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Research Article

A STUDY ON THE EFFECT OF ANTIEPILEPTIC DRUGS ON SERUM LIPID PROFILE AND CAROTID ARTERY INTIMA MEDIA THICKNESS IN CHILDREN BETWEEN 1 AND 12 YEARS

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ABSTRACT

Objectives: The objectives of this study were to know the effect of antiepileptic drugs (AED) on serum lipid profile and AIMT in children and to measure the serum lipid profile and CAIMT before starting antiepileptic drugs and 6 months after the use of antiepileptic drugs.

Methods: This study was a prospective comparative study conducted at Niloufer Hospital for women and children, Hyderabad between January 2019 and August 2020 in 78 children patients with seizures aged between 1 and 12 years of age includes both sex, taking antiepileptic drugs for the first time, and continuing for 6 months and more. Patients excluded who are having prior neurological or psychiatric disorder, genetic, or medical disorder.

Result: In this study, sample with levetiracetam total cholesterol at admission and 6 month after admission had significant positive correlation with p value of 0.014. With levetiracetam, low-density lipoprotein at admission and 6 months after admission had significant positive correlation with p value of 0.003.

Conclusion: Choice of AED has to be made carefully while starting AEDs in children with heart disease and risk of stroke which may, further, increase triglycerides and put the patient at further risk. Valproate, phenytoin, and levetiracetam can be used for control of seizures for children for long duration without much adverse effects.

Keywords: Lipid profile, Artery intima media, Antiepileptic drugs.

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INTRODUCTION

Epilepsy is among the commonly prevalent non-communicable disease, particularly related to Central nervous system [1]. The cumulative lifetime incidence of epilepsy is 3% and more than half of the cases begin in childhood. Seizures are common in pediatric age group and occur in approximately 10% of children. Epilepsy requires long-term anti-convulsant treatment. The overall aim in the treatment of epilepsy should be complete control of seizures and no adverse reaction due to medication with an optimal quality of life. Epidemiological, clinical, and experimental investigations have shown that antiepileptic drugs (AEDs) predispose to atherosclerosis by altering the lipid profile [2].

METHODS

This study was a prospective comparative study conducted at Niloufer Hospital for women and children, Hyderabad between January 2019 and August 2020 in 78 children patients with seizures aged between 1 and 12 years of age includes sex, taking antiepileptic drugs for the first time and continuing for 6 months and more. Patients excluded who are having prior neurological or psychiatric disorder, genetic, or medical disorder [1]. Patients with serious illness, malignancy, or other complications are also excluded for enrollment. All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice.

Data collected for baseline demographics, developmental history, serum lipid profile, and CAIMT were measured at baseline before starting antiepileptics and after 6 months of the therapy.

Statistical analysis

Data entry was done using Microsoft Excel 2013, version. Data analysis was done using SPSS 21.0 version. Data presented as mean. NOVA, paired samples t-test, and Pearson's correlation were used as tests of statistical significance. $p<0.05$ is considered as existence of statistical significance [3].

RESULTS

In this study, sample number of cases were 25 on Valproate with a Mean of 166.20 and 164.64 and with a Standard Deviation (SD) of 97.587 and 78.49 with total cholesterol (TC) at admission and after 6 months, respectively, with p value of 0.796. Mean of 104.40 and 96.56 and with a SD of 70.70 and 62.57 with low-density lipoprotein (LDL) at admission and after 6 months, respectively, with p value of 0.143. Mean of 126.27 and 168.88 and with a SD of 64.33 and 77.79 with triglycerides at admission and after 6 months, respectively, with p value of 0.001. Mean of 0.728 and 0.552 and with a SD of 0.4198 and 0.1960 with CIMT at admission and after 6 months, respectively, with p value of 0.0413 (Graph 1).

In this study, sample with valproate TC at admission and after 6 months had significant positive correlation with p value of 0.001. With valproate, LDL at admission and after 6 months had significant positive correlation with p value of 0.001. With valproate, triglycerides at admission and after 6 months had significant positive correlation with p value of 0.001. With valproate, CIMT at admission and after 6 months had non-significant negative correlation with p value of 0.144 [4].

With Valproate, TC 6 months after admission and CAIMT after admission had non-significant positive correlation with p value of 0.157. With valproate, LDL 6 months after admission and CAIMT after admission

had non-significant positive correlation with p value of 0.088. With valproate, TG 6 months after admission and CAIMT after admission had significant negative correlation with p value of 0.211 [2].

Phenytoin

In this study, sample number of cases were 15 on Phenytoin with a Mean of 122.93 and 132.53 and with a S.D of 33.53 and 40.98 with TC at admission and after 6 months, respectively, with p value of 0.065. Mean of 81.73 and 73.73 and with a S.D of 43.526 and 43.926 with LDL at admission and after 6 months, respectively, with p value of 0.122. Mean of 147.40 and 174.33 and with a S.D of 85.247 and 78.597 with Triglycerides at admission and after 6 months, respectively, with p value of0.053. Mean of 0.547 and 0.587 and with a S.D of 0.1767 and 0.2416 with CAIMT at admission and after 6 months, respectively, with p value of 0.138 (Graph 2).

In this study, sample with phenytoin TC at admission and 6 months after admission had significant positive correlation with p value of 0.001. With phenytoin, LDL at admission and 6 months after admission had significant positive correlation with p value of 0.001. With phenytoin, triglycerides at admission and 6 months after admission had significant positive correlation with p value of 0.001. With phenytoin, CIMT at admission and 6 months after admission was significant positive correlation with p value of 0.001.With phenytoin, TC 6 months after admission and CAIMT after admission had non-significant positive correlation with p value of 0.503 (Graph 3).

Levetiracetam

In this study, sample number of cases were 11 on levetiracetam with a mean of 143.55 and 144.55 and with a S.D of 23.628 and 23.619 with TC at admission and after 6 months, respectively, with p value of 0.857. Mean of 96.91 and 89.09 and with a S.D of 40.913 and 37.295 with LDL at admission and after 6 months, respectively, with p value of 0.319. Mean of 118.36 and 150.73 and with a S.D of 43.77 and 43.55 with triglycerides at admission and after 6 months, respectively, with p value of 0.013. Mean of 0.800 and 0.755 and with a S.D of 0.6132 and 0.5279 with CIMT at admission and after 6 months, respectively, with p value of 0.341.

In this study, sample with levetiracetam TC at admission and 6 month after admission had significant positive correlation with p value of 0.014. With levetiracetam, LDL at admission and 6 months after admission had significant positive correlation with p value of 0.003. With levetiracetam, triglycerides at admission and 6 months after admission had significant positive correlation with p value of 0.024. With levetiracetam, CIMT at admission and 6 months after admission had significant positive correlation with p value of 0.001. With levetiracetam, TC 6 months after admission and CAIMT after admission had non-significant positive correlation with p value of 0.518. With levetiracetam, LDL 6 months after admission and CAIMT after admission had non-significant negative correlation with p value of 0.671. With levetiracetam, TG 6 months after admission and CAIMT after admission had non-significant negative correlation with p value of 0.709.

n=11 r=0.219 p=0.518

This graph shows a positive correlation with TC with CAIMT at 6 months with r value of 0.219 and p value of 0.518.

n=11 r=−0.145 p=0.671

This graph shows a negative correlation of LDL with CAIMT at 6 months with r value of −0.145 and p value of 0.671

n=11 r=0.127 p=0.709

This graph shows a positive correlation with TRIGLYCERIDES with CAIMT at 6 month with r value of 0.127 and p value of 0.709

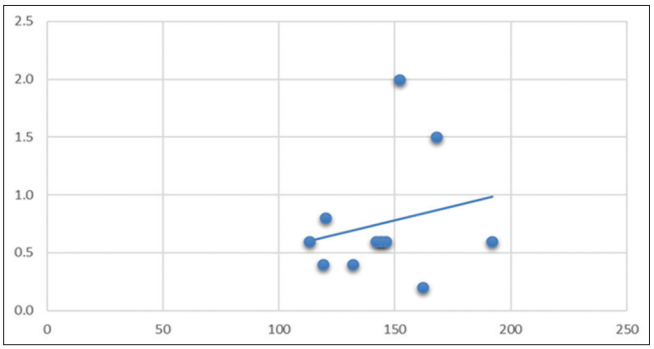
DISCUSSION

This study was analyzed to study the effect of AED on serum lipid profile and CAIMT. It also showed the correlation of lipid profile and CAIMT with AED. Seventy-nine patients were enrolled for the study out of which 28 patients were loss to follow-up. Hence, we ended with 51 patients, in which 49.0% (n=25) were female and 51.0% (n=26) were male. In this study, we compared CAIMT and various parameters of lipid profile with different drugs before initiation of treatment and at the end of 6 months and to know if there was correlation.

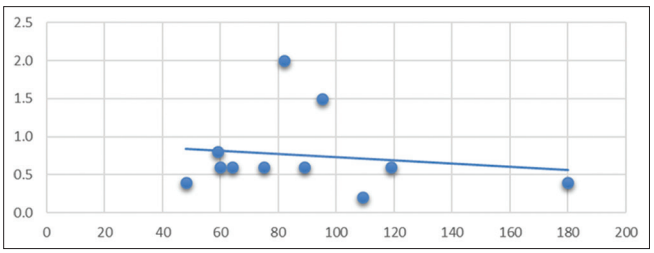
In this study with analysis of variance (ANOVA) between groups, there was a significant difference with a p value of 0.000, very less the reason being phenytoin being started in early age group, valproate is general avoided in infancy, and levetiracetam is not a first line drug. ANOVA for TC, LDL, TG, and CAIMT at admission between groups indicates that there was no significant difference and so selective bias is eliminated.

In this study with paired sample t-test with valproate (n=25), the mean TC at admission and 6 months was 166.20 and 164.64 with non-significant p value of 0.796. As there was no significant increase in TC with valproate usage, it can be started for children with risk factors for hyperlipidemia which may further increase the risk of future seizures and stroke.

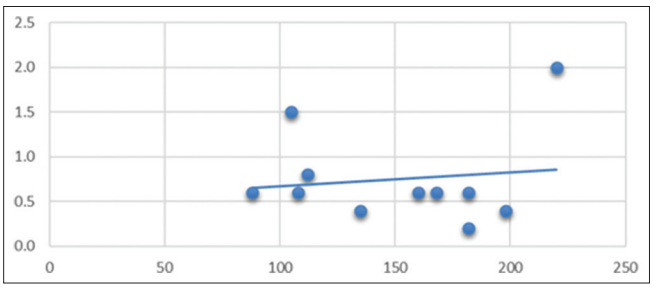
In this study with paired sample t-test with valproate (n=25), the mean LDL at admission and 6 months was 104.40 and 96.568 with non-significant p value of 0.143. As there was no significant increase in LDL



Graph 1: Total cholesterol Versus CAIMT at 6 months



Graph 2: LDL Versus CAIMT at 6 months



Graph 3: Triglycerides versus CAIMT at 6 months

with valproate usage, it can be started for children with risk factors for heart disease with family history of hyperlipidemias and dyslipidemias.

In this study with paired sample t-test with valproate (n=25), mean CAIMT at admission and 6 months was 0.728 and 0.552 with non-significant p value of 0.41. As there was no significant increase in CAIMT, valproate can be used in children with family history of strokes and dyslipidemias. Paired sample t-test with valproate, mean TG at admission and 6 months was 126.272 and 168.88 with significant p value of 0.000. As there was significant increase in TG with valproate, it has to be avoided in patients with risk of cardiovascular disease. Hypertriglyceridemia is also associated with obesity and metabolic syndrome.

In this study paired sample t-test with phenytoin (n=15), mean TC at admission and 6 months was 122.93 and 132.53 with non-significant p value of 0.065. As there was no significant increase in TC with phenytoin, it can be used in patients with seizures. Paired sample t-test with phenytoin (n=15), with mean LDL at admission and 6 months, was 81.73 and 73.73 with non-significant p value of 0.122.

In this study paired sample t-test with phenytoin (n=15), with mean CAIMT at admission and 6 months, was 0.547 and 0.587 with non-significant p value of 0.138.

Paired sample t-test with phenytoin, mean TG at admission and 6 months, was 147.40 and 174.33 with significant p value of 0.053. As there was significant increase in TG with phenytoin, it has to be avoided in patients with risk of cardiovascular disease.

In this study, paired sample t-test with levetiracetam (n=11), mean TC at admission and 6 months, was 143.55 and 144.55 with non-significant

Table 1: Age-wise distribution

	n	Mean	Std. Deviation	p-value
Valproate	25	5.528	2.9393	0.001
Phenytoin	15	1.220	0.2731	
Levetiracetam	11	4.218	2.3912	
total	51	3.978	2.9677	

Table 2: Sex distribution

	AEDS			Total
	Valproate	Phenytoin	Levitiracetam	
Gender				
Female				
Count	9	5	11	25
%	36.0%	33.3%	100.0%	49.0%
Male				
Count	16	10	0	26
%	64.0%	66.7%	0.0%	51.0%
Total				
Count	25	15	11	51
%	100.0%	100.0%	100.0%	100.0%

Chi-square = 14.613. Valproate

Table 3: Paired t-test

	Mean	n	Std. Deviation	p-value
Total cholesterol (at admission)	166.20	25	97.587	0.796
Total cholesterol (after 6 months)	164.64	25	78.491	
LDL (at admission)	104.40	25	70.704	0.143
LDL (after 6 months)	96.568	25	62.5762	
Triglycerides (at admission)	126.272	25	64.3362	0.001
Triglycerides (after 6 months)	168.88	25	77.796	
CAIMT (at admission)	0.728	25	0.4198	0.041
CAIMT (after 6 months)	0.552	25	0.1960	

LDL: Low-density lipoprotein

Table 4: Pearson's correlation (valproate)

	Pearson correlation coefficient	p-value
Total cholesterol at admission versus 6 months	0.965	0.001
LDL at admission versus 6 months	0.932	0.001
Triglycerides at admission versus 6 months	0.768	0.001
CAIMT at admission versus 6 Months	0.300	0.144
Cholesterol versus CAIMT at 6 months	0.292	0.157
LDL versus CAIMT at 6 months	0.348	0.088
Triglycerides versus CAIMT at 6 months	−0.259	0.211

Table 5: Paired t-test

	Mean	n	Std. Deviation	p-value
Total cholesterol (at admission)	122.93	15	33.533	0.065
Total cholesterol (after 6months)	132.53	15	40.986	
LDL (at admission)	81.73	15	43.526	0.122
LDL (after 6 months)	73.73	15	43.926	
Triglycerides (at admission)	147.40	15	85.247	0.053
Triglycerides (after 6 months)	174.33	15	78.597	
CAIMT (at admission)	0.547	15	0.1767	0.138
CAIMT (after 6 months)	0.587	15	0.2416	

LDL: Low-density lipoprotein

Table 6: Pearson's correlations (phenytoin)

	Pearson correlation coefficient	p-value
Total cholesterol at admission versus 6 months	0.895	0.001
LDL at admission versus 6 Months	0.908	0.001
Triglycerides at admission versus 6 months	0.822	0.001
CAIMT at admission versus 6 Months	0.936	0.001
Cholesterol versus CAIMT at 6 months	0.188	0.503
LDL versus CAIMT at 6 Months	0.204	0.467
Triglycerides versus CAIMT at 6 months	−0.433	0.107

Table 7: Paired t-test

	Mean	N	Std. Deviation	p-value
Total cholesterol (at admission)	143.55	11	23.628	0.857
Total cholesterol (after 6months)	144.55	11	23.619	
LDL (at admission)	96.91	11	40.913	0.319
LDL (after 6 months)	89.09	11	37.295	
Triglycerides (at admission)	118.36	11	43.773	0.013
Triglycerides (after 6 months)	150.73	11	43.557	
CAIMT (at admission)	0.800	11	0.6132	0.341
CAIMT (after 6 months)	0.755	11	0.5279	

Table 8: Pearson's correlation (levetiracetam)

	Pearson correlation coefficient	p-value
Total cholesterol at admission versus 6 months	0.713	0.014
LDL at admission versus 6 Months	0.804	0.003
Triglycerides at admission versus 6 months	0.671	0.024
CAIMT at admission versus 6 Months	0.976	0.001
Cholesterol versus CAIMT at 6 months	0.219	0.518
LDL versus CAIMT at 6 Months	−0.145	0.671
Triglycerides versus CAIMT at 6 months	0.127	0.709

p value of0.857. Paired sample t-test with levetiracetam (n=11), with mean LDL at admission and 6 months, was 96.91 and 89.09 with non-significant p value of 0.319.

In this study, paired sample t test with levetiracetam (n=11), with mean CAIMT at admission and 6 months, was 0.800 and 0.755 with non-significant p value of0.341. Paired sample t-test with levetiracetam, mean TG at admission and 6 months, was 118.36 and 150.73 with significant p value of 0.013. As there was significant increase in TG with levetiracetam, it has to be avoided in patients with risk of cardiovascular disease.

In this study, non-significant negative correlation was found for TG after 6 months and CAIMT after 6 months with valproate and with phenytoin. In this study, non-significant negative correlation was found for LDL after 6 months and CAIMT after 6 months with levetiracetam.

In this study, non-significant positive correlation was found for TC after 6 months and CAIMT after 6 months with valproate, with phenytoin and levetiracetam. Non-significant positive correlation was found for LDL after 6 months and CAIMT after 6 months with valproate and with phenytoin. Non-significant positive correlation was found for TG after 6 months and CAIMT after 6 months with levetiracetam.

The present study is comparable to the previous studies such as the study by Vishal *et al.* [5], which showed a significant increase in triglycerides with phenytoin and with levetiracetam. Increase in triglycerides has been found to be significant with phenytoin and levetiracetam at 6 months and 12 months.

The present study is also parallel to observations made by Manimekalai *et al*. [6], showed a significant increase in triglycerides with usage of valproate for 6 months with a significant p<0.0001and also parallel with Kumar *et al*. [7], showed a significant increase in TG with phenytoin.

Nadkarni *et al*. [8] did not find any significant difference in any parameter of lipid profile with respect to drug administration. Quilan *et al*. [9] showed a significant increase in CAIMT with valproate (MD=0.11,95% CI=0.06–0.15 mm) and Rosmaksoo *et al*. also showed a significant increase in CAIMT with phenytoin with p value of 0.00.

Vishal et al. showed significant increase in TC (p<0.001), LDL (p<0.009) with phenytoin, and TC (p<0.004) with Levetiracetam and LDL (p<0.056) being statically non-significant. Poojadewan *et al*. [10] showed a significant increase in mean TC (p<0.063,) with phenytoin and TG and LDL were not significant. Statically significant correlation was obtained between the use of phenytoin and serum TG levels (r=0.54, p<0.001)

Manimekalai *et al*. [6] showed a significant increase in TC (p=0.0001), LDL (p=0.029) with phenytoin and no statistical significant of TC, LDL, and TG with valproate and Levetiracetam. Emiliofranzoni *et al*. [11] showed a significant increase in TC with phenytoin, no significant change was observed with valproate, HDL and TG were no altered with any of the AED.

Limitations

First, since our results were based on observational studies, all of the possible cofounders might not have been controlled sufficiently. A particular concern relates to whether epilepsy itself or the prescribed AEDs plays a role in atherosclerosis.

The heterogeneity in CAIMT measurement may be due to inter observer variability.

CONCLUSION

Choice of AED has to be made carefully while starting AEDs in children with heart disease and risk of stroke which may, further, increase triglycerides and put the patient at further risk.

No increase in CAIMT, TC, and LDL may be due to genetic heterogeneity and isoenzyme variability between population.

To know the pathophysiology of these drugs on CAIMT and lipid profile, studies in larger population in different geographic regions are to be done further.

Valproate, Phenytoin, and levetiracetam can be used for control of seizures for children for long duration without much adverse effects.

CONFLICS OF INTEREST

Nil.

AUTHORS FUNDING

Nil.

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