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Research article

PREVENTIVE MEASURES NEEDED FOR LONG TERM USE OF CARBAMAZEPINE TO LOWER THE RISK FOR CORONARY HEART DISEASE

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ABSTRACT

Present cross sectional study was carried out with a view to evaluate the Carbamazepine risk for coronary heart disease. Lipid profile and Framingham point scores were studied in 60 Epilepsy patients on Carbamazepine. The epileptic patients were compared with age and sex matched 60 healthy controls. Framingham Point Scores were estimated by taking into consideration several parameters i.e. Age, Sex, Systolic blood pressure, HDL levels, Total cholesterol, and smoking history, as per guidelines of the Framingham Heart Study group We conclude that this drug significantly increases the risk for coronary heart disease in patients with respect to lipid profile and other parameters as described by the Framingham study group. Altogether, this drug may be one of the reasons for the high prevalence of CHD, which is increasing day-by-day due to the globalization.

Keywords: Carbamazepine, Epilepsy, Lipid Profile, Coronary heart disease

INTRODUCTION

In Latin seizure means "to take possession of". Seizure by definition is a paroxysmal event due to abnormal, excessive, hyper synchronous discharges from an aggregate of central nervous system (CNS) neurons[1]. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. About 50 million people worldwide have epilepsy, with almost 90% of these people being in developing countries[2]. In India itself, approximately 6 million people suffer from Epilepsy. Anticonvulsant drugs like Carbamazepine are in use since 1962[3] for long term antiepileptic therapy. This long term treatment may be associated with various metabolic abnormalities involving connective tissues, endocrine system and liver.

Coronary Heart Disease is defined as "impairment of heart function due to inadequate blood flow to the heart compared to its needs, caused by obstructive changes in the coronary circulation to the heart. Framingham heart study[4] started during the 1950s has played a major role in establishing the nature of CHD risk factors

and their relative importance. The major risk factors of CHD are elevated serum cholesterol, smoking, hypertension, and sedentary habits.

Previous studies by Framingham Heart Study group have shown that alterations in serum lipids predisposes to coronary heart disease[4]. Thus, Influence of Carbamazepine on serum lipids has been investigated many times leading to contradictory reports[5-9]. Moreover, alterations in lipid profile may vary in different populations and not many studies have been done in Indian scenario. Hence present study was carried out with a view to determine the association between long term use of Carbamazepine & changes in Lipid/Cholesterol metabolism and also to find the magnitude of risk for coronary heart disease as an effect of alterations in Lipid/Cholesterol metabolism by this drug, if any.

MATERIALS AND METHODS

Study Design: Cross-sectional study.

Setting: Psychiatry OPD and Department of Biochemistry of Raichur Institute of Medical Sciences, Raichur (Karnataka)

Study Subjects: A total of 120 subjects aged between 20 - 40 years were taken into study. 60 Epileptic patients who are exclusively on Carbamazepine (in a dosage of 200 mg BD) were compared with age and sex matched similar number of Healthy Controls.

Only subjects classified as Epileptic as per ILAE classification[11] and those exclusively taking Carbamazepine for epilepsy for a period of 6-12 months were included in the study. Whereas subjects having co-morbid conditions like hypertension, Diabetes, Tuberculosis, Obesity, etc. were excluded from the study.

Before carrying forward the subject selection, Institutional Ethics committee approval was taken.

Diagnostic Criteria: Epilepsy: The subjects are classified as per ILAE classification[11], Diagnosed by Psychiatry Department of Raichur Institute of Medical Sciences, Raichur.

Estimation of Lipid Profile: Total cholesterol, HDL-c and Triglycerides levels estimation done using Randox kits by Daytona Randox fully automated analyzer. LDL-c levels calculated as per formula by Friedewald et al.[10]

Collection of Blood sample: 12 hour overnight fasting blood sample in plain bulb is collected in the morning from anticubital vein using 21 gauze 5ml disposable syringe using a tourniquet and with all aseptic precaution.

Estimating the risk for coronary heart disease: Framingham Point Scores were estimated by taking into consideration several parameters i.e. Age, Sex, Systolic blood pressure, HDL levels, Total cholesterol, and smoking history, as per guidelines from Framingham Heart Study group[4]

Statistical Analysis: Data collected was analyzed using student t-test and chi square test. Values <0.05 were considered statistically significant.

RESULTS

Estimation of Lipid profile in Epilepsy patients on Carbamazepine and their Framingham score and related risks are tabulated in following tables

Table 1: Lipid Profile in Epilepsy patients on Carbamazepine, compared with Controls

Parameter	Cases (n=60)	Controls (n=60)	P Value
Total Cholesterol (mg/dl)	174.15 ± 14.43	164.27 ± 13.19	<0.001
HDL(mg/dl)	43.36 ± 5.26	45.65 ± 6.03	0.03
LDL(mg/dl)	104.74 ± 13.08	94.52 ± 15.09	<0.001
Triglycerides (mg/dl)	130.18 ± 15.13	120.45 ± 10.76	<0.001
TC/HDL	4.06 ± 0.51	3.67 ± 0.57	<0.001
LDL/HDL	2.45 ± 0.44	2.12 ± 0.51	<0.001
Framingham Risk %	0.45 ± 0.96	0.27 ± 0.76	0.17

Table 2: Age & Sex wise Distribution of Epilepsy patients on Carbamazepine

Age (yr)	Parameter	Male (n=15)	Female (n=24)	P – Value
20-30	**Total Cholesterol (mg/dl)**	161.93 ± 16.49	178.29 ± 11.52	0.003
	HDL (mg/dl)	43.33 ± 4.87	42.83 ± 4.94	0.759
	LDL (mg/dl)	94.76 ± 15.01	108.5 ± 10.60	0.005
	Triglycerides (mg/dl)	119.2 ± 13.54	134.79 ± 12.52	0.001
	TC/HDL	3.76 ± 0.44	4.20 ± 0.45	0.005
	LDL/HDL	2.21 ± 0.41	2.56 ± 0.40	0.013
30-40		**Male (n=9)**	**Female (n=12)**	
	Total Cholesterol (mg/dl)	182.22±11.78	175.08±9.83	0.199
	HDL (mg/dl)	45.89 ± 5.08	42.58 ± 6.45	0.205
	LDL (mg/dl)	109.27 ± 13.35	106.33 ± 8.99	0.579
	Triglycerides (mg/dl)	135.33 ± 23.50	130.83 ± 5.63	0.588
	TC/HDL (%)	4.02 ± 0.58	4.18 ± 0.55	0.535
	LDL/HDL (%)	2.41 ± 0.47	2.55 ± 0.46	0.524

Table 3: Framingham point scores depict the estimated 10-year % risk [(4)] for development of Coronary heart disease in Epilepsy patients on Carbamazepine

10 year % Risk	Males			Females		
	Total point scores	Cases	Controls	Total point scores	Cases	Controls
<1	<0	8	19	<9	36	30
1	0-4	10	9	9-12	-	-
2	5-6	4	1	13-14	-	-
3	7	-	-	15	-	-
4	8	1	-	16	-	-
5	9	1	1	17	-	-
>6	>10	-	-	>18	-	-
Total		24	30		36	30

Table 4: Age and Sex wise distribution of Framingham score in cases

	Male	Female	p-Value
Overall	1.125 ± 1.26	0	0.000225
20-30	0.73 ± 0.79	0	0.003
30-40	1.77 ± 1.64	0	0.011

Total cholesterol (TC), LDL and Triglycerides level were elevated very significantly ($p < 0.01$) in the cases, whereas significant ($p < 0.05$) reduction in protective HDL levels were noted. Further leading to significant elevation in TC: HDL and LDL: HDL ratios. Overall increase in framingham risk % is noted in the cases as compared to controls.

In age group of 20-30 years, very significant ($p < 0.01$) elevation is noted in TC, LDL and Triglycerides in Females when compared to males of the same age group. However, changes in levels of HDL are not in statistically

significant range. Overall, it leads to very significant change in TC: HDL ($p < 0.01$), and significant change in LDL: HDL ratios ($p < 0.05$).

However, in age group of 30-40 years, sex-wise no significant changes noted in lipid profile parameters. Very significant ($p < 0.01$) rise in 10 year % risk is noted in male cases. However, when divided into subgroups of age 20-30 and 30-40 years, significant ($p < 0.05$) elevation in risk is observed in 30-40 years group with very significant($p < 0.01$) rise in the young age group of 20-30 years is observed. Inspite of this difference in significance values, the mean increase in risk % is more in higher age group of 30-40 years.

In case of female study group, no significant difference noted in two groups of cases and controls,with all the females having < 1 % risk of developing CHD in 10 year period.

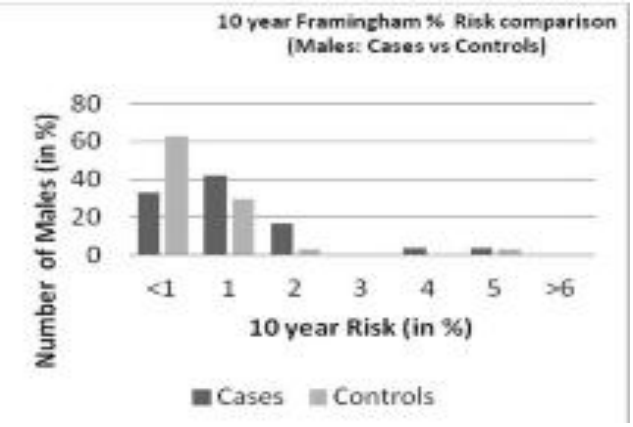

Fig 1: 10 year Framingham % risk comparison in Males

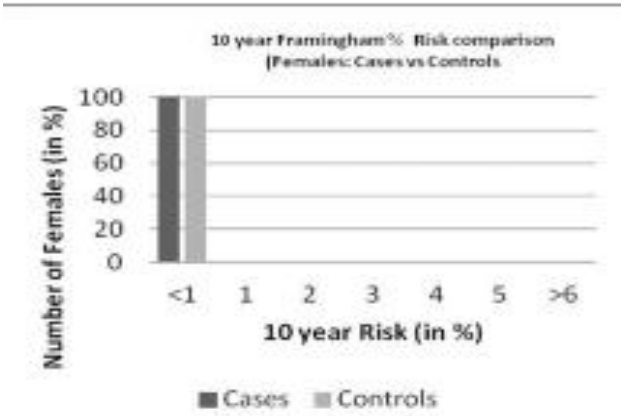

Fig 2: 10 year Framingham % risk comparison in Females

DISCUSSION

The action of Carbamazepine and its metabolites is now well understood with the advancement in pharmacological field. Neurons are allowed to communicate for long distance by the voltage – gated sodium channels which generate an action potential. The sodium channels which opens with generation of action potential are inactivated essentially by closing the channels. Carbamazepine acts by stabilizing the inactivated state of sodium channels. Thus the neurons are less excitable because very few channels are available to open subsequently. GABA receptor alpha 1, beta 2 and gamma 2 subunits are potentiated with carbamazepine.[12] The intake of carbamazepine not only affects the neurons but also other systems by inducing liver microsomal enzymes leading to alteration in metabolism of lipids, bile acids and bilirubin[13]

If Carbamazepine increases the risk of Coronary Heart Disease, it might lead to increase in patients' burden which they are already having. Hence, present study was carried out to evaluate the safety or risk of these drugs. For this purpose, we evaluated lipid profile in patients between age group of 20-40 years, receiving Carbamazepine for more than 6 months. From the study we found, statistically highly significant increase in Total Cholesterol (TC), LDL-c, and Triglycerides (Tg) level. However, there was also statistically significant fall in HDL-c levels, leading to increase in atherogenic ratio (TC/HDL and LDL/HDL ratio) in the study group. This can attribute to increase in Total cholesterol to increased levels of LDL and not because of the HDL levels, as reported previously in many reports[5-8]. This is consistent with the reports by Zeilthoper S et al. [(9)] who also attributed increased Total Cholesterol to increased LDL-c levels.

10 year % risk for development of Coronary heart disease by Framingham Point score reveals a score in Epilepsy patients on Carbamazepine to be less than 2% in the majority of the patients

(58 of 60), which reveals the safety of this drug; if other modifiable factors are in control like smoking habits, blood pressure.

CONCLUSION

Assessing and stratifying the risk for CHD, entire constellation of factors needs to be considered, not only just lipid profile. As Carbamazepine used in the treatment of Epilepsy is significantly raising Total cholesterol, LDL and Triglycerides level, routine lipid profile estimation is required in these patients. Moreover, due to various other predisposing factors for the risk of CHD and a significant increase in atherogenic ratios, periodic Lipid Profile estimation should be mandatory in the cases with presence of other risk factors like hypertension and smoking history, particularly in males. Other measures like the addition of Lithium Carbonate and Vitamin E [14] can be suggested in the treatment regimens to decrease the Carbamazepine dosage and hence its atherogenic effects and better outcome for the patient, as the prevalence of CHD is increasing day-by-day due to increased Globalization.

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