



A STUDY ON SERUM LEVEL OF FIBRINOGEN AND ITS PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH ACUTE ISCHEMIC STROKE

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ABSTRACT

Aim: To evaluate the co-relation between serum fibrinogen level and various factors like Age, sex, hypertension and diabetes mellitus in patients presenting with acute ischaemic stroke. To assess the prognosis and stroke outcome at the end of one month by modified Rankin's Scale. **Methods:** Patients admitted with history of acute onset stroke in medical wards in the department on medicine at MGM Hospital were studied from May 2019 to April 2021. A total of 100 patients were enrolled out of which 50 patients with acute ischaemic stroke (study group) and 50 persons without stroke (control group). **Results:** The mean fibrinogen levels were raised in the study group (612.2) with acute ischaemic stroke when compared to controls (296.8). 50% of the patients were more than 60 years of age and 62% of the study group were males and 38% were females. Older age group patients and females had higher levels of mean fibrinogen levels in the study group. Mean fibrinogen levels were high both in hypertensive (561.3) and normotensive patients (652) when compared to hypertensive (315.45) and normotensive (282.14) in the control group. Mean fibrinogen levels were high in the study group, both in diabetics (542.67) and non diabetics (642) when compared to diabetics (272.6) and non diabetics (307.14) in the control group. Mean fibrinogen levels were higher in patients with severe stroke (NHISS Score >16) group and also in group with modified Rankin's scale assessed at the end of one month >=4 in the study group. **Conclusion:** Mean fibrinogen levels were higher in patients with acute onset ischaemic stroke when compared to controls and clinical severity in the study group co-related with higher levels at the time of admission. The prognosis and outcome of stroke at the end of one month, assessed by modified Rankin's scale co-related with mean serum fibrinogen levels at admission.

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INTRODUCTION

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 Asians¹. Hence, Measurement of fibrinogen levels could be more useful than others as it is more specific to vascular disease.

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. It also interacts with monocytes/macrophages which are thought to play an important role in atherogenesis. This interaction also triggers the procoagulant activities. Normal serum Fibrinogen level is 233 to 496 mg/dl.

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.

Aim of the Study

- To evaluate the prognostic significance of serum fibrinogen with stroke severity by correlation with clinical outcome stroke scales.
- To evaluate the correlation between serum fibrinogen and various factors in stroke patients like Age, Sex, Hypertension, Diabetes Mellitus, Body mass index.

Background

Patients admitted with history of acute onset of stroke in medical wards in the Department of Medicine, Mahatma Gandhi Memorial Hospital were enrolled after excluding the exclusion criteria.

Age and sex matched persons not having focal neurological deficit and after verifying exclusion criteria via questionnaire

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were taken as controls.

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.

Exclusion Criteria

Elderly Patients (> 80 years), Haemorrhagic Stroke Patients (ICH, SDH) were excluded with the aid of CT scan, Patients with chronic kidney disease, liver cirrhosis were excluded, Patients with history of Transient ischemic attacks (TIA), History of recent surgery and trauma were excluded

Patients and Methods

- Study design: Prospective Cross-sectional study
- Period of study: November 2018 to May 2020.

Sample size: 100 subjects (50 cases + 50 controls)

Both cases and controls are investigated by following measures.

A detailed medical history including present, past, family and personal history were asked, General examination, Vitals monitoring including blood pressure, pulse rate , Body mass index, Detailed neurological examination, Examination of other systems, Severity score using National Institute of Health Sciences Scale at admission, Complete blood count, Renal function test, Liver function test, Blood sugars, Thyroid function tests, ECG, 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.

BIO Chemical Analysis

The above mentioned routine investigations were done at the time of admission. After overnight fasting, blood samples were taken in the morning to measure Cholesterol and fibrinogen. The plasma fibrinogen level was measured quantitatively by Clauss method.

Data Analysis

Statistical Analysis

Mean values of all parameters in subgroups were calculated by independent sample-t-test. To compare the distributions of dichotomous data viz., gender, age, 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.

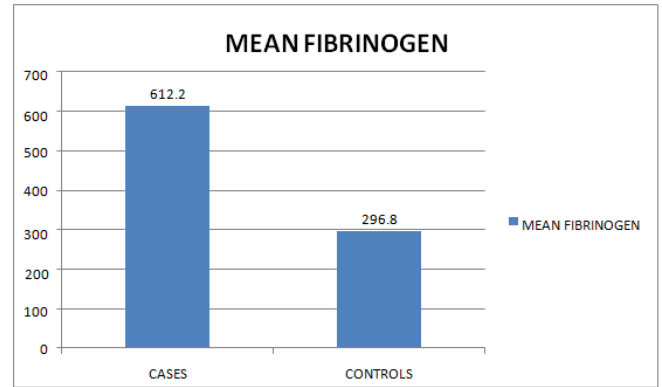
RESULTS

The total number of cases and controls were 50 respectively. The mean fibrinogen level among 50 cases was 612.20 mg% and the mean fibrinogen level among controls was 296.80 mg%. The p-value for mean fibrinogen levels between cases and controls was 0.001, which was statistically significant.

Table 1 Mean Fibrinogen Level Among Cases And Controls.

	Number	Mean Fibrinogen	Standard Deviation	STD. Error of Mean	P-Value
CASES	50	612.2	186.069	26.314	0.001
CONTROLS	50	296.8	134.854	19.071	

The mean fibrinogen level increases as age group increases both in cases and controls. There was statistically significant difference between mean fibrinogen level between cases and controls in all age groups except 30-39 years age-group, in which it was not significant.



Graph 1 Mean Fibrinogen Level Among Cases And Control

The minimum age of the patients in cases and controls was 35 years and the maximum age was 75 years. Among 50 cases, 6% were in 30-39 years, 22% were in 40-49 years, 22% were in 50-59 years, 28% were in 60-69 years and 22% were in 70-79 years. Likewise, among 50 controls, there were 6%, 22%, 22%, 28%, 22% in each of the above groups respectively. Among the cases, 31 were male and 19 were females. i.e., 62% were male s and 38% were females.

The mean fibrinogen level for males in cases was 590.32 and in controls was 350.65 respectively with a p value of 0.001. The mean fibrinogen value for females in cases was 647.89 and in controls was 208.95, respectively with a p-value of 0.001. Therefore, there was a statistically significant difference between mean fibrinogen level in both sexes between cases and control.

The number of hypertensives in cases was 22 which constitutes 44% of total cases and normotensives was 28 which constitutes 56% of total cases. The mean fibrinogen level among hypertensives among cases was 561.36 and in controls it was 315.45 with a p- value of 0.001.

The mean fibrinogen level among normotensives in cases was 652.14 and in controls it was 282.14 with a p value of 0.001. There was a statistically significant difference between mean fibrinogen level between hypertensive cases and controls, and also between normotensive cases and controls.

The mean fibrinogen level was more in both hypertensive and normotensive subjects in the study group as compared to control group. Among cases, the mean fibrinogen level was more in normotensives than hypertensives.

Among 50 cases, 30% i.e., 15 were having diabetes and 70% (35) not having diabetes. The mean fibrinogen level among diabetics in cases was 542.67 which is higher than the mean fibrinogen for diabetics in control, which was 272.67 with a p-value of 0.001 which was statistically significant. Similarly,

the mean fibrinogen level among non-diabetics in cases was 642 and in controls was 307.14 with a p-value of 0.001, which was statistically significant. Among cases and controls, the mean fibrinogen level was higher in non-diabetics than diabetics.

Among, the 50 cases, 25 (50%) were obese and 25 (50%) were non-obese. The mean fibrinogen level among obese in cases was 733.60 and the mean fibrinogen level among obese in controls was 312 with a p-value of 0.001. Similarly, the mean fibrinogen level among non-obese in cases was 490.8 and mean fibrinogen level among non-obese in controls was 281.60 with a p value of 0.001 Mean fibrinogen level was higher in obese patients than non-obese patients.

Among 50 cases, 60% (30) had high cholesterol levels and 40% (20) had normal cholesterol levels. The mean fibrinogen level among patients with hypercholesterol in cases was 662 and in controls was 304.67 with a p-value of 0.001. Similarly, the mean fibrinogen level among patients with normal cholesterol in cases was 537.5 and in controls was 285 with a p-value of 0.001. Therefore, there was a statistically significant difference between mean fibrinogen level both among persons with hypercholesterol and normal cholesterol between cases and control group. Among cases mean fibrinogen was higher in patients with higher cholesterol.

Table 2 Mean Fibrinogen

Groups	Mean fibrinogen						P-Value
	Cases			Controls			
	MEAN	S.D.	S.E.	MEAN	S.D.	S.E.	
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
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
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
OBESITY							
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
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

The severity of ischemic stroke was graded using National Institute of Health Stroke Scale score during admission. Based on the scores, the cases were classified as mild (score <5), moderately severe (score 6 - 15), severe (score 16 - 25) and very severe (score > 25).

Table 3 Nihss Score among Cases and Their Mean Fibrinogen Level

Nihss score	Number	Meanfibrinogen		
		Mean	S.D	Std. Error
Mild (<5)	10	312	110.635	34.986
Moderate (6-15)	13	560	93.452	25.919
Severe (16-25)	10	710	11.547	3.651
Very Severe (>25)	17	771.18	33.89	8.22

Among the cases, 10 had mild stroke, 13 had moderately severe stroke, 10 had severe stroke and 17 had very severe stroke. The mean fibrinogen level was 312, 560, 710, 771, respectively among mild, moderate, severe and very severe cases. Hence, it was obvious that the stroke severity increases with increased fibrinogen levels in cases during admission.

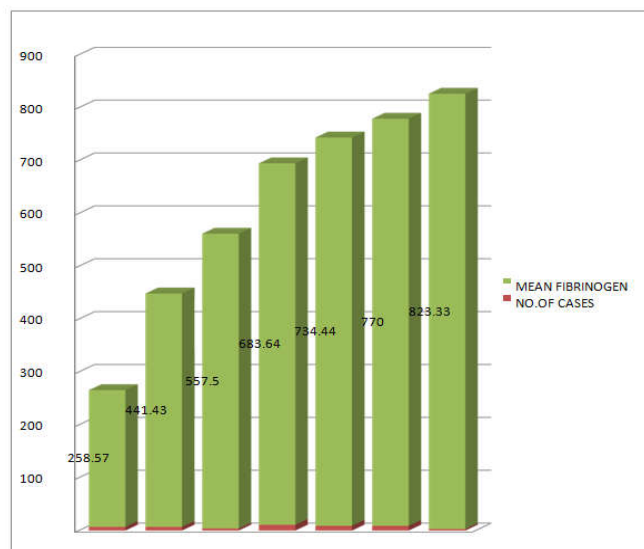
Potpara *et al*¹, identified the association of plasma fibrinogen with poor functional 30-day outcome in ischemic stroke. Turaj *et al*² examined 900 patients with acute ischemic stroke admitted within 24 hours of symptom onset. Case fatality rates at 1 year were higher in patients with fibrinogen levels over 350 mg/dL than in those with lower levels (45.7% versus 31.2%; P<0.001)

Table 4 Modified Rankin's Scale Score At 1 Month Among Cases And Their Mean Fibrinogen Level

MRS Score	Number	Meanfibrinogen		
		Mean	S.D.	Std.Error
At 1 Month				
0	7	258.57	83.95	31.73
1	7	441.43	32.367	12.234
2	4	557.5	5	2.5
3	11	683.64	33.548	10.115
4	9	734.44	22.423	7.474
5	9	764.44	25.55	8.517
6	3	823.33	37.859	21.858

The cases were followed up for one month and the morbidity and mortality were assessed using Modified Rankin's Scale at one month after the stroke onset. Based on the morbidity, the cases were assigned scores from 0 to 6(0 for no symptoms and 6 for death).

Among the 50 cases, 7 cases had a score of 0 with mean fibrinogen level of 258.57 (no symptoms), another 7 cases had a score of 1 with mean fibrinogen level of 441.43 (no significant disability despite symptoms), 4 cases had a score of 2 with mean fibrinogen level of 557.50 (slight disability), 11 cases had a score of 3 with mean fibrinogen level of 683.64 (moderately severe disability), 9 cases had a score of 4 with mean fibrinogen level of 734.44 (severe disability), 9 cases had a score of 5 with mean fibrinogen level of 764.44 (very severe disability) and 3 cases had a score of 6 with mean fibrinogen level of 823.33 (death). Hence, the severity and prognosis of stroke were worse with increased fibrinogen levels during admission



Graph 2 Modified Rankin's Scale Score At 1 Month Among Cases And Their Mean Fibrinogen Level

DISCUSSION

A total of 100 patients were enrolled in our study which comprises of 50 patients with acute ischemic stroke (study group) and 50 persons without stroke (control group). There was no statistical difference in the two groups ($p > 0.05$) regarding the baseline characteristics such as age, sex, diabetes, hypertension, obesity and hypercholesterolemia. Among the study group, 44% (22) were hypertensive, 30% (15) were diabetics, 46%, 50% (25) were obese, 60% (30) were having hypercholesterolemia.

Fibrinogen Level between Cases and Control Group

The mean fibrinogen level among cases was 612.20 with a standard deviation of 186.069 and standard error of mean 26.314. Likewise, the mean fibrinogen level among control group was 296.80 with standard deviation of 134.854 and standard error of mean 19.071, with a p value of 0.001 (< 0.05) which was statistically significant. del Zoppo *et al* [2] 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, Chawla KP, Rai HP, Jaiswal P [3] found higher Plasma fibrinogen levels in 56 patients of stroke, admitted in the hospital within 24 hours of symptoms.

Similar results were found in studies by Hazra B *et al* [378.67 in cases and 216.67 in controls], Mistry P *et al* [534 in cases and 445 in controls], the current study also demonstrated a significant increase in serum fibrinogen levels in ischemic stroke patients when compared with controls. Hazra B *et al*, [1] studies include patients with both ischemic and hemorrhagic stroke in study group whereas current study includes only ischemic stroke patients.

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 was higher in cases with hypertension, diabetes, obesity and hypercholesterolemia than that of seen in control groups, which was statistically significant.

Likewise, the mean fibrinogen level of normotensive, nondiabetic, nonobese and normal cholesterol patients in study group were higher than that of control group which was also statistically significant ($p < 0.05$).

The mean fibrinogen level was higher in patients with higher NIHSS score i.e., very severe neurologic impairment and lowest in patients with mild impairment, NIHSS score < 5

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. 3 patients died with a MRS score of 6 and mean fibrinogen level of 823.33. At the end of one month, patients with MRS score between 0 - 2, who had lower fibrinogen levels at initial presentation had no significant disability. Patients with MRS score > 2 had slight to significant

disability and, the mean fibrinogen level was more than 557.5.

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.

Hypertension and Fibrinogen

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, Lowe GD, Woodward M *et al* [4] has demonstrated plasma fibrinogen was higher among hypertensive subjects.

Samah Saif Alden Osman, *et al* [5] showed that fibrinogen levels are more in hypertensive patients when compared to controls which is statistically significant < 0.01 . This variation in our study may be due to the ethnicity and rural background of our study population in whom hypertension was present, but was not detected earlier and patients directly presented with acute ischaemic stroke.

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

1. Relation of fibrinogen to increased viscosity and peripheral vascular resistance.
2. 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.
3. 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.
4. Increased platelet activation.
5. Increased activity of the coagulation system.
6. Decreased function of the fibrinolytic system.

Diabetes and Fibrinogen

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, Lowe GD, Woodward M *et al* [6] 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

1. 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.
2. Endothelial dysfunction which is common in diabetics, which causes decreased fibrinolytic activity and hence increased plasma fibrinogen levels.
3. 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 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.

Variations in the results of above studies may be related to.,

1. Ethnic back ground of the population.
2. Small size of study population.
3. Small size of study population.
4. Variation in age sex distribution.
5. Variation in the method used for fibrinogen estimation.

Obesity and Fibrinogen: 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

1. There is a positive association between obesity (skinfold thickness) and plasma insulin concentration, hyperinsulinemia thereby stimulates fibrinogen synthesis.
2. It is possible that the interaction between obesity and physical inactivity may promote dyslipidaemia and increased plasma fibrinogen

CONCLUSION

- The mean fibrinogen level increased as age increased in both cases and controls.
- The mean fibrinogen level was more in females compared to males in both cases and controls.
- The mean fibrinogen level was more in hypertensive and normotensive cases as compared to controls. Among cases, the mean fibrinogen level was more in

normotensives than hypertensives.

- The mean fibrinogen level was more in diabetic and nondiabetic cases as compared to controls. Among cases and controls the mean fibrinogen level was higher in non-diabetics than diabetics
- The mean fibrinogen was higher in high cholesterol group than normal cholesterol group among cases and controls.
- Although. The mean fibrinogen level was significantly more in obese group in cases as compared to controls, even amongst controls the mean fibrinogen level was higher in obese group than non obese group.
- Serum fibrinogen level was higher in patients with acute ischemic stroke compared to controls. Among patients higher serum fibrinogen level correlates with:
 - Clinical severity assessed by National Institute of Health Stroke Scale.
 - Poor prognosis and stroke outcome at end of one month after stroke onset, assessed by Modified Rankin's Scale.
- Hence, serum fibrinogen levels should be recommended for all ischemic stroke cases for assessment of clinical severity and prognosis.

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