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Research Article

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A Prospective Study on Effect of Monotherapy Antiepileptics on Hematological Parameters and Various Biochemical Parameters in Epilepsy Patients

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ABSTRACT

Objective: Epilepsy is a neurological disorder which often requires lifelong treatment with antiepileptic drugs (AEDs). Prolonged use of AEDs is associated with changes in vascular risk markers. Hence, the study was designed to evaluate the effect of older generation AEDs (carbamazepine and phenytoin) and newer generation AED (levetiracetam) monotherapy on the markers of vascular risk in epilepsy patients. Methods: This study was carried out in the neurology department of a tertiary care hospital for a period of 7 months. Clinical and biochemistry reports of 90 patients were collected in designed case report forms. All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) 17 and Graph Pad Prism 7.0. Results: We observed statistically significant changes in the liver enzyme level and glycated hemoglobin (HbA1c) in carbamazepine and phenytoin received groups. We did not observe any statistically significant difference in the above parameters in levetiracetam group but this group showed a significant change in complete blood count. Conclusion: Careful monitoring of the liver enzymes and HbA1c at regular intervals throughout the treatment course is considered necessary in epileptic patients undergoing long-term treatment with enzyme inducing AEDs.

Keywords: Epilepsy; Carbamazepine; Phenytoin; Levetiracetam; Vascular disease

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INTRODUCTION

Epilepsy is a neurological disorder characterized by the recurrent and unpredictable occurrence of seizure. A Seizure is a sudden surge of electrical activity in the brain which produces transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neuron. The word “epilepsy” requires an event of at least one epileptic seizure [1]. World Health Organization (WHO) estimates that 8 per 1000 population worldwide have epilepsy. Prevalence of epilepsy is higher in developing countries as compared to developed countries [2]. In developing countries like India, the incidence of epilepsy which is a measure of number of new persons with epilepsy per 100,000 populations per year ranges from 100-190 per 100,000 populations, whereas in most developed countries it may range from 40-70 per 100,000 populations [3]. Identifying a people with epilepsy is difficult. Therefore, estimation of incidence and prevalence are difficult to achieve precisely. Epidemiological studies suggest that 70-80% of people developing epilepsy will go into remission, while the remaining patients continue to have seizures [4]. The most common risk factors for epilepsy are cerebrovascular disease, brain tumour, alcoholic, traumatic head injuries and malformations of cortical development, genetic inheritance, and infections of the central nervous system [5]. Different types of epilepsy have different causes and their spread depends of age, racial, social class, geographic, or national boundaries [6]. The term “antiepileptic” is used synonymously with

"anticonvulsant" which describes drugs that are used to treat "epilepsy". The goal of AED therapy in patients with epileptic seizures is to achieve a seizure-free status without adverse effects [7]. Though AEDs are categorized into different types on the basis of their mechanism of action, chemical structure and pharmacokinetics they are most commonly recognized as older and newer generation AEDs. The older generation AEDs includes bromides, phenobarbital, primidone, phenytoin, ethosuximide, carbamazepine, and valproate. Newer generation AEDs includes vigabatrin, felbamate, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide and lacosamide. Newer generation AEDs exhibit both safety and improved tolerability when compared with older agents [8,9]. Patients with epilepsy often require lifelong treatment with medications. Empirical evidence suggests that prolonged use of AEDs is associated with changes in vascular risk markers, particularly carbamazepine and phenytoin might modify some vascular risk factors [10]. In addition, some researchers found that newer antiepileptic drugs like lamotrigine and levetiracetam has no influence on vascular markers [11]. Vascular disease is an unusual condition which affects the blood vessel, arteries and veins. Carbamazepine and phenytoin are the most frequently prescribed older generation AEDs. Levetiracetam and lamotrigine are often prescribed newer AEDs [12]. Both carbamazepine and phenytoin inhibits sustained repetitive firing by blocking use-dependent sodium channels [13]. Levetiracetam produces antiepileptic effects via adherence to the synaptic vesicle protein SV2A and modulation of neurotransmitter release [14]. Therefore, carbamazepine, phenytoin and levetiracetam are chosen for our study. The present study was designed to evaluate the effect of older generation AEDs (carbamazepine and phenytoin) and newer generation AED (levetiracetam) monotherapy on hematological and various biochemical parameters in epilepsy patients.

MATERIALS AND METHODS

The study entitled "Assessment of potential effect of monotherapy anti-epileptics drug usage on the markers of vascular risk in epilepsy patients" was conducted as a prospective observational study in the Neurology department of Tertiary Care Hospital for a period of 7 months (September 2016 – March 2017). The study protocol was approved by the institutional ethics committee of RVS Institute of Medical Sciences (Approval no: IEC/RVSIMS/2016/5).

Consent from Hospital Authority

The protocol of the proposed study was submitted as printed copies to the medical superintendent and neurologists for review and approval. Guidance of the senior neurologist available was extended on request from the scholar. Consent from the hospital authorities and neurologists were obtained before accessing the data from the patients. Patients who fulfilled the inclusion criterion were documented from the case sheets and recorded in a separately designed case report form. Written informed consents were obtained after explaining the study protocol to each individual patient.

Study Design and Sample Size

A total of 90 patients with epilepsy were enrolled in the study. Patients of both the genders with epilepsy, 18-60 years of age were included in the study. A known history of cerebrovascular/ cardiovascular disease, tension, renal or hepatic disease, diabetes mellitus; psychiatric history or any other concomitant disease which may lead to unreliability in clinical assessment; significant alcohol, drug or medication abuse, tobacco users; women who were pregnant or lactating were excluded from the study.

The study comprised of three groups and each group included 30 patients as follows:

- Group I: 30 patients who received Carbamazepine
- Group II: 30 patients who received Phenytoin
- Group III: 30 patients who received Levetiracetam

Treatment responses were assessed and reviewed at R0 (baseline-before drug therapy), R1 (6 months after drug therapy).

Data Collection

Laboratory reports of all study subjects were collected from the laboratory of tertiary care hospital where study was conducted. Information regarding patients' age, sex, diagnosis, treatment duration, medication history, complete blood count, liver enzymes, HbA1c was collected in a case report form.

Statistical Analysis

Comparison between the groups was analyzed by means of one way analysis of variance (ANOVA), chi square test and student t-test to determine the presence or absence of statistically significant difference wherever necessary. Wherever computed, a P value of less than 0.05 was considered significant, since the confidence interval was maintained at 95%. Bivariate analyses were carried out by Pearson correlation. All statistical analyses were performed using IBM SPSS 17 and Graph Pad Prism 7.0.

RESULTS

90 patients who fulfilled the inclusion criteria were enrolled in the study. The demographic characteristics of the patients included in the study are shown in Table 1. Epilepsy patients in the study have been segregated into different age quartiles as shown in Figure 1.

Table 1: Baseline demographic characteristics of studied population

Character		Group			
		I	II	III	P value
Age (years)		33(19-58)	36(18-60)	34(18-59)	0.5327*
Gender	M	11(37)	19(63)	11(37)	0.0569**
(%)	F	19(63)	11(37)	19(63)	
BMI (kg/m^2)		21.5(18.5-24.6)	20.95(18.5-24.3)	20.95(18.6-24.1)	0.9271*
Coexisting disease (%)		12(40)	12(40)	16(53)	0.4958*

*One way ANOVA **Chi-square test

Statistically significant difference in the above parameters was not found between the groups.

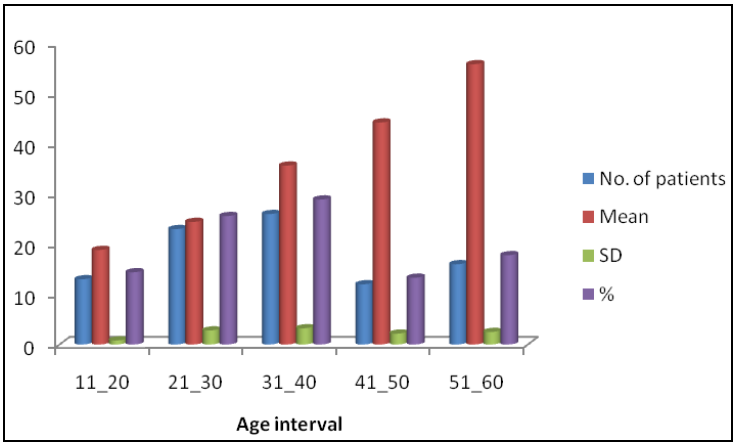

Figure 1: Age wise distribution

The mean (SD) age of the studied population was found to be 35.1 (12.71) years with a median age of 34 years.

Table 2: Comparison of baseline and post-treatment complete blood count

Parameter	Review	GROUP			P value*
		I (mean±SD)	II (mean±SD)	III (mean±SD)	
Hemoglobin	R0	13.65 ± 1.33	13.65 ± 2.02	13.60 ± 1.79	0.9163
	R1	13.49 ± 1.53	13.46 ± 2.10	12.9 ± 1.90	0.3972
	P value**	0.0197	0.0042	<0.0001	
Red blood cell (RBC)	R0	4.99 ± 0.55	4.95 ± 0.65	5.25 ± 0.55	0.1218
	R1	4.92 ± 0.57	4.82 ± 0.72	4.52 ± 0.47	0.1085
	P value**	0.0015	0.1776	<0.0001	
White blood cell (WBC)	R0	9294.66 ± 2814.90	9787 ± 2815	9099.33 ± 1675.79	0.559
	R1	9260 ± 2818.04	9731 ± 2736.72	9021.66 ± 1658.76	0.5385
	P value**	0.1261	0.1999	0.0013	
Platelet count	R0	3.09 ± 0.61	3.20 ± 0.60	3.36 ± 0.68	0.2678
	R1	2.70 ± 0.60	2.70 ± 0.66	2.65 ± 0.66	0.1066
	P value**	0.0304	0.0002	<0.0001	

*One way ANOVA **Paired T test

Effect of AEDs on Hematological Parameters

Presence of statistically significant difference in complete blood count (hemoglobin, red blood cell, white blood cell, platelet count) between baseline and sixth month (intra group comparison) was determined by means of student t test whereas one way ANOVA was used to determine inter group difference. A mean decrease in the above levels was observed during the sixth month. Inter group comparison showed significant reduction in the parameters was seen in levetiracetam treated group when compared to the other two groups as shown in Table 2.

Effect of AEDs on HbA1c

HbA1c level was observed to be significantly increased in carbamazepine and phenytoin treated patients but significant change was not seen in levetiracetam group as shown in Table 3.

Table 3: Comparison of baseline and post-treatment HbA1c level

Parameter	Review	GROUP			P value*
		I (mean ± SD)	II (mean ± SD)	III (mean ± SD)	
HbA1c	R0	5.85 ± 1.04	6.17 ± 1.84	5.73 ± 0.79	0.0167
	R1	6.65 ± 0.96	6.53 ± 1.79	5.76 ± 0.79	0.4105
	P value**	<0.0001	<0.0001	0.1033	

Effect of AEDs on Liver Enzymes

Changes in liver enzyme level after 6 months of treatment were found to be significantly high in carbamazepine and phenytoin treated groups which are shown in Table 4.

Table 4: Comparison of baseline and post-treatment liver enzymes level

Parameter	Review	GROUP			P value*
		I (mean ± SD)	II (mean ± SD)	III (mean ± SD)	
Aspartate aminotransferase (AST)	R0	25.9 ± 11.18	24.2 ± 9.86	23.23 ± 9.31	0.6005
	R1	30.46 ± 10.87	29.13 ± 10.26	25 ± 9.39	0.1097
	P value**	<0.0001	<0.0001	0.397	
Alanine aminotransferase (ALT)	R0	29.65 ± 13.73	28.48 ± 14.60	26.29 ± 12.43	0.6349
	R1	33.79 ± 13.75	33.63 ± 13.85	26.42 ± 11.81	0.0122
	P value**	<0.0001	0.0247	0.6453	

DISCUSSION

Atherosclerosis is an inflammatory disease which is the leading cause of death in the developed countries. Certain epidemiological studies have indicated that death rate from atherosclerosis related cardiovascular disease (CVD) are slightly elevated in epileptic patients taking AEDs [15]. In the current study, effectiveness of carbamazepine, phenytoin and levetiracetam on vascular risk markers has been comparatively evaluated. Since phenytoin and carbamazepine are enzyme inducing AEDs, the mechanism by which they affect the vascular markers are closely related [16]. The liver being the primary organ for drug metabolism of AEDs is subjected to drug-induced toxicity that leads to mild and transient elevations of the hepatic enzymes to fatal hepatic failure [17]. Carbamazepine and phenytoin are potent enzyme inducers and induce cytochrome P450 system which is associated with mild elevation of liver enzyme. The hepatotoxicity induced by antiepileptic drugs occurs either as a result of the production of reactive toxic metabolites, immune-allergic reactions or obstruction in bile flow and cholestasis. In our study, liver enzymes were increased in the patients who received carbamazepine and phenytoin which is similar to previous results [18,19]. AEDs are hematotoxic. Folate is important for cells and tissues that rapidly divide e.g. bone marrow. Folic acid is considered biologically active after its conversion to dihydrofolic acid in the liver by dihydrofolate reductase [20]. This conversion is blocked by AEDs. Nearly all of the cellular elements in the blood (WBCs, RBCs and platelets) are involved in the pathogenesis of atherosclerosis. These markers play a role in the development of coronary heart disease (CHD) in asymptomatic patients and also predict recurrent events and death in patients who already have CHD [21]. Anti-folic acid activity of AEDs is responsible for bone marrow depression that results in blood dyscrasias like thrombocytopenia, leucopenia and aplastic anemia [22]. This agrees with the result of our study which is shown in Table 2. Certain enzyme inducing AEDs affects blood sugar level by precipitating insulin resistance. High blood glucose can damage your blood vessels and the nerves that control your heart [16,23]. The value of HbA1c is increased after 6 months of treatment in carbamazepine and phenytoin treated patients as shown in Table 3.

CONCLUSION

This study conclude that enzyme inducer AEDs like carbamazepine and phenytoin is strongly associated with increased levels of liver enzymes and HbA1c whereas levetiracetam showed significant change only in complete blood count. Elevated level of HbA1c and liver enzymes during treatment might be associated with an increased risk of developing hepatotoxicity and vascular disease in patients with epilepsy. Therefore, careful monitoring of liver enzymes and HbA1c in epileptic patients undergoing long-term treatment with enzyme inducing AEDs is considered necessary.

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