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ORIGINAL RESEARCH

Evaluation of effect of valproatevs levetiracetam monotherapy on serum lipid profile and serum thyroid profile in children with seizure disorder: A retrospective observational comparative Study

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ABSTRACT

Aims & Objectives: To determine and compared the effect of Valproate and levetiracetam monotherapy on Thyroid and lipid profile in children with seizure disorder**. Material and Methods:** This comparative study will be carried out in Department of Paediatrics. The study population will be children with seizure disorder aged 1-15 years patient who registered and in follow up in O.P.D of guru Gobind Singh Medical hospital receiving levetiracetam or valproate monotherapy for more than 6 months. Thirty children will be enrolled in each group (Valproate and levetiracetam). After obtaining the written and informed consent from the parent/guardian of the children baseline details will be recorded as per a predesigned proforma. Fasting serum sample of 1.5 ml each for thyroid function (T3, T4 and TSH) and lipid profile (Total Cholesterol, Triglycerides, HDL-C LDL-C) will be obtained between 8.00and 10.00 a.m. in plain vial. Samples will be transported to lab immediately with icepack and processed immediately. Thyroid function will be processed by chemiluminescent immunoassay method by Beckman Coulter analyser. Lipids profile will be processed by Beckman Coulter Analysers. Reference range for Thyroid functions and lipid profile will be taken as per our laboratory references. **Results:** In the VPA group, male patients comprised 37.5%, which was lower compared to 50% in the Levetiracetam group. This difference was not statistically significant ($p = 0.321$). The sex ratio in the VPA group was 0.6:1 for males to females, indicating a higher proportion of females in the Valproate group. The mean weight, height, and mid-upper arm circumference in the Valproate group were 30.6 ± 15.66 kg, 122.03 ± 28.39 cm, and 11.17 ± 1.26 cm, respectively, compared to 24.13 ± 11.91 kg, 114.1 ± 25.41 cm, and 11.34 ± 1.4 cm in the Levetiracetam group. Although there was a trend toward higher weight, greater height, and higher body mass index in the Valproate group, these differences were not statistically significant ($p > 0.05$). MRI scans were performed in 24 patients—14 from the Valproate group and 10 from the Levetiracetam group. The remaining 38 patients were clinically diagnosed with epilepsy and managed with antiepileptic drug (AED) therapy without MRI imaging. In the Valproate group, MRI findings were normal in 2 patients (6.25%), whereas in the Levetiracetam group, MRI was normal in 5 patients (16.67%). Specific abnormalities in the Valproate group included one case each of encephalitis and West syndrome, hyperintensities with meningeal enhancement, and neurocysticercosis. Additionally, two patients had hyperintensity in the periventricular region, and two had periventricular leukomalacia. In the Levetiracetam group, hemicortical atrophy and non-communicating hydrocephalus were observed in one patient each. MRI findings suggestive of sequelae of hypoxic insult or hypoxic-ischemic encephalopathy (HIE) were seen in 5 patients (15.8%) in the Valproate group and in 3 patients (9.99%) in the Levetiracetam group. However, these differences in MRI findings between the two groups were not statistically significant ($p > 0.05$). Electroencephalography (EEG) was conducted in only 7 patients—3 in the Valproate group and 4 in the Levetiracetam group. EEG was not performed in the remaining 55 patients (90.63% in the Valproate group and 86.67% in the Levetiracetam group), who were clinically diagnosed with seizures. Among the patients who underwent EEG, one patient in the Valproate group showed

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seizure activity, and another showed wave slowing. In the Levetiracetam group, two patients had seizure activity, and one had generalized wave slowing. The EEG findings between the two groups were also not statistically significant ($p > 0.05$).
Conclusion: The present study is one of the first studies from North India in a Government Medical College to exclusively assess the effect of valproic acid (VPA) and levetiracetam (LEV) therapy on thyroid and lipid profile in children presenting with seizures. The role of VPA on disturbance in thyroid hormone milieu can be observed in our study in the form of mean elevation of TSH levels significantly in VPA vs LEV group. At the same time, we can see the protective role of LEV therapy on lipid profile parameters in having a statistically significant reduction in the various ratios, viz LDL/HDL, TGs/HDL and TC/HDL ratio. This finding can be of paramount importance in deciding the ideal treatment of children with seizure disorders in future, especially with underlying atherogenic potential. But, further prospective studies with an increased sample size considering the various confounders and involving a healthy control group can give definitive guidance in this regard in the future.

Keywords: valproic acid, levetiracetam,thyroid

INTRODUCTION

Seizures are brief episodes resulting from abnormal, excessive, or synchronous neuronal activity in the brain, often presenting with abrupt and involuntary skeletal muscle movements. The International League Against Epilepsy (ILAE) classifies seizures by their onset—focal, generalized, or unknown—and further subdivides them based on awareness and motor symptoms. The 2017 ILAE classification system involves three levels: identifying the seizure type, the type of epilepsy (focal, generalized, combined, or unknown), and the specific epilepsy syndrome. Each stage integrates etiology, as understanding the underlying cause is crucial for choosing effective, long-term antiepileptic treatment.[1,2,3]

In pediatric patients, seizures are often triggered by factors such as family history, fever, infections, neurological comorbidities, prematurity, or prenatal exposure to substances like alcohol or tobacco. While most pediatric seizures respond well to first-line antiepileptic drugs (AEDs), a subset of children experience drug-resistant epilepsy that necessitates lifelong treatment. Older AEDs such as carbamazepine and valproic acid remain widely used, but newer AEDs like levetiracetam and topiramate offer improved safety profiles and are effective for children who do not respond to traditional therapies.[4,5,6]

Valproic acid (VPA) is a short-chain fatty acid that increases GABA levels in the brain and is commonly prescribed for various seizure types. While effective, it has been associated with adverse effects, including somnolence, dizziness, hepatotoxicity, and rare but serious complications such as Stevens-Johnson syndrome. Levetiracetam (LEV), a second-generation AED, is approved for treating focal, myoclonic, and generalized seizures and is known for its relatively favorable safety profile. However, LEV may cause mood changes, irritability, and cognitive issues. It is minimally metabolized by the liver and eliminated mostly unchanged by the kidneys.[7,8]

Antiepileptic medications can also affect the endocrine system, particularly thyroid function. Thyroid hormones like T3, T4, and TSH are essential for normal growth and metabolism. While some studies have found elevated TSH levels in children taking VPA, others have reported no significant changes. LEV's effects on thyroid hormones are even less understood. In addition to hormonal changes, VPA has been linked to disruptions in lipid metabolism, including elevated cholesterol and triglycerides, increasing cardiovascular risk in later life. LEV does not appear to influence lipid profiles significantly.[9,10]

Given the potential for VPA and LEV to alter thyroid function and lipid profiles, especially in children, regular monitoring and individualized treatment plans are critical. These drugs may impact metabolism through various mechanisms, including enzyme induction and oxidative stress. Despite their widespread use, limited and conflicting data exist on their long-term metabolic effects in pediatric patients.[11,12] Therefore, this study aims to compare the effects of valproate and levetiracetam mono therapy on thyroid function and serum lipid profiles in children with seizure disorders, to guide safer and more effective treatment

MATERIALS AND METHODS

The present comparative study was conducted over one and a half years in the Department of Pediatrics, Guru Gobind Singh Medical College and Hospital, Faridkot. The study focused on children aged 1–15 years with epilepsy who had been on monotherapy with either Valproate or Levetiracetam for at least six months and were attending follow-up sessions in the pediatric OPD. Inclusion criteria were age between 1–15 years, on monotherapy for six months or more, and informed consent from parents. Exclusion criteria included children with systemic diseases affecting lipid or thyroid profiles, those on medications altering these parameters, on polytherapy, or whose parents refused consent.

The sample size was calculated based on a previous study evaluating thyroid-stimulating hormone (TSH) levels in children treated with Valproate and Levetiracetam. With an alpha error of 5% and power of 80%, the required sample size was 30 children per group. All eligible children meeting the inclusion criteria and visiting the pediatrics OPD during the study period were enrolled using a purposive sampling technique, following informed consent from

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guardians.

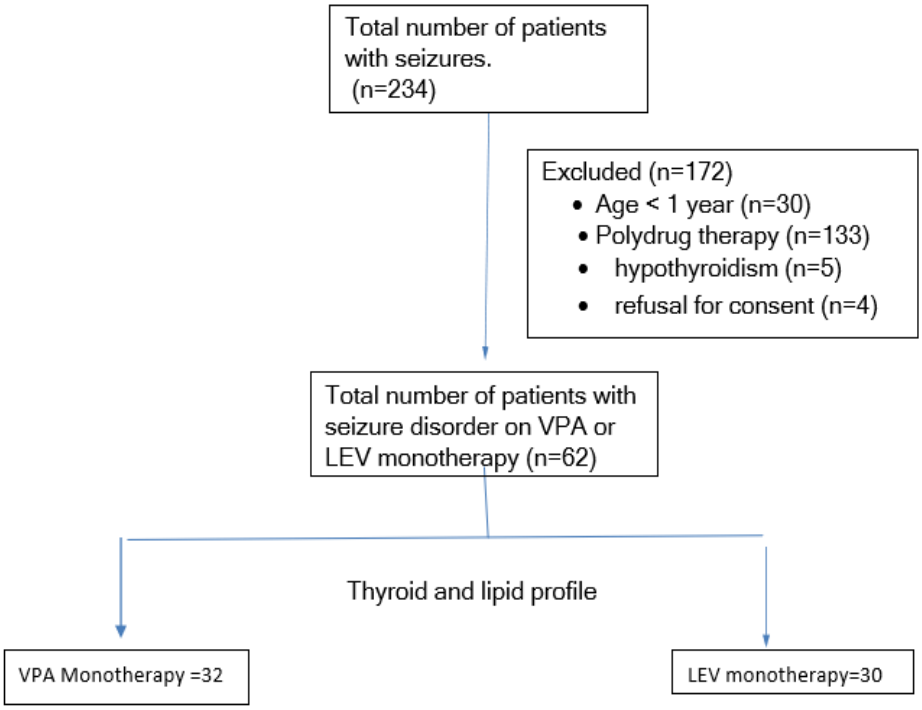
Data were collected using a structured interview and clinical examination. Detailed demographic and clinical information such as age, sex, seizure type, onset, etiology, MRI and EEG findings, drug dosage and duration, family history of cardiovascular diseases, and anthropometric measurements (height and weight) were recorded using a predesigned proforma. A thorough clinical examination was also conducted for each child. Blood samples were collected in the morning (fasting) to assess thyroid (T3, T4, TSH) and lipid profiles (Total Cholesterol, Triglycerides, HDL-C, LDL-C, and VLDL).

Blood samples were drawn in plain vials, stored at -20°C, and processed in the laboratory using Beckman Coulter analyzers. Thyroid function was assessed via chemiluminescent immunoassay, and lipid profiles were evaluated using standard protocols. Proper storage and handling of specimens were ensured, including backup procedures in case of equipment failure. The test results were interpreted using standard reference values provided by the laboratory.

Descriptive statistics will be used to summarize baseline variables. Categorical outcome variables will be analyzed using the Chi-square test with continuity correction, or Fisher's exact test when one or more expected cell counts are less than 5. Numerical variables will first be assessed for normality using the Kolmogorov-Smirnov test. Variables showing a normal distribution will be compared using the unpaired t-test, following assessment of variance equality through Levene's test (F-test). For non-normally distributed data, appropriate non-parametric tests, such as the Mann-Whitney U test, will be used. A p-value of less than 0.05 will be considered statistically significant. Data analysis will be performed using IBM SPSS version 23 (SPSS Inc., New York, USA), and the statistician conducting the analysis will be blinded to the intervention groups.

Bias Control: We minimized selection bias by including consecutive eligible patients and blinding the statistician to the treatment group.

No imputation was done for missing data; patients with incomplete profiles were excluded from analysis trail flow of study



RESULTS

Table 1: Comparison of Gender Distribution in Sodium Valproate and Levetiracetam Groups

	Sodium valproaten=32 n(%)	Levetiracetamn=30 n(%)	P value
Male	12(37.5%)	15(50.0%)	0.321
Female	20(62.5%)	15(50.0%)	
Mann Whitney tes twas used for Median values			

In the VPA group, male patients comprised 37.5%, which was lower compared to 50% in the Levetiracetam group. This difference was not statistically significant (p = 0.321). The sex ratio in the VPA group was 0.6:1 for males to females, indicating a higher proportion of females in the Valproate group.

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Table 2: Comparison of Anthropometry Parameters in the Sodium Valproate and Levetiracetam Groups

Anthropometric criteria	Sodium Valproate group n=32 n(±SD)	Levetiracetam group n=30 n(±SD)	P value*
Weight (kg)	30.6(±15.66)	24.13(±11.91)	0.100
Z score for Weight for age	1.07(±0.57)	0.988(±0.44)	0.516
Height(cm)	122.03(±28.39)	114.1(±25.41)	0.252
Z score for Height for age	0.706(±0.59)	1.1.64(±3.01)	0.403
Mid Upper Arm Circumference(cm)	11.17(±1.26)	11.34(±1.4)	0.717
Body mass index (kg/m^2)	19.14(±4.97)	17.64(±1.52)	0.120
Z Score for Body Mass Index for age	0.96(±0.56)	1(±0.62)	0.773
*Chi square test was used			

The mean weight, height, and mid-upper arm circumference in the Valproate group were 30.6 ± 15.66 kg, 122.03 ± 28.39 cm, and 11.17 ± 1.26 cm, respectively, compared to 24.13 ± 11.91 kg, 114.1 ± 25.41 cm, and 11.34 ± 1.4 cm in the Levetiracetam group. Although there was a trend toward higher weight, greater height, and higher body mass index in the Valproate group, these differences were not statistically significant ($p > 0.05$).

Table 3: Comparison of systemic parameters in Sodium Valproate and Levetiracetam Groups

Systemic Involvement	Sodium Valproate group N=32	Levetiracetam group N=30	P value*
Central Nervous System			
Higher Mental Functions			
Normal	26(81.2%)	25(83.3%)	0.830
Abnormal	6(18.8%)	5(16.7%)	
Any cranial Nervepalsy	0(0%)	0(0%)	>0.05
Tone			
Normal	26(81.2%)	25(83.3%)	0.956
Increased	5(15.6%)	16.7(10%)	
Decreased	0(0%)	0(0%)	
DeepTendon Reflexes			
Normal	26(81.2%)	25(83.3%)	0.398
Hyper reflexia	0(0.0%	1(3.3%%)	
Hypo reflexia	6(18.8%)	3(10.0%)	
Absent	0(0%)	1(3.3%)	
Plantar reflex			
Flexor	27(84.4%)	27(90.0%)	0.436
Extensor	5(15.6%)	3(10.0%)	
Signs of meningeal irritations	0(0%)	0(0%)	>0.05

Table 4: MRI Findings in Sodium Valproate and Levetiracetam Groups

MRI Findings	Sodium Valproate group n=32 n(%)	Levetiracetam group n=30 n(%)	P value*
Normal	2(6.25%)	5(16.67%)	0.171
Encephalitis, West Syndrome	1(3.12%)	0(0%)	>0.05
Hemicortical Atrophy	0(0%)	1(3.33%)	>0.05
Hyperintensities With Meningeal Enhancement	1(3.13%)	0(0%)	>0.05
Neurocysticercosis	1(3.13%)	0(0%)	>0.05
Non-Communicating Hydrocephalus	0(0%)	1(3.33%)	>0.05
Periventricular Leukomalacia	4(12%)	0(0%)	>0.05
Sequel Of Hypoxic Insult? HIE	5(15.8%)	3(9.99%)	>0.05
*Chi square test was used			

MRI scans were performed in 24 patients—14 from the Valproate group and 10 from the Levetiracetam group. The remaining 38 patients were clinically diagnosed with epilepsy and managed with

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antiepileptic drug (AED) therapy without MRI imaging. In the Valproate group, MRI findings were normal in 2 patients (6.25%), whereas in the Levetiracetam group, MRI was normal in 5 patients (16.67%). Specific abnormalities in the Valproate group included one case each of encephalitis and West syndrome, hyperintensities with meningeal enhancement, and neurocysticercosis. Additionally, two patients had hyperintensity in the periventricular region, and two had periventricular leukomalacia.

In the Levetiracetam group, hemicortical atrophy and non-communicating hydrocephalus were observed in one patient each. MRI findings suggestive of sequelae of hypoxic insult or hypoxic-ischemic encephalopathy (HIE) were seen in 5 patients (15.8%) in the Valproate group and in 3 patients (9.99%) in the Levetiracetam group. However, these differences in MRI findings between the two groups were not statistically significant ($p > 0.05$). Electroencephalography (EEG) was conducted in only 7 patients—3 in the Valproate group and 4 in the Levetiracetam group. EEG was not performed in the remaining 55 patients (90.63% in the Valproate group and 86.67% in the Levetiracetam group), who were clinically diagnosed with seizures. Among the patients who underwent EEG, one patient in the Valproate group showed seizure activity, and another showed wave slowing. In the Levetiracetam group, two patients had seizure activity, and one had generalized wave slowing. The EEG findings between the two groups were also not statistically significant ($p > 0.05$).

Table 5: Comparison of Type of Seizures in Sodium Valproate and Levetiracetam Groups

Type of seizures	Sodium Valproate group n=32 n(%)	Levetiracetam group n=30 n(%)	P value*
GTCS	30(93.8%)	29(96.7%)	0.346
Focal	2(6.2%)	1(3.3%)	
*Chi square test was used			

Table 6: Comparison of Anti-Epileptic Therapy Duration in Sodium Valproate and Levetiracetam Groups

	Sodium Valproate group n=32 Median(IQR)	Levetiracetam group n=30 Median(IQR)	P value*
Median Duration of AED in months	24(12,60)	24(12,39)	0.879
Values are shown in. Median (IQR 25th and IQR 75th centile) *Mann Whitney U test was used			

Table 7: Dose of Antiepileptic Drug (AED) in mg/kg/day

mg/Kg/day	Sodium Valproate group n=32 n(%)	Levetiracetam group n=30 n(%)	P value*
<20	4(12.5%)	3(10%)	0.119
20-40	24(75.0%)	27(90%)	
>40	4(12.5%)	0(0%)	
;*Chi square test was used for categorical variables			

Table 8: Comparison of current median dose in the Sodium Valproate and Levetiracetam groups

Anti-Epileptic Parameter	Sodium Valproate group n=32 n(IQR)	Levetiracetam group n=30 n (IQR)	P value*
Median current dose In mg per kg per d**	25(20,30)	25(20,30)	0.930
Values are shown in. Median (IQR 25th and IQR 75th centile) *Mann Whitney U test was used*			

Table 9: Comparison of Median Age at Onset of Seizure in Sodium Valproate and Levetiracetam Groups

Parameter	Sodium Valproate group n=32 Median(IQR)	Levetiracetam group n=30 Median(IQR)	P value*
Age at onset Of seizures in months	24(12,57)	24(12,48)	0.714
.*Mann Whitney test was used for Median values(IQR 25th and IQR 75th centile)			

In the VPA group, the median age of seizure onset was 24 months, with an interquartile range (IQR) of 12 to 48 months. The LEV group also showed a median age of onset of 24 months, but with a narrower IQR of 12 to 24 months. One outlier was noted in the LEV group, where the age of onset was 120 months. The difference between the two groups was not statistically significant ($p = 0.714$).

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Table 10: Comparison of Mean Values of Individual Components of Thyroid Function Tests in the Sodium Valproate Group and Levetiracetam Group

	Sodium Valproate group n=32	Levetiracetam group n=30	P value
fT3(pg/dl)	3.452(±1.16)	3.537(±1.14)	0.773
fT4(ng/dl)	0.900(±0.50)	1.504(±1.85)	0.082
TSH (pg/ml)	5.53(±3.64)	3.040(±0.89)	0.001
Values are shown in Mean (SD).* Independent T test was used			

Table 11: Comparison of FT3 as per age in Sodium Valproate group and Levetiracetam group.

	Sodium Valproate group n=32	Levetiracetam group n=30	P value*
fT3			
Normal	25(78%)	30(100%)	0.007
Increased	0(0%)	0(0.0%)	
Decreased	7(21%)	0(0.0%)	
Chi square test was used			

Table12: Comparison of FT4 as per age in Sodium Valproate group and Levetiracetam group

	Sodium Valproate group N=32 n(%)	Levetiracetamgroup N=30 n(%)	P value*
Normal	22(68.75%)	30(100%)	0.001
Increased	0(0%)	0(0%)	
Decreased	10(31.25%)	0(0%)	
Chi square test was used			

Table 13: Comparison of TSH as per age in the Sodium Valproate group and Levetiracetam group

	Sodium Valproate group N=32 n(%)	Levetiracetam group N=30 n(%)	P value*
Normal	27(84.4%)	100(0%)	0.024
Increased	5(15.6%)	0(0%)	
Decreased	0(0%)	0(0%)	
Chi square test was used			

Table 14: Comparison of presence of Any Thyroid Function test abnormality in Sodium Valproate and Levetiracetam groups.

Any Thyroid Function Test abnormality	Sodium Valproate Group n=32 n(%)	Levetiracetam Group n=30 n (%)	P*value
Normal	22(68.8%)	30(100%)	0.001
Abnormal	10(31.2%)	0(0%)	
*Chi square test was used			

Table 15: Comparison of Mean Values of Individual Components of the Lipid Profile Between the Sodium Valproate and Levetiracetam Groups

	Sodium Valproate group n=32 Mean (±SD)	Levetiracetam group n=30 Mean (±SD)	P-value*
Total Cholesterol (mg/dl)	141.56(±33.31)	133.07(±24.64)	.261
TG(mg/dl)	101.84(±36.68)	110.97(±48.29)	.404
HDL(mg/dl)	35.13(±11.51)	44.03(±13.15)	.006
LDL(mg/dl)	84.08(±32.58)	78.03(±20.07)	.386
VLDL(mg/dl)	21.76(±9.12)	21.13(±10.68)	.801
Values are shown in Mean (SD).*Independent T test was used TC=Total cholesterol, HDL=High density lipoprotein, LDL=Low density lipoprotein, VLDL=Very low density lipoprotein TG= Triglycerides,			

Table 16: Comparison of Mean Values of Lipid Profile Component Ratios Between the Sodium Valproate and Levetiracetam Groups

	Sodium Valproate group n=32 Mean(±SD)	Levetiracetam group n=30 Mean(±SD)	P value*
LDL-C/HDL-C	2.59(±1.43)	1.96(±0.87)	.044

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TC/HDL-C	3.37(±2.73)	1.86(±1.88)	.014
TGs/HDL-C	2.75(±2.81)	1.45(±1.69)	.033

Table 17: Comparison of Age-Related Cholesterol Levels Between the Sodium Valproate and Levetiracetam Groups

Total Cholesterol	Sodium Valproate group N=32 n(%)	Levetiracetam group N=30 n(%)	P value*
Normal	30(93.8%)	30(100%)	0.164
Increased	2(6.2%)	0(0%)	
Decreased	0(0.0%)	0(0%)	
*Chi square test was used			

Table 18: Comparison of Age-Related LDL Levels Between the Sodium Valproate and Levetiracetam Groups

	Sodium Valproate group N=32 n(%)	Levetiracetam group N=30 n(%)	P value*
Normal	28(87.5%)	26(86.7%)	0.922
Increased	0(0%)	0(0%)	
Decreased	4(12.5%)	4(13.3%)	

*Chi square test was used

Table 19: Age-Related Comparison of HDL Levels Between the Sodium Valproate and Levetiracetam Groups

	Sodium Valproate group N=32 n(%)	Levetiracetam group N=30 n(%)	P value*
Normal	11(34.4%)	20(66.7%)	0.011
Increased	0(0%)	0(0%)	
Decreased	21(65.6%)	10(33.3%)	

*Chi square test was used

Table 20: Age-Related Comparison of VLDL Levels Between the Sodium Valproate and Levetiracetam Groups

	SodiumValproate group N=32 n(%)	Levetiracetam group N=30 n(%)	P value*
Normal	32(100%)	29(96.7%)	0.298
Increased	0(0%)	1(3.3%)	
Decreased	0(0%)	0(0%)	
*Chi square test was used			

Table 21 Comparison of presence of any lipid profile abnormality in Sodium Valproate and Levetiracetam groups

Any Lipid Profile abnormality	Sodium Valproate group n=32 n(%)	Levetiracetam group n=30 n(%)	P value*
Absent	7(21%)	15(50%)	0.021
Present	25(78.1%)	15(50%)	
*Chi square test was used			

DISCUSSION

This comparative study titled "Evaluation of the Effect of VPA vs LEV Monotherapy on Serum Lipid Profile and Serum Thyroid Profile in Children with Seizure Disorder – A Comparative Study" was conducted from January 2021 to October 2022 in the Departments of Paediatrics and Biochemistry at Guru Gobind Singh Medical College and Hospital, Faridkot. The study aimed to evaluate the effects of valproic acid therapy versus LEV therapy on thyroid and lipid profiles in patients who had been on these drugs for more than six months. A total of 60 patients aged between 1 and 15 years were targeted for the study. Ultimately, 32 children in the valproic acid group and 30 in the LEV group were evaluated after meeting the inclusion and exclusion criteria outlined in the methodology.

In the present study, the age group of the enrolled study population was ≥12 months and ≤144 months. The median (IQR) of age was 68.5 (39-120) months in VPA group and 54 (30-84 months) in LEV group. Mean age was 76.41±51.74 months in VPA and 64.7±44.48 in LEV group in the present study. In a studies done by Rahman U et al , Aggrawal et al,

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Doneray et al age group taken was 36 months to 144 months , 24 months -144 months ,24 months-180 months each respectively in the valproic acid group[13,14,15]. In Nishiyama M et al, which included only patients on LEV the age group enrolled was from 24 months to180 months[16]. Mean age was 80 months in the study by Yuskel et al which was comparable to our study (76.41 months) for VPA group. In LEV group studies by Attilakos et al, Nadakarni et al the age group of children included in their studies were 24 months to 180 months [17,18] whereas in the study by Gopi Shrikanth M et al it was 12 to 144 months, which is the same as our study[19]. The mean age in the study by Attilakos et al was 81.6 months, which was different from our LEV group (64.7 months). Median age was not calculated in any of these studies.[17]

In our study, in the VPA group, out of 32 enrolled patients, males constituted 37.5% (12/32) and female 62.5% (20/32) of the population, whereas in out of the 30 patients in LEV group equal number of males and females were enrolled. In VPA group studies by Yuskel et al, Doneray et al population enrolled included 13 males and 16 females vs 40 males and 16 females, respectively, which was similar to our study, [20]. In LEV group studies by attilakos et al, saheta et al a comparable number of population to our current study viz 18 males and 21 females,13 males and 17 females respectively [17] was enrolled whereas in a study by El Farahtay et al,10 males and 2 females were enrolled, which were different from our population.[21]

In our study population, mean weight, height, mid upper arm circumference and BMI in the VPA group was 30.6 kg ± 15.66 kg, 122.03 ± 28.39 cm, 11.17 ± 1.26 cm,19.14±4.97 as compared to 24.13 ±11.91 kg, 114.1 ± 25.41 cm and 11.34 ± 1.4 cm in the LEV group respectively. In the VPA group there was a trend of more weight, more height, and more body mass index, which is similar as in study by Vafee sahi et al while in other studies anthropometric parameters were not compared[22]. Out of the studies done in LEV group, in one of the study by Attilakos et al weight was 25.3 ±15.4 Kg and height was 121.1±24.2 cm which was comparable as our study population. In rest of the other studies anthropometric parameters were not compared.[17]

The higher mental functions were abnormal in 18.8% patients in the VPA group as compared to the 5(16.7%) patients in the LEV group. The muscle tone in 15.6% patients in the VPA group was increased as compared to the 53.3% patients in the LEV group. None of the patients in either group had hypotonia. Deep tendon reflexes were normal and decreased in 81.2% and 18.8% patients respectively in the VPA group. In the LEV group, they were Normal, increased, with Hyporeflexia, and absent in 83.3%, 3.3%%, 10.0% and 3.3% patients respectively. All these CNS examination parameters were having no statistically significant difference in the two groups (p value > 0.05). Similarly, all the other systemic examinations pertaining to cardiovascular system, respiratory system and abdominal systems were similar in both the groups with no statistical significance. (p>0.05). No study compared the underlying clinical profile of patients suffering from seizures, who were on AEDs.

In the patients comprising of VPA group, GTCS type of seizure was present in 93.8% patients and focal seizure in remaining 6.2% patients. In a study by El-Farahaty et al [21], partial seizures were seen in 95% and 100 % of their study population in the VPA group and LEV group respectively. Only 5% population of the VPA group had generalized seizures. The difference may be attributable to the underlying differences in the pathophysiology of seizures in the two study populations.

Mean duration of AED therapy for VPA and LEV was 37.1±29.03 months and 28±24.44 months respectively in our study. In study by Karatoprak et al mean duration of VPA was 30.2±11.6 months and LEV was 24.6±11.2 months [23]. In almost all the studies the thyroid profile and lipid profile were taken at least after 6 months of AED therapy just like our study, with most of them having baseline values also. Our study had this limitation of not having the baseline values as all these patients were already on VPA or LEV monotherapy for at least more than 6 months, when these samples were taken.

In our study dose of AED in mg per kg per day for VPA and LEV groups was compared. In the dose group of <20 mg/kg/day, 12.5% patients in VPA and 10% in LEV group were present respectively. Similar values for the dose group of 20-40 mg/kg/day for VPA and LEV groups were 75.0% and 90% respectively and in the dose group of >40 mg/Kg/day, only 12.5% patients belonging to the VPA group alone were present. p value was found to be 0.119 for this data which was statistically not significant. No other study as per our knowledge has done comparison on the basis of daily dose strength being given in VPA and LEV group.

The median current dose in the both the VPA group and LEV group was 25 mg/kg/day. The mean values for the two groups were 26.4±8.63 mg/kg/day and 26.3±8.80 mg/kg/day in the VPA group and LEV group respectively. The difference between the two doses being given was not having any statistical significance. In a study by Karatoprak et al, the mean dosage of VPA was 20.5 ±7.5 mg/kg/day, whereas the mean dosage of LEV was described as 27.7 ±8.5 mg/kg/day [23]. These values are almost similar to our study.

In the VPA group median age of onset of seizures was 24 months, with an interquartile range of 12 to 48 months. The similar median value for the LEV group was also 24 months, and IQR was 12 to 24 months. This data was statistically insignificant. No other study compared the mean age of onset of seizures to the best of our knowledge.

The mean absolute value of T3 was 3.452 (±1.16)

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pg/dl in VPA group versus 3.537 (±1.14) pg/dl in the LEV group. The mean absolute value of T4 was 0.90(±0.50) (ng/dl) in the VPA group versus 1.504(±0.08) (ng/dl) in the LEV group. Both mean T3 and T4 values in the two groups were statistically not significant (p=0.773 and p=0.082, respectively). In the VPA group the mean TSH value was significantly higher than in the LEV group [5.53(±3.64)] pg/ml vs [3.040(±0.89), p=0.025. These values are similar as in study by Cansu et al done on VPA patients [24], where in mean fT4 (ng/ml) was 1.29 ± 0.25, mean ft3 (pg/ml) was 3.16 ± 0.74 and mean TSH (µIU/ml) was 3.17 ± 1.53 which shows increase in TSH level which is similar as our study.

In a study by Vainionpaa et al mean fT4 was15.8±2.4, ft3 was 35.3±0.6 and TSH was 2.1±0.8. FT3. fT4 levels were normal, but increase in TSH level in the subclinical hypothyroidism range was evident in the VPA group[25]. Similarly, in the study by Aggarwal et al, in VPA group, the mean T3 values were 4.53±1.9, T4 values were 1.40±0.63, and TSH values were 4.53±1.9 [13]. In the study by Sahu et al, the median range titres of fT4 were 13.7 pmol/L, of TSH were 3.6 mU/ml in the VPA group of patients [26]. Kafadar et al showed no change in fT4 and fT3 concentration whereas TSH levels were significantly higher after 12 months of VPA treatment [27].

Our study revealed the need for supplementing seven patients in the VPA group with thyroxine as their fT3 levels were low for age and TSH levels were also elevated. We couldn't get the repeat tests and further evaluations done in this group including anti TPO antibodies in these patients as our study entailed to just undertake the thyroid profile and lipid profile testing done just once and these patients didn't report again for retesting during the study period as they were lost to follow up. In a study by Attilalkos et al on LEV group of patients, T4 (ng/dL) after 12 months of therapy was 8.78 ± 1.56 ng/ml, p value 0.486, fT4 (ng/dL) 1.37 ± 0.13, p value 0.349 and TSH (µIU/mL) 3.26 ± 1.56 p value 0.218 which was statistically not significant and is similar to our current study.[17]

Our study shows that VPA group patients had significantly lower values of fT3 (21% vs 0%) and fT4 (31.25% vs 0%) and higher values of TSH (15.6% vs 0%) when compared with LEV group (p value <0.05). The patients in the VPA group had 22% more chances of having lower T3 as compared to the LEV group [p=0.007)]. The patients in the VPA group had 31% more chances of having lower T4 as compared to the LEV group [p value=0.001]. The patients in the VPA group had 16% more chances of having higher TSH as compared to the LEV group [p=0.024]. Cansu et al in their study found that fT3 was decreased in 3% children and 6.6% had serum fT4 levels below the reference range [24]. There was a trend of increase in serum TSH levels throughout the study with a significant difference. The grossly different percentage can be attributed to the different study population and reference values and underlying prevalence of hypothyroidism as such which may be different in the two population groups. As we didn't rule out the cause of thyroid dysfunction being attributable to underlying dietary deficiencies or primary thyroidal illness as we had symptomatic patients who required thyroxine supplementation. All other studies involving the role of drugs into affecting thyroid function revealed the presence of subclinical hypothyroidism rather than overt hypothyroid state requiring therapy in our study.

In our current study comparison of abnormality in any of the thyroid profile parameter was done. It showed that there was significant difference in the VPA and LEV groups. 10 (31.25%) of the patients in the VPA group had at least one parameter abnormality as compared to 0% in the LEV group (p value <0.05). Thus, it was inferred that in VPA group there are 31% more chances of having any thyroid function test abnormality vs none in LEV group. This type of comparison wasn't done in any of the studies.

In our study the mean absolute value of individual components of lipid profile in the two groups revealed the mean absolute values in VPA group vs LEV group for total cholesterol, TG and LDL as, 141.56(±33.31);133.07(±24.64), 101.84(±36.68);110.97(±48.29) mg/dl and 84.08(±32.58) mg/dl;78.03(±20.07) respectively. The p- value for the same was statistically not significant. The mean absolute value of High-density lipoprotein in the VPA group was significantly lower than in the LEV group (35.13(±11.51) vs 44.03(±13.15) mg/dl, p=.0066).

In a study by Saheta et al,[28] comparison of lipid profiles in VPA and LEV group was done. The mean values in VPA group vs LEV group for total cholesterol, TG and LDL were 157.06±36.05;128.67±31.37, 128.83 ±24.65;104.72 ±19.81 and 90.61 ± 19.03;73.98 ± 11.68 mg/dl respectively. The mean values for High density lipoprotein in VPA vs LEV group were 40.99±4.60 and 46.44±4.86 mg/dl respectively. VPA group had a decrease in level of HDL as comparable to our study. The results of this study are similar as our current study. In LEV group study, done by Aaltikos et al,[17] after 12 months of treatment mean total cholesterol was 159.7 ± 30.8 mg/dl, p value being 0.985. For HDL, the values were 57.0 ± 12.3 mg/dl, p value being 0.420, for LDL it was 92.3 ± 28.5 mg/dl, p value being 0.164 which was non-significant. Mean TG values were decreased, being 52.5 ± 20.6 mg/dl with a p value < 0.001 which was statistically significant. Our results also showed a decline in the trend of TGs in the LEV group of patients. This similarity might be chance occurrence or might be due to some still unknown mechanism of action of LEV responsible for reduction in TGs.

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This needs to be further corroborated by larger prospective trials involving LEV use in patients. In another study by Aditi Dhir et al, mean serum total cholesterol in mg/dL (SD; range) was 148.3(26.9; 90-189) with a p value of 0.002, mean serum HDL cholesterol in mg/dL (SD; range) was 43.5 (9.9; 23-50) with a p value of 0.37 and mean serum triglycerides mg/dL (SD; range) was 96.9 (38.6; 50-226) with a p value <0.001. In another study by El-Farahaty et al in the VPA vs LEV group, Cholesterol, LDL, TG, and HDL levels were 164.7±28.5;130±4.8, 101.8±20.2;80.2±8.4, 78.65±12.7;69.0±8.87 and 44.8±6.83;43.16±2.98 respectively [21]. These studies show higher levels of serum cholesterol and triglycerides in children on VPA monotherapy, which is not seen in our study. This difference may be attributed to a different age group in their study population (3-18 years), geographical variations and dietary preferences.

Cholesterol levels were increased in 6.2% patients on valproic acid group as compared to none in the LEV group and valproic acid group had 6.2% more chances of having elevated cholesterol levels than the LEV group. 15.6% of patients in the valproic acid group versus 10% of patients in the LEV group had increased triglyceride values. There were 5.6% more chances of elevated triglycerides in the valproic acid group than LEV group. LDL was decreased both in the valproic acid group and LEV group to the tune of 12.5% and 13.3% respectively. VLDL was increased in only one patient (3.3%) in the LEV group. All these values in the cholesterol, triglycerides, LDL and VLDL when compared in the two groups were statistically insignificant. (p>0.05). HDL levels were decreased in 65.6% cases in the valproic acid group as compared to 33.3% in the LEV group. The valproic acid group had 32.4% increased chances of having decreased HDL levels as compared to the LEV group. This difference was statistically significant. (p=0.011). Studies on the effect of VPA and LEV on percentage involvement of individual parameters of lipid profile are not available to the best of our knowledge.

In our study, the mean absolute value of ratio of low-density lipoprotein to High-density lipoprotein (LDL/HDL) in the VPA group was significantly higher than in the LEV group (2.59(±1.43) vs 1.96(±0.87), p=0.044). Similarly, the mean ratio of total cholesterol to High-density lipoprotein (TC/HDL) in the VPA group was significantly higher than in the LEV group (3.37(±2.73) vs 1.86(±1.88), p=0.014). The mean absolute value of ratio of triglyceride to High-density lipoprotein (TGs/HDL) in the VPA group was significantly higher than in the LEV group (2.75(±2.81) vs 1045(±1.69), p=0.033). In the study by El- Farahaty et al,[21] the LDL/HDL ratio in VPA vs LEV group was 2.31±0.7 and 1.86±0.22 respectively, p value being <0.01. Similarly, for TC/HDL ratio in VPA vs LEV group was 3.6±0.90 and 3.03±0.14 respectively, p value being <0.001. These findings are similar with our study. In the study by Attilakos et al involving LEV monotherapy, LDL/HDL ratio after 12 months of therapy was 1.72±0.71 which was statistically significantly (p=0.025) decreased from the baseline values[17]. Similarly, the ratio of TGs/HDL after 12 months of therapy was 0.99±0.49 which was also statistically significantly decreased from baseline values. (p=0.003).

In our current study we compared abnormality in any parameter of lipid profile. It showed that in VPA group there were 21 % more chances of derangement in atleast one parameter whereas in LEV group there 50 % chance for the same. No other study has evaluated the role of any lipid abnormality in their study population to the best of our knowledge.

Finally, from the above discussion, we can conclude that VPA therapy has a significant detrimental effect on both thyroid profile as well as lipid profile parameters. The same has also been reflected in the observations of the present study. LEV therapy has virtually no effect on the thyroid profile, as can be evidenced by the above discussion and our study observations. Our study did show a possible favourable effect of LEV monotherapy on serum lipids in children with epilepsy. There was a decreasing trend in the TGs, TGs/HDL-C ratio, and LDL-C/HDL-C ratio. Studies by El Farahaty et al and Attilakos et al also corroborate the above findings, [21,17]. Many Individuals with high TGs/HDL-C or LDL-C/HDL-C have a greater risk for cardiovascular disease due to the imbalance between atherogenic and protective lipoproteins[29,30]. This suggests that these changes in lipid profile observed in our LEV study group may have a beneficial effect on later cardiovascular disease risk in children with epilepsy. The protective effects of LEV monotherapy on thyroid and lipids in the patients seem to have led us believe that probably we have found the perfect drug for seizures in the form of Levetiracetam. But it is too rosy to have a blanket statement for verifying this and further prospective studies involving larger cohorts across different geographical locations, different underlying disease processes leading to seizures and dietary preferences as confounders to be taken care of will be required for basing recommendations of using LEV as primary monotherapy for children with seizure disorder.

CONCLUSION

The present study is one of the first studies from North India in a Government Medical College to exclusively assess the effect of valproic acid (VPA) and levetiracetam (LEV) therapy on thyroid and lipid

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profile in children presenting with seizures. The role of VPA on disturbance in thyroid hormone milieu can be observed in our study in the form of mean elevation of TSH levels significantly in VPA vs LEV group. At the same time, we can see the protective role of LEV therapy on lipid profile parameters in having a statistically significant reduction in the various ratios, viz LDL/HDL, TGs/HDL, and TC/HDL ratio. This finding can be of paramount importance in deciding the ideal therapeutic treatment of children with seizure disorders in the future, especially with underlying atherogenic potential. But, further prospective studies with an increased sample size, taking into consideration the various confounders and involving a healthy control group, can give definitive guidance in this regard in the future. These findings may not be generalizable to children with polytherapy or in different geographical settings.The study's limitations include its single-center nature, a relatively small sample size, the absence of a healthy control group, and the lack of follow-up assessments to monitor correction of thyroid or lipid abnormalities

Ethics Approval

The study was approved by the Institutional Ethics Committee of the college,. Waiver of consent for retrospective data analysis was obtained."

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