ORIGINAL ARTICLE

A STUDY ON FIBRINOGEN LEVELS IN PATIENTS OF ACUTE STROKE

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ABSTRACT

Introduction: Risk factor for stroke includes diabetes, hypertension, smoking and hyperlipidemia and these have been linked to abnormalities of haematology and coagulation such as increased fibrinogen. The present study is designed to investigate the association between plasma fibrinogen levels and acute stroke.

Methodology: The present study was a cross sectional study done in the Medicine ward/ICU of a tertiary care hospital. Plasma fibrinogen level was done of 50 patients presenting with acute stroke admitted in Medicine ward/I.C.U of tertiary care hospital. Detailed history was taken to find out the risk factors such as hypertension, diabetes, Smoking and overweight. In addition to routine investigations as per standard protocol in the evaluation of stroke patient, fasting plasma fibrinogen level was estimated.

Results: The mean age in the present study was 58.52 years. The maximum numbers of patients were in the age group 60-69 years. In 86% of cases were having higher fibrinogen level. There were 23(46%) smokers among patients. Non smokers, Normotensives, Non obese and non diabetics had higher fibrinogen levels than smokers which were not statistically significant.

Conclusion: Mean fibrinogen level was lower in patients of acute stroke with any of risk factors like smoking, hypertension, diabetes and obese than in patients of acute stroke without any of these risk factors. This difference was not statistically significant in this study but further large study can be planned to prove this.

Keywords: Acute Stroke, Fibrinogen, Hypertension, Diabetes

INTRODUCTION

In urban India stroke accounts for 1% mortality of all hospital admissions, 4% in all medical cases and about 20% in all disorders of central nervous system.[1] Risk factor for stroke includes diabetes, hypertension, smoking and hyperlipidemia and these have been linked to abnormalities of haematology and coagulation such as increased fibrinogen.[1]

Most cerebrovascular accidents are manifest by the abrupt onset of focal neurologic deficit as if the patient is "struck by the hand of the God."[2] Stroke is defined as an abrupt neurologic deficit that is attributable to focal vascular cause. Risk factors for stroke are hypertension, atrial fibrillation, carotid stenosis, hyperlipidemia, diabetes, myocardial infarction, atrial myxomas and smoking.[2]

Fibrinogen is a soluble plasma glycoprotein that consists of three nonidentical pairs of polypeptide chains (Aα, Bβ and γ chains).[3] In the first phase of thrombus formation soluble fibrinogen is converted into insoluble fibrin by thrombin. Thrombin cleaves Aα and Bβ chains thereby releasing fibrin peptides, these fibrin peptides initiate a process in which fibrin monomers begin to gel. These fibrin monomers polymerise to form fibrin polymers. This process continues and elongation of polymers causes formation of protofibrils. Once a critical Mass of long protofibrils is established, the protofibrils form lateral contacts with other protofibrils thereby forming fibrin clot. Fibrin clot thereby potentiates formation of thrombosis. Epidemiological observations indicate that high plasma fibrinogen levels strongly correlate with the frequency of two major thrombotic complications of atherosclerosis, stroke as well as myocardial infarction. Thrombosis is increasingly recognized as a central mechanism in stroke and myocardial infarction, and fibrinogen is believed to be involved in events thought to play a major role in thrombosis. Therefore elucidation of the relationship between fibrinogen and thrombosis may strengthen the predictive value of this protein and suggest new treatment in management of stroke.[4]

Hence this study is designed to investigate the association between plasma fibrinogen levels and acute stroke.

METHODOLOGY

The present study was a cross sectional study done in the Medicine ward/ICU of a tertiary care hospital. Plasma fibrinogen level was done of 50 patients presenting with acute stroke admitted in Medicine ward/I.C.U of tertiary care hospital fromJanuary 2015 to November 2016.

Method of collection of data: The study was carried out on 50 consecutive patients admitted to Medicine ward/I.C.U of tertiary care hospital, Surat with acute stroke within 24 hour of symptoms. Detailed history were taken to find out the risk factors such as hypertension, diabetes, Smoking and overweight. Hypertension was diagnosed by JNC VIII criteria.[2]Diabetes was diagnosed by American Diabetes Association criteria[2]. Smoking was recorded in terms of number of cigarette pack years smoked. Thorough general and systemic examination was carried out. In addition to routine investigations as per standard protocol in the evaluation of stroke patient, fasting plasma fibrinogen level was estimated. Patients were followed up till they were discharged from the hospital.

Inclusion Criteria: All patients fulfilling all of the below criteria were included in the study

1) Patients presenting with acute stroke within 24 hours of onset of symptoms & CT/MRI scan. Shows cerebral infarct or haemorrhage.
2) Patients willing to give informed written consent.

Patients with evidence of uremia, infection, active hepatic disease, active hepatic disease, undergone surgery in last three months and not willing to give informed written consent were excluded from the study.

Detailed history, clinical examination and relevant laboratory investigations were done as per proforma.Fasting plasma fibrinogen was estimated in patients and age, sex and risk matched controls.The plasma fibrinogen was measured quantitatively by Clauss method.

Venous blood was collected in an evacuated siliconized blood collection tube containing 1 volume 0.11mol/lt of Sodium citrate (3.8%) and 9 volumes of whole blood, which was centrifuged for 15 min at RCF of 2000g.The buffer which was provided in the Dade Behring fibrinogen estimation kit was used to prepare 1:10 dilution of patient's plasma sample. 0.2 ml diluted (50µl) citrated plasma sample was incubated for 1 minute, then 25µl of thrombin reagent was added at room temperature and clotting time was then determined at 37^0 centigrade using a coagulation instrument.

The fibrinogen concentration was then determined by matching the clotting time from the standard provided and prepared in the Dade Behring fibrinogen estimation kit Dade Behring Marburg, Marburg, Germany.

RESULTS

There total 50 patients presented with acute stroke within 24 hours of onset of symptoms & CT/MRI scan and fulfilling inclusion criteria. This all patients were included in the study.

Table 1: Age wise and fibrinogen level wise distribution of cases (N=50)

Variables	No. (%)
Age group (in years)	
30-39	3 (6.0)
40-49	11 (22.0)
50-59	11 (22.0)
60-69	15 (30.0)
≥70	10 (20.0)
Fibrinogen level (mg/dl)	
Less than 200	2 (4.0)
200-400	5 (10.0)
400-800	43 (86.0)

Table 2: Gender wise distribution of cases and their mean fibrinogen level (N=50)

Gender	No. (%)	Mean +- SD	p-Value
Males	31 (62.0)	595.16± 195.26	0.40477
Females	19 (38.0)	641.05±173.46	

Table 3: Relation of different risk factors with mean fibrinogen level

Patients	No.	Mean fibrinogen (mg%)	p-Value
Smoking			
Smokers	23	596.09±204.02	0.539199
Non smokers	27	629.26±175.32	
Hypertension			
Hypertensive	21	563.81± 206.09	0.113364
Normotensive	29	648.62±165.55	
Diabetes			
Diabetic	15	545.33±210.84	0.0907205
Non diabetic	35	643.43± 171.94	
BMI			
>30	9	597.78±169.02	0.613588
<30	41	632.16±186.56	

The mean age in the present study was 58.52 years. The youngest patient was of age 35 years. The oldest patient was of age 84 years. The maximum numbers of patients were in the age group 60-69 years.

In the present study minimum plasma fibrinogen level was 180mg/dl and maximum was 850mg/dl. Normal fibrinogen value is 150-400. [31] In 86% of cases were having higher fibrinogen level.

Among 50 patients studied, 62% were Male and 38% were Female. Males had mean fibrinogen of 595 and females had mean fibrinogen of 641. This difference was not statistically significant. (p-Value > 0.05)
In the present study there were total 44 patients were having ischemic strokes and their mean fibrinogen level was 615 mg% and there were total 6 patients were having haemorrhagic strokes and their mean fibrinogen level was 588 mg%.

There were 23(46%) smokers among patients. Non smokers had higher fibrinogen levels than smokers which were not statistically significant.Among normotensive patients mean fibrinogen level was higher than hypertensive patients, mean values in hypertensive was 563 whereas it is 648 in patients who are normotensive. This difference was not statistically significant. In present study non diabetics had higher fibrinogen levels which were not statistically significant. In patients who were obese, mean fibrinogen level was 597 and in non obese patients, mean fibrinogen level was 632. Non obese patients had higher fibrinogen level than obese individuals. The difference was not statistically significant.

DISCUSSION

The present study involved 50 patients presenting with acute stroke admitted in Medicine ward/I.C.U. The mean fibrinogen level was 615 mg% in ischemic group. Mistry PP et al., in their study involving 56 patients admitted in the hospital within 24 hours of onset of symptoms. The levels were found to be raised significantly (531.73mg %) compared to those of the age and sex matched control group (445.78mg %).[1] When the levels of plasma fibrinogen in stroke group with one risk factor were compared to those of individuals with comparable control group with same risk factor, a significant difference was observed. Hazra B et al., in their study involving 33 patients of cerebral thrombosis and 30 patients with cerebral hemorrhage admitted within 24 hours of onset of stroke concluded that the mean plasma fibrinogen concentration in patients of cerebral thrombosis (378.67 mg/dl) is significantly higher when in the control group (216.67).[5]

Variation in the level of fibrinogen in the above studies may be due to variation in ethnicity or the method of fibrinogen assay or may be due to age group and sex of the patient selected for the study.

AJ lee[6] and TW Maede[11] have shown that fibrinogen level increases with age. This study also demonstrates an increasing trend of fibrinogen with age. Fibrinolytic activity reduces as age advances because of, [7] As age advances there is change in orientation of gpIIa/IIIb receptor causing decreased fibrinolytic activity which accounts for increased plasma fibrinogen levels as age advances.

It is likely that mutation accumulation of plasma fibrinogen plays a significant role in the changes of fibrinogen with age.

The increase of variance with age is the product of unrepaired evolutional damage in different levels of organization, and the mutations causes increased fibrinogen levels as age advances.

AJ lee[6] and TW Maede11 have shown males have higher fibrinogen when compared to females. This study has shown that fibrinogen was increased in females than males amongst Higher fibrinolytic activity in females explained the lower fibrinogen levels in females when compared to males. Ernst E has demonstrated that smoking is associated with increased plasma fibrinogen levels.[8]

This study has shown increased fibrinogen levels in patients amongst smokers as compared to non-smokers which was not statistically significant.

Other studies have demonstrated that in smokers, the plasma fibrinogen is elevated because,

Smoking activates lung macrophages which releases IL-4 which increases fibrinogen synthesis14Smoking decreases fibrinolytic activity[9]

Smoking causes endothelial damage resulting in activation of coagulation system and release clotting factors[10]

Anjula Jain et al has demonstrated fibrinogen levels are higher in hypertensives.[11] Lee AJ has demonstrated plasma fibrinogen was higher among hypertensive.[6] In this study hypertensive patients had higher fibrinogen than normotensives which was not statistically significant.

Several plausible mechanisms could explain an observed association between elevated fibrinogen levels and hypertension[12],

Relation of fibrinogen to increased viscosity and peripheral vascular resistance

Hyperinsulinemia and insulin resistance is common amongst hypertensive and hyperinsulinemiais known to cause decreased fibrinolytic activity. Hence increased fibrinogen levels in hypertensives.

Markers of inflammation, such as IL-6 and IL-8 are elevated in hypertension and causes reduced consumption of fibrinogen, thereby contributing to increased plasma fibrinogen in hypertension, increased platelet activation, increased activity of the coagulation system and decreased function of the fibrinolytic system.

Meade TW [13] and Ernst E [8] have shown that obese individuals have higher fibrinogen levels. Obese in-

dividuals had higher fibrinogen levels compared to non-obese patients which were not statistically significant.

The mechanisms underlying increased plasma fibrinogen in patients who had over weight are,

There is a positive association between obesity (skin fold thickness) and plasma insulin concentration, hyperinsulinemia thereby stimulates fibrinogen synthesis.

It is possible that the interaction between obesity and physical inactivity may promote dyslipidaemia and increased plasma fibrinogen.

In this study diabetics had higher fibrinogen than non diabetics.The exact mechanism of increased fibrinogen levels in diabetics is unknown, possible mechanisms include[14],

Insulin stimulates cholesterol synthesis in smooth muscle cells and macrophages of the arterial walls, stimulates the proliferation and migration of smooth muscle cells. It also enhances the formation of fibrinogen.

Endothelial dysfunction which is common in diabetics, which causes decreased fibrinolytic activity and hence increased plasma fibrinogen levels.

The plasma glucagon concentration is positively related to the plasma fibrinogen concentration. Thus,fibrinogen production is markedly enhanced in diabetic patients, and this alterationis likely to determine the observed hyperfibrinogenemia in these patients. Hyperglucagonemia may contribute to the increased fibrinogen production.

Thus, insulin concentrations (and probably also glucose profiles) may need to be maintained at the lowest attainable level in type 2 diabetes to prevent increased fibrinogen synthesis and concentrations.

CONCLUSION

The maximum numbers of patients of acute stroke were in the age group 60-69 years. Mean fibrinogen level was lower in patients of acute stroke with any of risk factors like smoking, hypertension, diabetes and obese than in patients of acute stroke without any of these risk factors. This difference was not statistically significant in this study but further large study can be planned to prove this.

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