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Unravelling the Role of Plasma Fibrinogen in Acute Stroke

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ABSTRACT

Background: A stroke is described as a sudden neurological deficit with a focused vascular origin. Atrial fibrillation, carotid stenosis, myocardial infarction, hypertension, diabetes, hyperlipidaemia, obesity, smoking and atrial myxomas are all risk factors for stroke. Stroke mortality in urban India accounts for 1% of all hospital admissions, 4% of all medical cases, and around 20% of all central nervous system illnesses. Diabetes, hypertension, smoking, and hyperlipidaemia are risk factors for stroke and have been linked to alterations in haematology and coagulation, including elevated fibrinogen levels.

Methodology: The present case-control study was conducted among 50 cases of acute stroke and 50 controls without stroke history. Plasma fibrinogen of 50 consecutive patients with acute stroke presenting to the OPD/Casualty or getting admitted to Shri Ram Murti Smark Institute of Medical Sciences was compared with 50 controls who is not suffering from stroke. An unpaired t-test was applied to compare the mean fibrinogen level of the two groups. For statistical significance p value less than 0.05 was taken with 95% confidence interval.

Result: fibrinogen level among the control group (267.0±98) was low compared to patients with overall stroke (428.8±97.8), either ischemic (470±80.5) or haemorrhagic stroke (387.6±97.6).

Conclusion: Patients with Ischemic Stroke having a mean Fibrinogen level of (508.8 mg/dL ± 74.6) and haemorrhagic stroke with 487.5±66 mean fibrinogen level had the worst outcome. There was a significant difference in mean fibrinogen levels among survival and non-survival groups of patients in ischemic and haemorrhagic stroke.

INTRODUCTION

According to World Health Organization guidelines, a stroke is described as "rapidly developing clinical symptoms of focal (or global) impairment of brain function lasting longer than 24 hours (unless stopped by surgery or death) with no clear cause other than a vascular origin".[1]

A stroke is described as a sudden neurological deficit with a focused vascular origin. Atrial fibrillation, carotid stenosis, myocardial infarction, hypertension, diabetes, hyperlipidaemia, obesity, smoking and atrial myxomas are all risk factors for stroke. Stroke mortality in urban India accounts for 1% of all hospital admissions, 4% of all medical cases, and around 20% of all central nervous system illnesses. Diabetes, hypertension, smoking, and hyperlipidaemia are risk factors for stroke and have been linked to alterations in haematology and coagulation, including elevated fibrinogen levels. [2]

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Epidemiological findings show a substantial correlation between high plasma fibrinogen levels and the likelihood of myocardial infarction and stroke, the two main thrombotic consequences of atherosclerosis. Fibrinogen is known to be involved in processes that are thought to have a significant role in thrombosis. Thrombosis is becoming recognised as a central mechanism in stroke and myocardial infarction.[3]

Stroke is the third most common cause of disability and the second most common cause of death globally. In various regions of India over the past 20 years, the crude stroke prevalence ranged from 44.29 to 559/100,000 people and Cumulative incidence of stroke has varied across the nation's diverse regions, from 105 per lakh to 152 per lakh per year. [4]

Elevated fibrinogen levels are linked to carotid stenosis, peripheral vascular disease, atherosclerosis, and coronary heart disease.[5]Higher plasma fibrinogen levels in stroke patients are associated with an increased risk of poor functional outcome, short-term death, and new cardiovascular events.[6]

It is challenging to ascertain whether fibrinogen is a cause or a marker of elevated risk of cardiovascular disease due to the acute-phase feature of fibrinogen and the connections with environmental risk factors of cardiovascular disease [such as smoking and oral contraceptive (OC) use].[7,8]

However, there is debate concerning the connection between hyper fibrinogenaemia and the risk of a second stroke. Fibrinogen has been implicated in a number of studies as a risk factor for ischemic stroke.[9] Increased plasma fibrinogen in high-risk patients with coronary heart disease predicts short-term death. Fibrinogen may be used as a marker for both acute phase response and atherosclerosis. These characteristics might be important for the long-term results of an ischemic stroke. Thus, it makes sense to speculate that high fibrinogenaemia may be a reliable indicator of mortality in those patients. In one study with 128 patients, the modest predictive value of elevated plasma fibrinogen in stroke survivors was discovered, but only in univariate analysis. Multiple minor investigations produced conflicting findings. There is not much proof at this time.[10]

Fibrinogen (FIB) is a vital coagulation factor and an inactive precursor of fibrin. In addition to its role in coagulation, FIB plays an important part in systemic inflammation. Fibrinogen levels may be higher in stroke patients compared with nonstock patients. High levels of fibrinogen can increase the risk of stroke and consequently induce a poorer out- come. [11,12]

Therefore, clarifying the link between fibrinogen and thrombosis may increase the protein's predictive usefulness and provide a novel stroke care strategy. Consequently, the purpose of this investigation is to ascertain whether plasma fibrinogen levels are related to acute stroke.

METHODOLOGY

This case-control study was conducted at the Shri Ram Murti Smark Institute of Medical Sciences. A total of 100 participants were included using a non-probable convenient sampling technique, consisting of 50 patients diagnosed with acute stroke and 50 control subjects without any history of stroke. The stroke group was further divided into 25 cases of ischemic stroke and 25 cases of hemorrhagic stroke.

Patients with acute cerebrovascular accidents, confirmed by CT scans showing cerebral infarction or hemorrhage, were included as cases. Controls were selected based on age, gender, and matching risk factors such as hypertension, diabetes, smoking, and alcohol consumption, ensuring they had no history of stroke.

Exclusion criteria for both cases and controls included evidence of uraemia, infection, active hepatic disease, myocardial infarction within the last three months, or any surgery in the last three months.

Data for the 50 acute stroke cases were collected within 24 hours of symptom onset. A detailed history was taken to identify risk factors. Each patient was followed up until discharge from the hospital.

We assessed serum fibrinogen levels 48 hours post-admission in the medical biochemistry department using the COATRON M1-TECO GMBH and FIBROTEK FIB fibrinogen assay kit from R2 Diagnostics, Inc., South Bend, Indiana, USA. The standard range for fibrinogen levels is 250–350 mg/dL.

Hypertension is diagnosed according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) criteria.[13] This classification includes normal blood pressure (systolic < 120 mmHg and diastolic < 80 mmHg), prehypertension (systolic 120-139 mmHg or diastolic 80-89 mmHg), Stage 1 hypertension (systolic 140-159 mmHg or diastolic 90-99 mmHg), and Stage 2 hypertension (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg). The diagnosis is based on the average of two or more properly measured, seated blood pressure readings taken during two or more office visits.

Diabetes is diagnosed using the American Diabetes Association (ADA) criteria,[14,15] which include a fasting plasma glucose (FPG) level of ≥ 126 mg/dL after an 8-hour fast, a 2-hour plasma glucose level of ≥ 200 mg/dL during an oral glucose tolerance test (OGTT), a hemoglobin A1c (HbA1c) level of ≥ 6.5%, or a random plasma glucose level of ≥ 200 mg/dL in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. These stringent criteria ensure the accurate diagnosis and management of diabetes to prevent associated complications.

The study focused on comparing plasma fibrinogen levels between the 50 acute stroke patients and the 50 control subjects. Blood samples were collected and analyzed to determine the plasma fibrinogen levels, aiming to es-

tablish any significant differences and correlations with acute stroke incidences.

SPSS version 25 was used for statistical data analysis. Unpaired t test was applied to compare mean fibrinogen level of two groups. For statistical significance p value less than 0.05 was taken with 95% confidence interval.

RESULTS

The study included total 100 participants among them 50 were control and 50 were stroke patients. Among stroke patient, 25 were haemorrhagic stroke patient and 25 were ischemic stroke patient. The study ran through the age group of study-participants of 40 to 84 years, out of which 54% female and 46% males.

Statistical test applied between control group and cases in table 1. Mean age of control group were 63±9 which was higher compared to stroke patient group (62±10.1) however the difference was statistically insignificant and the both group were comparable. 13 stroke patients uses alcohol and 29 had positive history of tobacco use. 26% of control study group had overweight compared to 48% of stroke patients classify as BMI more than 25 as depicted in Table 1.

As per seen in table no. 2, fibrinogen level among control group (267.0±98) was low compared to patients with overall stroke (428.8±97.8) , either ischemic (470±80.5) or haemorrhagic stroke (387.6±97.6). Difference of fibrinogen level of cases and control was statistically significant.

Table 1: Comparison of Socio-demographic profile of control group with stroke cases

Alcohol use	Control group	Stroke cases			p value
		Haemorrhagic	Ischemic	Total case	
Age (years)	63±9	61±9.7	64±10.4	62±10.1	0.60
Male	23 (46%)	13 (52%)	10 (40%)	23 (46%)	>0.05
Female	27 (54%)	12 (48%)	15 (60%)	27 (54%)	>0.05
Alcohol user	10 (20%)	6 (24%)	7 (28%)	13 (26%)	0.35
Tobacco users	9 (18%)	15 (60%)	14 (56%)	29 (58%)	<0.001*
BMI >25	13 (26%)	11 (44%)	13 (52%)	24 (48%)	0.023*

Table 2: Comparison of mean fibrinogen level of control group with stroke cases

Study group	Fibrinogen (mg/dL) [Mean±SD]	p value #
Control (n=50)	267.0±98	-
Total Stroke Case (n=50)	428.8±97.8	<0.001*
Ischemic (n=25)	470±80.5	<0.001*
Haemorrhagic (n=25)	387.6±97.6	<0.001*

Unpaired t test applied between control group mean fibrinogen level with stroke patients

Table 3: Comparison of mean fibrinogen level of stroke cases according to their survival status

Outcome	Fibrinogen (mg/dL) (Mean±SD)		p value #
	Alive	Died	
Ischemic Stroke	428±66	508.8±74.6	0.008*
Haemorrhagic Stroke	356±84.3	487.5±66.4	0.002*

Unpaired t test was applied

As shown in Table no. 3, Patients with Ischemic Stroke consisting Mean Fibrinogen level of (508.8 mg/dL ± 74.6) and haemorrhagic stroke with 487.5±66 mean fibrinogen level had worst outcome. Haemorrhagic Stroke consisting Mean Fibrinogen level of (356 mg/dL +- 84.3) and ischemic stroke patients with mean 428±66 survived well. There was significant difference of mean fibrinogen levels among survival and non-survival group of patients in ischemic and haemorrhagic stroke.

DISCUSSION

Present case control study was done among 100 participants with randomly selected 50 stroke patients and 50 patients in control group without stroke. Out of total 100 patients 46% were men and 54% were female.Mean age of patient among control were 63±9 years and among stroke group was 62±10.1 years. A similar study was done by Rizwan et al. included 118 patients, 79 of whom (66.9%) were men and 39 (33.1%) were women. Patients' ages ranged from 28 to 78, with a mean age of 49.46 + 9.35 years which was lower compared to our study findings.[16]*Males had significantly greater fibrinogen levels than females that might be due to more use of tobacco consumption by male compared to females, and these levels increase with age.[17]*

26% participants from the control group were seen to have BMI more than 25. Whereas among haemorrhagic stroke patient 44% and ischemic stroke patients 52% had BMI more than 25. According to the Bingi S., B Balaji. Et al. study The mean body mass index (BMI) in Group B was not statistically different from Group A. When compared to Group B, where 68 percent of the participants had a BMI between 21 to 25, 24% had a BMI between 26 to 30, and 8% had a BMI between 15 to 20, subjects in Group A had a BMI of between 21 to 25, 24% between 15 to 20, and 18% had a BMI of between 26 % 30.[18]

There was no significant association linked to past alcohol use with Stroke as 76% of Haemorrhagic Stroke and

72% of Ischemic Stroke had no history of Alcohol use. This conclusion goes parallel with Control group as well, having only 20% of participants having use of alcohol out of 50 subjects. According to Bingi S., B Balaji. Et al. study, It was noted that the non-alcoholic study group's plasma fibrinogen levels were substantially higher than those of the other groups ($F = 31.27$, $P < 0.001$). Between alcoholic controls and non-alcoholic controls, alcoholic cases and alcoholic controls, and alcoholic cases and non-alcoholic controls, there was no statistically significant difference in plasma fibrinogen levels, $P > 0.05$.[18]

Tobacco consumption was seen to be significantly associated with Stroke cases. 60% of patients with Haemorrhagic Stroke and 56% of, the patients with Ischemic Stroke were seen to have previous/current Tobacco use. For instance, a study by Lu et al. found that current tobacco use only increases the risk of ischemic stroke, whereas former smokers have an increased risk of both ischemic and hemorrhagic stroke of between 50 and 60 percent.[19] Ischemic stroke is not the only type of stroke linked to smoking, according to Shah et al. study; risks for intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) are also increased. Two publications detailing the risk of hemorrhagic stroke among male and female smokers were published in 2003 by Kurth et al. The percentage of hemorrhagic stroke attributed to smoking was 4-12% in men and 1-9% in women, according to a study by Woodward et al. The equivalent percentages for ischemic stroke were 11–27 and 1-22%.[20]

In present study it is average fibrinogen level (428.8±97.8 mg/dL) of total stroke patients was higher than control group.Where, ischemic stroke patients mean fibrinogen level was 470±80.5 mg/dL and haemorrhagic stroke was 387.6±97.6 mg/dL. Difference of fibrinogen level of cases and control was statistically significant. Similar to our finding Samir et al[21] study found a statistically significant increase in serum fibrinogen levels in stroke groups compared with a non-stroke group (P .001).

There was no a significant difference in fibrinogen levels based on gender, Alcohol use or smoking, corroborating the findings of Bruno et al.[22], who evaluated fibrinogen levels once in 1525 individuals with noninsulin-dependent diabetes. In contrast, Giansante et al.[23] discovered that male smokers had higher fibrinogen readings in 516 normal participants, whereas this was the opposite in non-smokers. According to Samir et al. cut-off value of fibrinogen ≥ 557 mg/dL seems to be a guide for prediction of mortality in the ischemic stroke patients.[21]Similarly our study revealed that a cut-off value of serum fibrinogen ≥508.8 mg/dL could be considered as a predictable value in determining the development of ischemic stroke supporting the results of similar studies. [24,25]

One of the major limitations of our study was the measurement of fibrinogen after the occurrence of acute stroke, making it difficult to distinguish hyperfibrinogenaemia as a cause or a result (as one of the acute phase reactants), as well as the lack of serial daily measurement of fibrinogen with its impact on prognosis and outcome, necessitating a long-term prospective cohort study that followed high-risk individuals for the development of acute stroke with routine monitoring. The measurement of fibrinogen 48 hours after intensive care unit admission without a precise correlation to the stroke's start was the second. Lastly, this research did not take into account the correlation between imaging results and the Glasgow Coma Scale and fibrinogen levels.

CONCLUSION

Acute stroke patients made up the majority of the population above 60 years of age. When compared to the control group, the mean fibrinogen level among stroke patients was approximately two times greater. Mean fibrinogen levels were higher in acute stroke patients compared to control group. Higher fibrinogen in stroke cases might be associated with tobacco use, as tobacco use history was more among cases then control group which was statistically significant. Further study needs to be done to prove the association between tobacco and fibrinogen level. Patients with poor outcome had higher mean fibrinogen level compared to patients who survived at the end of the study.

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