients with Seizure Disorder Due To Antiepileptic Drugs

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ABSTRACT

Background: Seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in brain.[1,2] It can present as anything from violent convulsions to unusual experiences that are difficult for others to witness.
Objective: Methods: This Cross-sectional study was conducted among patients attending Medicine, Neurology OPD/Patients Admitted in Department of General Medicine, Subbaiah Institute of Medical Sciences, Shivamogga, Karnataka, India. The study was conducted over a period of 1 year after obtaining clearance from institutional ethical committee. Duration of study was August 2022 to August 2023.
Result: The mean total cholesterol in patients who received phenytoin was 165.90 ± 23.70 and in patients who received levetiracetam was 113.06 ± 17.22. (p=0.001). The mean HDL-C in patients who received phenytoin was 48.78 ± 9.35 and in patients who received levetiracetam was 45.36 ± 7.07. (p=0.11). The mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. (p=0.001). The mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22. (p=0.001)
Conclusion: patients on phenytoin displayed elevated serum lipid profile levels (TC, LDL-C and TG). Thus, TC levels, LDL-C levels and TG levels can be an important marker for estimating the risk of cardiovascular disease in epilepsy patients.

Keywords*: Lipid Profile Level, Seizure Disorder, Antiepileptic Drugs.*

INTRODUCTION

Epilepsy is the most prevalent chronic brain disorder that not only affect the individual but also disturbs family and society. Several factors, including the type of seizure, the epilepsy syndrome, the underlying etiology, the presence or absence of abnormalities on the interictal electroencephalogram (EEG), and other patient-related factors like age, the presence of associated neurological abnormalities, and the presence of comorbid conditions, can be used to predict the probability of having a second seizure following the first one.[1]

The International League Against Epilepsy (ILAE) defines a person as having resolved epilepsy if they have not experienced a seizure in the last ten years, five of which have been without medication.[2] Epilepsy is the two or more unprovoked seizure due to chronic, underlying process.[3] Epilepsy One of the most prevalent brain disorders that affects not only the individual but also families and society at large.[4] In India, 12 million people suffer from epilepsy. Just India bears 1/6 of the world's weight.[5] Epilepsy has an incidence of approximately 0.3-0.5% in various groups worldwide, with a prevalence estimated at 5–30 persons per 1000.[3] It has been observed that antiepileptic drugs (AED), raise serum levels of lipoproteins, total cholesterol, and low-density lipoprotein (LDL), which accelerate atherosclerosis and increase the risk of vascular illnesses.[6]

A significant rise or decrease in a particular circulating lipid or lipoprotein is indicative of a lipoprotein metabolism disorder. Primary disorders are those resulting from genetic abnormalities, while secondary disorders are caused by other

medical illnesses or environmental exposures. It is crucial to correctly detect and treat lipoprotein problems since they can have a variety of clinical repercussions, the most notable of which is early atherosclerotic cardiovascular disease (ASCVD).[7]

As there is chronic use of AED for epilepsy,chronic neuropathic pain,migraine , anxiety; there is need for study to determine AED effect on Lipid profile to decrease the risk of atherosclerosis

MATERIAL AND METHODS

This Cross-sectional study was conducted among patients attending Medicine, Neurology Opd/Patients Admitted in Department of General Medicine, Subbaiah Institute of Medical Sciences, Shivamogga, Karnataka, India. The study was conducted over a period of 1 year after obtaining clearance from institutional ethical committee. Duration of study was August 2022 to August 2023

Inclusion Criteria

Patients with seizure disorder who are on AEDs (Phenytoin and Levetiracetam).

Exclusion Criteria

1. Patients on hypolipidemic drugs
2. patients with Diabetes Mellitus
3. Patients with stroke,IHD.
4. Patients on isoniazid ,warfarin.
5. Patients on more than one antiepileptic drug.
6. Patients with chronic liver and kidney disease.

SAMPLE SIZE ESTIMATION

Based on previous study conducted by Manimekalai K et al. Evaluation of effect of antiepileptic drugs on serum lipid profile among young adults with epilepsy in a tertiary care hospital in Pondicherry.

$$n = 2\frac{S^2(Z1 + Z2)^2}{(M1 - M2)^2}$$

Substituting the values in the above formula, sample size obtained is 31.
Since there are 2 groups, total sample size is 31*2= 62.

METHODOLOGY

Patients of 18 years and above and meeting the selection criteria were enrolled into the study. Written informed consent was taken from each patient willing to participate in the study. Patients were categorized into two groups based on treatment they were receiving for epilepsy for a minimum of 6 months into Phenytoin and Levetiracetam groups. Blood samples drawn for lipid profile.Lipid profile status was compared in between the 2 groups.

RESULTS

The mean age of patients receiving phenytoin was 59.81 ± 14.94 and mean age of patients receiving Levetiracetam was 41.97 ± 15.63 years. Using independent sample T test, comparison of the mean age between the groups was statistically significant. (p=0.001)

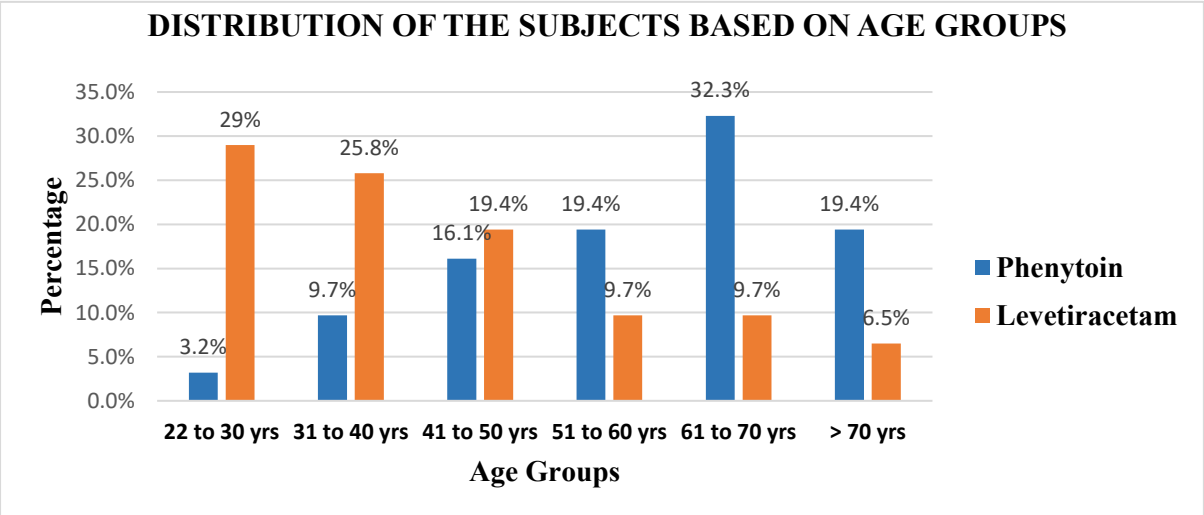

FIGURE1: Distribution of the subjects based on age groups

10 patients (16.1%) belonged to the age group of 22 to 30 years, of which, 1 patient (3.2%) received phenytoin and 9 patients (29%) received levetiracetam. 11 patients (17.7%) belonged to the age group of 31 to 40 years, of which, 3 patients (9.7%) received phenytoin and 8 patients (25.8%) received levetiracetam. 11 patients (17.7%) belonged to the age group of 41 to 50 years, of which, 5 patients (16.1%) received phenytoin and 6 patients (19.4%) received levetiracetam. 9 patients (14.5%) belonged to the age group of 51 to 60 years, of which, 6 patients (19.4%) received phenytoin and 3 patients (9.7%) received levetiracetam.

13 patients (21%) belonged to the age group of 61 to 70 years, of which, 10 patients (32.3%) received phenytoin and 3 patients (9.7%) received levetiracetam. 8 patients (12.9%) belonged to the age group of >70 years, of which, 6 patients (19.4%) received phenytoin and 2 patients (6.5%) received levetiracetam. The association between age groups and treatment received was statistically significant. (p=0.008)

19 patients (30.6%) were females, of which, 10 patients (32.3%) received phenytoin and 9 patients (29%) received levetiracetam. 43 patients (69.4%) were males, of which, 21 patients (67.7%) received phenytoin and 22 patients (71%) received levetiracetam. The distribution of the subjects based on gender was statistically not significant. (p=0.78)

TABLE 1: Distribution of the subjects based on co-morbidities

Co-morbidities		Treatment		Total
		Phenytoin	Levetiracetam	
Hypertension	Count	14	20	33
	%	45.16%	64.51%	53.2%
None	Count	17	11	29
	%	54.83%	35.5%	46.8%
Total	Count	31	31	62
	%	100.0%	100.0%	100.0%
Chi-square value- 2.34				
p value-0.125				

33 patients (53.2%) had hypertension, of which, 14 patients (45.16%) received phenytoin and 20 patients (64.51%) received levetiracetam. The distribution of the subjects based on comorbidities was not statistically significant. (p=0.125)

TABLE 2: Distribution of the subjects based on alcohol consumption

Alcohol		Treatment		Total
		Phenytoin	Levetiracetam	
No	Count	16	16	32
	%	51.6%	51.6%	51.6%
Yes	Count	15	15	30
	%	48.4%	48.4%	48.4%
Total	Count	31	31	62
	%	100.0%	100.0%	100.0%

Out of 62 patients, 30 patients (48.4%) consumed alcohol, of which, 15 patients (48.4%) received phenytoin and 15 patients (48.4%) received levetiracetam.

TABLE 3: Distribution of the subjects based on smoking

Smoking		Treatment		Total
		Phenytoin	Levetiracetam	
No	Count	20	21	41
	%	64.5%	67.7%	66.1%
Yes	Count	11	10	21
	%	35.5%	32.3%	33.9%
Total	Count	31	31	62
	%	100.0%	100.0%	100.0%
Chi-square value- 0.072				

p value-0.788

Out of 62 patients, 21 patients (33.9%) were smokers, of which, 11 patients (35.5%) received phenytoin and 10 patients (32.3%) received levetiracetam. The distribution of the subjects based on smoking was statistically not significant. (p=0.78)

TABLE 4: Distribution of the subjects based on BMI

BMI		Treatment		Total
		Phenytoin	Levetiracetam	
Healthy	Count	13	20	33
	%	41.9%	64.5%	53.2%
Overweight	Count	18	11	29
	%	58.1%	35.5%	46.8%
Total	Count	31	31	62
	%	100.0%	100.0%	100.0%
Chi-square value- 3.175				
p value-0.075				

Out of 62 patients, 33 patients (53.2%) had healthy BMI, of which, 13 patients (41.9%) received phenytoin and 20 patients (64.5%) received levetiracetam. 29 patients (46.8%) had overweight BMI, of which, 18 patients (58.1%) received phenytoin and 11 patients (35.5%) received levetiracetam. The distribution of the subjects based on BMI was statistically not significant. (p=0.075)

The mean BMI in patients receiving phenytoin was 25.26 ± 2.90 and mean BMI in patients receiving levetiracetam was 23.85 ± 2.23. Using independent sample T test, the comparison of mean BMI between the groups was statistically significant. (p=0.03)

TABLE 5: Comparison of the mean duration of treatment (in months) between the groups using independent sample T test

Groups	N	Minimum	Maximum	Mean	S.D	Mean diff	p value
Phenytoin	31	6.0	360.0	57.26	66.34	29.64	0.032*
Levetiracetam	31	6.0	180.0	27.61	35.13		

The mean duration of treatment in patients receiving phenytoin was 57.26 ± 66.34 months and mean duration of treatment in patients receiving levetiracetam was 27.61 ± 35.13. Using independent sample T test, the comparison of mean duration of treatment between the groups was statistically significant. (p=0.03)

The mean total cholesterol in patients who received phenytoin was 165.90 ± 23.70 and in patients who received levetiracetam was 113.06 ± 17.22. (p=0.001)

The mean HDL-C in patients who received phenytoin was 48.78 ± 9.35 and in patients who received levetiracetam was 45.36 ± 7.07. (p=0.11)

The mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. (p=0.001)

The mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22. (p=0.001)

Using independent sample T test, the comparison of mean lipid profile between the groups was statistically significant. (p=0.001)

DISCUSSION

In the present study, the mean age of patients receiving phenytoin was 59.81 ± 14.94 and mean age of patients receiving Levetiracetam was 41.97 ± 15.63 years. (p=0.001). Majority of the patients (32.3%) receiving phenytoin belonged to the age group of 61 to 70 years and majority of the patients (29%) receiving levetiracetam belonged to the age group of 22 to 30 years. (p=0.008). A higher male preponderance was observed in the present study in phenytoin group (67.7%) and in levetiracetam group (71%). In a study by Seetlani NK et al lipid values found to be more deranged in patients aged 41-50 years.[8] A higher male preponderance was found in a study by Chen Z et al (51%) which were in concurrence with the findings of the present study.[9]

Cigarette smoke increases the metabolism of phenytoin, a widely used anti-epileptic agent, by inducing cytochrome P450 enzymes in the liver. Therefore, cigarette smoke may reduce the clinical effect of phenytoin.[10] In the present study 33.9% were smokers of which 11 patients (35.5%) received phenytoin and 10 patients (32.3%) received levetiracetam. (p=0.78). 48.4% consumed alcohol of which 15 patients (48.4%) received phenytoin and 15 patients (48.4%) received levetiracetam. Study by Rao Ch S et al observed that there was a significant increase in total cholestrol and LDL-C in tobacco users as compared to non tobacco users. [11] Another study by Jain RB et al noted that smoking is associated with adverse lipid/lipoprotein profiles among adult population. They observed that their patients showed higher TG and normal levels of HDL, LDL and TG.[12] Vu KN et al supported the causal role of regular low-to-moderate alcohol consumption in increasing HDL-C, reducing TG, total cholesterol, and LDL-c, and provides evidence for the novel finding that low-to-moderate consumption of alcohol reduces apoB and LDL-c levels.[13]

In this study mean total cholesterol in patients who received phenytoin was 165.90 ± 23.70 and in patients who received levetiracetam was 113.06 ± 17.22 thereby showing increased TC levels in the phenytoin group compared to levetiracetam. (p=0.001) These results were in concurrence with another study by Manimekalai K et al which showed that TC in patients receiving phenytoin was 186.5 ± 7.87 and mean TC in patients receiving levetiracetam was 170.90 ± 8.41.[4]

The mean HDL-C in patients who received phenytoin was 48.78 ± 9.35 and in patients who received levetiracetam was 45.36 ± 7.07 (p=0.11) thereby showing increased HDL-C levels in the phenytoin group compared to levetiracetam, however, the comparison was not statistically significant. (p=0.11). This is in contrary with another study by Manimekalai K et al which showed that HDL-C in patients receiving phenytoin was 71.1 ± 3.14 and mean HDL-C in patients receiving levetiracetam was 65.90 ± 3.16.[4] which showed significant increase in HDL-C levels.

In the present study, the mean LDL-C in patients who received phenytoin was 95.54 ± 13.66 and in patients who received levetiracetam was 72.37 ± 11.45. (p=0.001) thereby showing increased LDL-C levels in the phenytoin group compared to levetiracetam. Another study by Sudha et al compared the HDL-C levels at baseline and at 6 months and they observed that LDL-C levels in patients on phenytoin were 114.66±20.26 and at 6 months were 119.63±19.09. Also, LDL-C levels in patients on levetiracetam were 112.7±33.08 and at 6 months were 113.5±32.29.[14]

In the present study, the mean triglycerides in patients who received phenytoin was 148.07 ± 33.11 and in patients who received levetiracetam was 101.38 ± 9.22. (p=0.001) thereby showing increased triglycerides levels in the phenytoin group compared to levetiracetam. These results were in concurrence with another study by Manimekalai K et al which showed that triglycerides level in patients receiving phenytoin was 133.7 ±4.50 and mean TG in patients receiving levetiracetam was 125.80 ± 4.78.[4]

The results in our study findings are similar to those other investigations done by P Kumar et al., Pelkonen et al., Nikkila et al., and Luoma et al., also reported same findings i.e. an increase in TG, LDL-C and HDL-C levels in epileptic patients on long-term treatment with Phenytoin.[15,16]

It is possible that phenytoin will cause the CYP enzyme to become activated. These are the enzymes that trigger the CYP51 enzyme. The housekeeping gene CYP51, which is a member of the cytochrome P450 super family, is involved in the biological process of cholesterol synthesis in humans. The enzyme system known as CYP450 is involved in the processes of cholesterol production as well as cholesterol metabolism. Particularly important for the synthesis of cholesterol is the enzyme CYP51A1. The fact that there have been no detectable effects on lipid metabolism suggests that levetiracetam does not seem to be an inducer of the CYP51 enzyme.[17,18]

Overall, the comparison of mean lipid profile between the groups was statistically significant in the present study with patients on phenytoin displaying elevated serum lipid profile levels(TC, LDL-C and TG). (p=0.001) Thus, TC levels, LDL-C levels and TG levels can be a an important marker for estimating the risk of cardiovascular disease in epilepsy patients.

CONCLUSION

TC levels, LDL-C levels and TG levels can be an important marker for estimating the risk of cardiovascular disease in epilepsy patients.

According to this study, phenytoin and other CYP enzyme inducer anti-epileptic drugs are highly linked to higher amounts of TC, LDL-C, and TG, while levetiracetam did not show any major changes. Therefore, people who are taking inducer anti-epileptic drugs should have their blood cholesterol level checked on a regular basis.

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