Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE7, 2023

PROGNOSTIC SIGNIFICANCE OF SERUM FIBRINOGEN LEVEL IN ACUTE ISCHEMIC STROKE PATIENTS: A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY

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Abstract

Background: Stroke is the third commonest cause of death worldwide, after coronary heart disease (CHD) and all types of cancer. Fibrinogen is an independent risk factor for stroke and also predictor of future recurrences of stroke. Hence, Measurement of fibrinogen levels could be more useful than others as it is more specific to vascular disease.

Methods: A prospective hospital-based case control (cross sectional) study was conducted on 100 subjects: 50 Age and sex matched controls not having focal neurologic deficit & 50 newly diagnosed acute ischemic stroke patients admitted in Medicine ward at Index Medical College Hospital & Research Centre, Indore.

Results: There was a significant difference between mean fibrinogen level among cases and controls. A statistically significant correlation was observed between the mean fibrinogen level in the study group and age. The mean fibrinogen level among males and females in study group was higher than control group ($p<0.05$). The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score <5.

Conclusion: Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with: Clinical severity assessed by National Institute of Health Stroke Scale and Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale.

Keywords: acute ischemic stroke, serum fibrinogen level, severity and outcome.

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INTRODUCTION

Stroke is defined by WHO as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of vascular origin'.[1] This includes both cerebral infarction or intracerebral and subarachnoid hemorrhage. A time window of 24 h distinguishes stroke from transient ischaemic attack (TIA), which is defined as a neurological deficit lasting less than 24 h. The term cerebrovascular disease compasses all vascular disease affecting the brain including stroke, vascular dementia, and asymptomatic cerebrovascular disease.[1,2]

The onset of ischemic cascade induces the initiation of inflammation, excitotoxicity, nitric oxide production, free radical damage and apoptosis, which all play a role in tissue injury. The molecular consequences due to brain ischemia include changes in cell signalling and its transduction, metabolism, gene regulation or expression.[3,4] There will be release cytokines, like interleukin-1(IL-1) and tumor necrosis factor-α (TNF-α) after onset of ischemia which leads to leucocyte activation, recruitment and adhesion to the endothelium.[2] These leucocytes obstruct the vessel together with monocytes /macrophages. Reperfusion, and systemic inflammatory process also stimulate the inflammatory response, which hampers the effect of thrombolytic therapy.[5]

In the normal conditions, the body responds to inflammatory and infective conditions, by means of cytokines, primarily IL-6 and IL-1. The most important acute phase reactants in cerebrovascular ischemia are C-reactive proteins (CRP), serum amyloid A protein, and fibrinogen.[6]

Fibrinogen plays a key role in blood clotting. Its association with increased incidence of stroke is related to its ability to promote thrombosis or clot formation by causing platelets to clump inside blood vessels.[1] It also interacts with monocytes/macrophages which are thought to plays an important role in atherogenesis. This interaction also triggers the procoagulant activities. Normal serum Fibrinogen level is 233 to 496 mg/dl. Fibrinogen bridges adjacent platelets together to form platelet aggregates and results in arterial thrombosis leading to ischemic stroke.[7,8]

It is an independent type of risk factor for recurrences of stroke apart from age, smoking, hypertension, diabetes and other risk factors. It is also a predictor of future recurrences of stroke and adverse cardiovascular events. Hence, fibrinogen levels are to be measured in patients with stroke at the earliest and to be treated.[9,10]

Fibrinogen plays significant role in a number of physiological and pathological processes like inflammation and atherogenesis and thrombogenesis. This is due to infiltration of blood vessel wall by fibrinogen, increase in blood viscosity and its, hemorheological effects, increased aggregation of platelets and subsequent thrombus formation. The binding of fibrinogen to ICAM-1 receptors on vascular endothelium mediate the platelet adhesion. Fibrinogen causes damage of endothelium and its dysfunction by a variety of mechanisms. This is supported by the decrease in intimal fibrinolytic activity and plasminogen level observed in cardiovascular disease.[11,12]

Fibrinogen plays a role in the process of aggregation of platelets. It crosslinks the platelets by the process of binding the glycoprotein IIb-IIIa receptor on the surface of platelets. This is more relevant with the adventure of glycoprotein IIb-IIIa receptor inhibitors. Hence,

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Measurement of plasma fibrinogen levels could be more useful than other acute phase reactants such as C-reactive protein, as fibrinogen is more specific to vascular disease.[13]

In advent of same, the present study was planned to evaluate the prognostic significance of serum fibrinogen with stroke severity by correlation with clinical outcome stroke scales. Additionally, we also evaluated the correlation between serum fibrinogen and various factors in stroke patients like Age, Sex, Hypertension, Diabetes Mellitus, Body mass index.

Material and Methods

Study design and participants

After approval from the institutional ethical committee this prospective hospital-based case control cross sectional study was conducted on a total of 100 subjects among which 50 were controls & 50 were newly diagnosed acute ischemic stroke patients (based on CT Brain plain) admitted in Medicine ward with history of acute onset stroke at Department of Medicine at Index Medical College Hospital & Research Centre, Indore from May 2022 to April 2023. Age and sex matched persons not having focal neurologic deficit and after verifying exclusion criteria via questionnaire were taken as controls. Informed consent in the prescribed form was obtained from all patients included in the study after explanation of the probable benefits in local language.

Inclusion Criteria

- All patients presenting with new onset focal neurological deficit following ischemic stroke, within 48 hours of onset of stroke are taken into study.
- Patients with new onset stroke with risk factors of hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol were included.

Exclusion Criteria

- Elderly Patients (> 80 years) were excluded.
- Individuals with associated Connective Tissue disorders and Rheumatic heart disease, coronary artery disease were excluded.
- Patients with chronic kidney disease and uraemia were excluded.
- Patients with infective, malignant etiology for stroke were excluded.
- Patients with liver diseases like cirrhosis were excluded.
- Patients with history of Transient ischemic attacks (TIA) or Reversible ischemic neurological deficit (RIND), cerebrovascular accidents (CVA) were excluded.
- Haemorrhagic Stroke Patients (ICH, SDH) were excluded with the aid of CT scan.
- History of recent surgery and trauma were excluded.

Method

Both cases and controls were investigated by following measures. A detailed medical history including present, past, family and personal history were asked. General examination, Vitals

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monitoring including blood pressure, pulse rate, body mass index (BMI), detailed neurologic examination, systemic examination, Severity score using National Institute of Health Sciences Scale at admission was also recorded. Complete blood count, Renal function test, Serum cholesterol, Serum fibrinogen, ECHO cardiogram, CT brain plain, Reassessment of morbidity and mortality using Modified Rankin's scale scores at one month follow-up.

Blood collection & laboratory methods

After overnight fasting, blood samples were taken in the morning. Blood sugar, cholesterol and fibrinogen were measured. The plasma fibrinogen level was measured quantitatively by Clauss method (Principle: Fibrinogen is a soluble plasma protein which is converted to an insoluble polymer mediated through thrombin, resulting in clot formation. This thrombin mediated clotting time of diluted plasma is inversely proportional to fibrinogen concentration of the plasma). Venous blood is collected in an evacuated siliconized tube containing 1 volume 0.11 mol/lt of sodium citrate (3.8%) and 9 volumes of whole blood which is centrifuged for 15 minutes at RCF of 2000 g. the buffer provided in the kit is used to prepare 1: 10 dilution of patient's plasma sample. 0.2 ml of diluted (50µl) citrated plasma is incubated for one minute, then 25 µl of thrombin reagent is added at room temperature and clotting time is then determined at 37˚ C using a coagulation instrument. The Fibrinogen concentration is then determined by matching the clotting time from the standard provided and prepared in the kit.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) 25.0 version, IBM, Chicago. Mean values of all parameters in subgroups were calculated by independent sample-t- test. To compare the distributions of dichotomous data viz., gender, age, smokers, presence of hypertension or diabetes and fibrinogen levels, Chi-square test was used. Association between acute ischemic stroke and fibrinogen level was assessed by logistic regression model. ANOVA test was used to assess the association between stroke scales and fibrinogen level. A p-value of less than 0.05 was considered to be statistically significant.

Results

The study group comprises of 50 patients with acute ischemic stroke. Among the study group, 48% (24) were hypertensive, 32% (16) were diabetics, 44% (22) were smokers, 30% (15) were alcoholics, 52% (26) were obese, 62% (31) were having hypercholesterolemia. The two groups were statistically matched regarding baseline characteristics. In this study, the mean fibrinogen level among cases was 614.20 with a standard deviation of 184.051 and standard error of mean 25.814. Likewise, the mean fibrinogen level among control group was 295.90 with standard deviation of 135.124 and standard error of mean 18.951, with a p value of 0.001 (< 0.05) which was statistically significant.

	Number	Mean	SD	STD. Error	P value
Cases	50	614.20	184.051	25.814	0.001
Control	50	295.90	135.124	18.951	

Table 1. Mean Fibrinogen level among Cases and Controls

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The minimum age of the patients in cases and controls was 35 years and the maximum age was 75 years. Among 50 cases, 8% were in 30-39 years, 20%were in 40-49 years, 24% were in 50-59 years, 28% were in 60-69 years and 20% were in 70-79 years. Likewise, among 50 controls, there were 8%, 20%, 24%, 28%, 22% in each of the above groups respectively. Among the cases, 32 were male and 18 were females. i.e., 64% were males and 36% were females.

The mean fibrinogen level in the study group increases as age advances, which was higher than that of control group, with a p- value of 0.001 which was statistically significant. The mean fibrinogen level among males and females in study group was higher than control group which was statistically significant ($p<0.05$). In the study group, the mean fibrinogen level of hypertensive, diabetic, smokers, alcoholic, obese and hypercholesterolic patients were higher than that of seen in control groups, which was statistically significant (Table 2). Likewise, the mean fibrinogen level of normotensive, non-diabetic, nonsmokers, non-alcoholics, non-obese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant ($p<0.05$) (Table 2).

				MEAN		**FIBRINOGEN**		
S.NO	**CHARACTERS**		**CASES**			**CONTROLS**		**p Value**
		MEAN	**S.D.**	**S.E.**	**MEAN**	**S.D.**	**S.E.**	
1	**Sex**							
	Male	590.32	197.37	35.449	350.65	139.76	25.102	0.001
	Female	647.89	164.78	37.802	208.95	61.72	14.161	0.001
2	**Blood pressure**							
	Hypertensive	561.36	198.67	42.356	315.45	157.23	33.522	0.001
	Normotensive	652.14	168.44	31.833	282.14	115.19	21.769	0.001
3	**Diabetes**							
	Present	542.67	209.91	54.2	272.67	133.5	34.468	0.001
	Absent	642	169.42	28.638	307.14	136.03	22.993	0.001
4	**Smoking**							
	Present	594.78	202.84	42.295	332.17	148.05	30.87	0.001
	Absent	627.04	173.02	33.298	266.67	116.95	22.507	0.001
5	**Alcohol use**							
	Present	577.14	188.08	50.268	328.57	133.06	35.562	0.001
	Absent	625.83	186.14	31.023	284.44	135.36	22.56	0.001
6	**Body weight**							
	Obese	733.6	57.146	11.429	312	131.846	26.369	0.001
	non obese	490.8	191.614	38.323	281.6	138.795	27.759	0.001

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7	**Cholesterol**							
	High	662	164.283	43.763	304.67	128.378	23.439	0.001
	Normal	537.5	195.714	43.763	285	146.629	32.787	0.001

Table 2. Comparison of mean serum fibrinogen level among cases and controls with baseline characters like sex, blood pressure, diabetes, smoking, alcohol use, body weight and cholesterol level with p value < 0.001 which is statistically significant.

The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score <5. The mean fibrinogen level in mild impairment cases was 311, moderately severe cases was 559, severe cases was 709 and very severe cases was 772.02. Hence, it was clear that the fibrinogen levels were higher in patients with acute ischemic stroke with very severe impairment (Table 3).

	No. Of	**Mean**	**Fibrinogen**	
NIHSS Score	Cases		Cases	
		Mean	S.D.	S.E.
Mild (<5)	11	311	111.243	33.987
Moderate (6-15)	12	559	92.543	25.985
Severe (16-25)	12	709	11.656	3.781
Very Severe (>25)	15	772.08	33.67	9.12

Table 3. Mean fibrinogen level among cases with mild, moderate, severe and very severe impairment assessed based on NIHSS score at the onset of stroke. NIHSS – National Institute of Health Stroke Scale

After one month of acute ischemic stroke onset, the morbidity and mortality were assessed using Modified Rankin's Scale (MRS). It was found that the outcome was worse in cases with higher fibrinogen levels. There were 4 dead with a MRS score of 6 and mean fibrinogen level of 822.44. The mean fibrinogen level in patients with no symptoms at one month after stroke onset was 259.17 (MRS score 0). The mean fibrinogen level in patients with MRS score of 1 was 440.15 and they had no significant disability despite symptoms. The mean fibrinogen level in patients with slight disability (MRS score2) was 556.50. The mean fibrinogen level for MRS score of 3, 4 and 5 were 682.52, 735.45 and 763.50 respectively (Table 4).

MRS Score	**No. Of Cases**	**Mean Fibrinogen**		
		Cases		
At 1 Month		Mean	S.D.	S.E.
0	8	259.17	82.95	32.78
1	6	440.15	33.167	12.354
2	5	556.50	5.1	2.52

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3	10	682.52	32.784	10.218
4	8	735.45	22.454	7.567
5	9	763.50	25.55	8.671
6	4	822.44	36.898	22.121

Table 4. Mean fibrinogen level among cases with morbidity outcome with (scores 0 to 6) assessment done at one month follow up using MRS score. MRS – Modified Rankin Scale

Discussion

Stroke is the third commonest cause of death worldwide, after coronary heart disease (CHD) and all types of cancer. In urban India, stroke accounts for 1% mortality in all hospital admissions, 4% in all medical cases and about 20% in all the disorders of central nervous systems. Unlike the Caucasians, Asians have a higher prevalence of stroke. The number of persons who died from stroke was more than three times that for CHD, among the Asians. Hence, Measurement of fibrinogen levels could be more useful than others as it is more specific to vascular disease. It is an independent type of risk factor for recurrences of stroke apart from age, smoking, hypertension, diabetes and other risk factors. It is also a predictor of future recurrences of stroke and adverse cardiovascular events.

A statistically significant increase in serum fibrinogen levels was observed in ischemic stroke patients when compared with controls in present study with values being 614.20 and 295.90 respectively. Similar results were found in studies by Anuradha P et al.[14] and Mistry P et al[15]. Zoppo et al[16] showed that patients with lower initial fibrinogen levels (<4.5 g/L) had better functional outcomes even when corrected for age and initial stroke severity mg%). Mistry P[15] found higher Plasma fibrinogen levels in 56 patients of stroke, admitted in the hospital within 24 hours of symptoms. The mean fibrinogen level in the study group increases as age advances, which was higher than that of control group, with a p- value of 0.001 which was statistically significant. The mean fibrinogen level among males and females in study group was higher than control group which was statistically significant ($p<0.05$).

In this study, the mean fibrinogen level of hypertensive, diabetic, smokers, alcoholic, obese and hypercholesterolic patients among cases were higher than that of seen in control groups, which was statistically significant ($p = 0.001$). Likewise, the mean fibrinogen level of normotensive, non-diabetic, nonsmokers, non-alcoholics, non-obese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant ($p = 0.001$). The mean fibrinogen level is higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score<5. The mean fibrinogen level was higher in the study group both among hypertensives and normotensives, but the levels were more elevated in normotensives. Hence, in our study no significant correlation was found with fibrinogen level elevation between hypertensive and normotensive patients with acute ischaemic stroke. In control group serum fibrinogen levels were higher in subjects with hypertension. Lee AJ et al[17] has demonstrated plasma fibrinogen was higher among hypertensive subjects. Similar results were observed by Anuradha P et al.[14] Several plausible mechanisms could explain an observed association between elevated fibrinogen levels and hypertension, mainly being; relation of fibrinogen to increased viscosity and peripheral vascular resistance, increased platelet activation, increased

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activity of the coagulation system, decreased function of the fibrinolytic system, reduced consumption of fibrinogen caused by elevated levels of markers of inflammation, such as IL-6 and IL-8 contributing to increased plasma fibrinogen in hypertension and lastly the third and final component of Virchow's triad refers to abnormalities in blood constituents, such as clotting or hemostatic factors and platelet activation. Many of the blood constituents associated with hypertension and its complications are components of the coagulation and fibrinolytic pathways. Indeed, the process of thrombogenesis is a fine balance between these 2 systems.[18,19]

In the study group the mean fibrinogen level were higher in both diabetics and non-diabetics as compared to the control group. In the study group as well as the control group the serum fibrinogen levels were higher in non-diabetic subjects than in diabetic patients. This maybe attributed to the non-detection of diabetic status in the subjects who are mostly from rural background and low socioeconomic status and do not undergo regular medical check-up. In our study we could not establish a causal relationship between diabetes and elevated fibrinogen levels in patients with acute ischaemic stroke Lee AJ et al[17] study showed that plasma fibrinogen levels are higher in diabetics than non-diabetics.

According to Rotterdam study, there was lack of association between diabetes duration and plasma fibrinogen and there was no correlation of fibrinogen was found with duration of diabetes in De Silva et al study. The exact mechanism of increased fibrinogen levels in diabetics is unknown, possible mechanisms include:

a. 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;

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

c. The plasma glucagon concentration is positively related to the plasma fibrinogen concentration. Thus, fibrinogen production is markedly enhanced in diabetic patients, and this alteration is likely to determine the observed hyperfibrinogenaemia 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.

Mean fibrinogen level was higher in obese patients than nonobese patients in study group than in control group. Among controls, the levels were higher in obese than non-obese. Meade TW have shown that obese individuals have higher fibrinogen levels. In the study of Esko Venninen et al, showed that persons with higher BMI associated with increased plasma fibrinogen levels. Ditschumit HH et al and Folsom AR found that obesity was independently related to mean plasma fibrinogen level and fibrinogen level decreased after reduction of weight. The mechanisms underlying increased plasma fibrinogen in patients who are overweight are: Firstly, there is a positive association between obesity (skinfold thickness) and plasma insulin concentration, hyperinsulinemia thereby stimulates fibrinogen synthesis. Secondly, it is possible that the interaction between obesity and physical inactivity may promote dyslipidaemia and increased plasma fibrinogen

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After one month of acute ischemic stroke onset, the morbidity and mortality were assessed using Modified Rankin's Scale (MRS). It was found that the outcome was worse in cases with higher fibrinogen levels. Hence, it was clear that among the cases, the acute ischemic stroke was very severe in patients with higher fibrinogen levels. Also, the outcome at the end of one month was poor in patients with higher fibrinogen levels during stroke onset.

However, the present study had few limitations mainly contributed by Variations in the ethnic background of the population, small sample size of study population, variation in age sex distribution and lastly variation in the method used for fibrinogen estimation.

Conclusion

Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with: Clinical severity assessed by National Institute of Health Stroke Scale and Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale. Fibrinogen is associated with risk factors for stroke. Therefore, elevated fibrinogen levels provide a mechanism for the risk factors to exert their effect.

Fibrinogen is increased following an acute stroke as an acute phase reactant. Also, fibrinogen predicts vascular events in established atherosclerotic disorders. Hence, chronically raised fibrinogen in high-risk individuals appears to be an independent risk factor for stroke. Measures such as cessation of smoking, weight reduction, increased physical activity and control of blood pressure decreases plasma fibrinogen level, thereby reduces stroke occurrence in high-risk individuals in future.

Therefore, plasma fibrinogen measurement can be used as a screening for at risk persons for stroke and other vascular events and also as a prognostic marker following an acute stroke. The measures to decrease plasma fibrinogen levels can be included in preventive strategies against stroke.

ACKNOWLEDGMENT

None

DECLARATIONS

Funding: No external source of funding

Conflict of interest: None

Ethical approval: Ethical clearance was obtained from the Institutional Ethics Committee of Index Medical College Hospital & Research Centre, Indore (M.P.), India. Written informed consent was obtained from the subjects before enrolling in the study. Confidentiality of patient information was maintained.

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