STUDY ON PLASMA D-DIMER FOR EARLY DIAGNOSIS OF ISCHEMIC STROKE

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Abstract

Background: *Plasma D-Dimer is a biomarker of thrombo-embolism and a sensitive indicator of subclinical coagulopathy. Its level begins to rise within the first 6 hours of onset of symptoms of acute ischemic stroke. The availability of a rapid diagnostic test like plasma D-Dimer in acute ischemic stroke would be a substantial adjunct to CT and MRI. The test for plasma D-Dimer is quick and easy to perform based on principle of latex agglutination. This study is taken to estimate Plasma D-Dimer level in ischemic stroke patients and to see its role in early diagnosis, and also to differentiate different types of acute ischemic stroke in Bangladeshi population.*

Methods: *This case control study was conducted in Dhaka Medical College Hospital (DMCH) from July 2010 to June 2012. Plasma D-Dimer was estimated by latex agglutination method in DMCH laboratory. Fifty stroke patients (age, 58.36±14.8 years; sex-M/F: 34/16) and 50 age matched control (58.80±15.01 years; sex-M/F: 36/14) were enrolled. In ischemic stroke group all patients were presented from 4 hours to 3 days. CT scan of brain revealed both cortical and subcortical lesion (56%), subcortical lesion (34%) and cortical lesion (10%). The CT volume of the involved brain lesion was 19.95±4.92 cm^3. The value of plasma D-Dimer were evaluated in both control and ischemic stroke patients, correlated with CT size of infract and different types of acute ischemic strokes.*

Results: *Qualitative analysis of plasma D-Dimer reveals 76% positive and 24% negative in the ischemic stroke group. On the other hand, plasma D-Dimer value was only 6% positive and 94% negative in the control group. Qualitative analysis of plasma D-Dimer differs significantly (χ^2=50.64; p=0.001) between the two groups. The analysis also reveals 76% sensitivity and 94% specificity of the Plasma D-Dimer test. Quantitative measurement of plasma D-Dimer (p=0.001) was 804±120 ηg/ml and 126±16 ηg/ml in ischemic and control groups respectively. The plasma concentration of D-Dimer between the two groups was statistically highly significant (t=31.21; p=0.001). Mean plasma D-Dimer level was highest in embolic infarct (1700±964 ηg/ml) followed by atherothrombotic (536±234 ηg/ml) and lowest in lacunar (100±00 ηg/ml) subtype.*

Keywords: *Ischemic stroke, Plasma D-Dimer.*

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Introduction

The World Health Organization (WHO) has defined stroke as a clinical syndrome occurring due to sudden cerebral dysfunction producing focal rather than global neurological deficit persisting for more than 24 hours or the patient dies within 24 hours, vascular in origin, non-epileptic and non-traumatic in nature[1].

Stroke is a major cause of mortality and morbidity around the world. It is the third most

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common cause of death in developed countries after coronary heart disease and cancer[2]. Stroke is the commonest neurological disorder of adult life and about 50% of neurological diseases among the adult admitted patients in general hospital are due to stroke. Incidence of stroke varies with age, sex, race and country to country. In general, its incidence is 150 to 300 per 100,000 populations and prevalence is 600 per 100,000 populations[3,4]. It is the single most important cause of severe disability in people living in their own home. In USA the number of stroke patientsis about 700,000 per year[5]. Stroke caused about 4.4 millions deaths per year and one quarter of this recorded in developing countries[6].

Of all stroke patients, about 85 percent are due to ischemic infarction and 15 percent are due to hemorrhage. But in a study in Bangladesh on stroke patients revealed that 57.84% are ischemic and 42.16% are hemorrhagic Stroke[7].

Embolic or thrombotic occlusion of large arteries has been identified as the main cause of stroke, but other causes include abrupt occlusion of small penetrating arteries, arteritis, arterial dissection, venous occlusion and profound anemia or hyperviscosity. Unfortunately, about 35% all ischemic events remain classified as cryptogenic[8]. Ischemic stroke is an etiologically heterogenous disease. Identification of the specific cause in every patient is very important because early diagnosis, acute management, assessment of clinical progression and long-term strategies is necessary to prevent recurrence[3].

Haemostatic activation may be an important cause, or contributor for progression of ischemic stroke. There is evidence of increased thrombin generation and fibrin turnover, altered fibrinolytic activity, and disturbed endothelial function in acute stroke. Due to differences in the etiopathological process of different subtypes of ischemic stroke, some authors hypothesized that different stroke etiologies might be associated with a specific plasma protein expression pattern and explored the role of different proteins, such as D-Dimer as haemostatic markers in ischemic stroke[3,9,10].

Plasma D-Dimer value is identified in patients at high risk for stroke progression and remain as an independent predictor[11,12]. Raised D-Dimer is a constant finding in thrombogenic disorders. In a study by Barber and his colleagues in 2004 reported increased levels of D-Dimer during the acute phase of ischemic stroke and related to this worse vital function and functional prognosis and to a higher risk of recurrence during follow-up[11]. In addition, plasma D-Dimer value is highest in association with cardioembolic mechanism. A controlled study reported that patients with cardioembolic stroke had raised mean levels of D-Dimer, and has higher risk of new embolisms[13]. In 2011, Alvarez-Perez concluded in his study that there was a continuous activation of coagulation and fibrinolysis characterized by raised D-Dimer in ischemic stroke[14]. This study is taken for early identification of acute ischemic stroke patients in Bangladeshi population, thus stroke patients may be benefited with thrombolytic therapy with reduction of substantial morbidity and mortality.

Methods

This case control study was conducted in Dhaka Medical College Hospital (DMCH), Dhaka, from July 2010 to June 2012. Purposive sampling was done in 100 cases includes 50 cases and 50 controls within 3 days of stroke. Relevant data were collected in preformed data sheet. Age and sex matched healthy volunteers were recruited as control. Plasma D-Dimer was measured by latex agglutination method.

Patients with history of ischemic stroke within 3 days of theincidence attending in the stroke clinic of Department of Neurology or admitted in the Department of Neurology and Internal Medicine through the Outpatient and Emergency Department of DMCH were recruited for the study. The patients older than 18 years with clinical features and CT evidence of ischemic stroke without concomitant anticoagulation therapy were enrolled for the

study. The patients were examined first by the investigator and finally verified by the co-guide. Clinical diagnosis of stroke was done according to National Institute of Neurological Disorders and Stroke (NINDS) criteria[15]. Then CT scan was done to confirm the diagnosis and volumetric measurement of the infarction done by using following formula: A×B×C/2, where A is the largest diameter and B is the perpendicular diameter of the ischemic lesion, as measured, and C is the sum of the thickness of the slices where the lesion was visible[16]. The clinical features, risk factors, other investigation findings and relevant data were collected in a preformed data sheet for each patient by the investigator. Age and sex matched healthy volunteers were recruited as control. Controls were patient's attendant, hospital staffs and voluntary blood donors. Estimation of plasma D-Dimer was done in the Department of Hematology of DMCH and was monitored by investigator and supervised by Hematologist.

Statistical analysis was performed with the help of computer by using statistical package for social science (SPSS). All data were expressed in frequency, t-test or Chi-square (χ^2) test or as appropriate. The levels of significance accepted at Pvalue < 0.05.

Results

A total of 50 cases and 50 controls were included in the study and they were divided into five age groups. In ischemic stroke group, 16% patients were from 18-40 years age group and the maximum number of patients was found in 61-70 years group which is 32%. The mean (±SD) of ages were 58.36±14.80 and 58.80±15.01 in the ischemic stroke and control group respectively. The age difference was not statistically significant (t= 0.15, p= 0.990) between the two groups. The study comprises 34 (68%) male and 16 (32%) female in the ischemic stroke group while there were 36 (72%) male and 14 (28%) female in the control group. There was no significant difference in sex between two groups (χ^2=0.19,p=0.441) (Table-I).

Table-I

Distribution of age and sex in the study and control groups

Age Groups (in years)	Ischemic stroke group n=50 (%)	Control group n=50 (%)	t / χ^2 value	P value
18 – 40	8 (16)	8 (16)		
41- 50	11 (22)	10 (20)		
51 – 60	7 (14)	8 (16)		
61 – 70	16 (32)	12 (24)		
> 70	8 (16)	12 (24)		
Total	50 (100)	50 (100)		
Mean±SD	58.36±14.80	58.80±15.01	0.15	0.990
Sex Male	34 (68%)	36 (72%)		
Female	16 (32%)	14 (28%)	0.19	0.441

Table-II

Showing Duration of symptoms and time of occurrence of stroke

Variables	Ischemic stroke group n=50 (%)
Duration of symptoms (hours)	33.49±28.71
Time of occurrence	
Sleep	19 (38)
Work	31 (62)

The occupational status of the study subjects were placed in five categories. The categories were service holders, businessmen, laborers, farmers and house wives. In the control group 36%, 30%, 10%, and 24 % were service holders, businessmen, laborers and house wives while in the case group 10%, 8%, 22%, 28% and 32 % were service holders, businessmen, laborers, farmers and house wives respectively. The occupational status between the two groups differ significantly (χ^2=30.53,p=0.001) (Fig.-1). Regarding the economic status, 62%, 34% and 4% were in lower, middle, higher economic class in ischemic stroke group; while 34%, 40% and 26% in lower, middle and higher economic class in control group respectively. There was significant statistical difference between the two groups regarding the economic class (χ^2=12.39, p=0.002) (Fig.-2).

Fig.-1: *Distribution of occupations in the studied subjects*

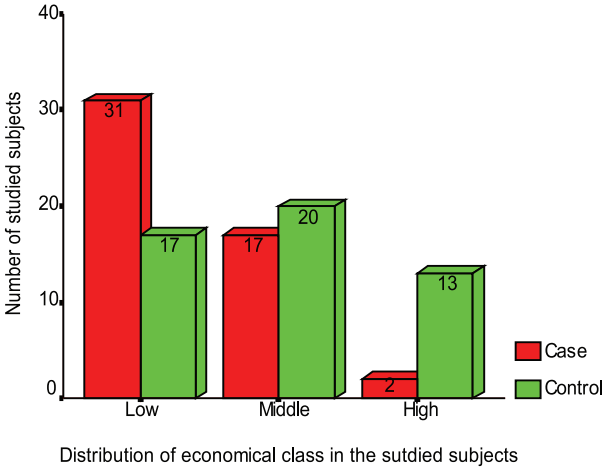

Fig.-2: *Distribution of economical status in the studied subjects*

In ischemic stroke group all patients presented within 4 hours to 3 days. The mean duration of symptoms was 33.49±28.71 hours. The study showed that 62% patients had the attack during work and remaining 38% had attack at sleep (Table-II). Majority of patients presented with hemiplegia (98%) and speech disturbances (86%). Only few patients presented with unconsciousness (12%) and seizure (8%) (Table-III).

Table-III

Clinical presentation in cases

Variables	Ischemic stroke group n=50 (%)
Hemiplegia	49 (98)
Speech involvement	43 (86)
Unconsciousness	6(12)
Seizure	4 (8)

Hypertension is the most prevalent risk factor found in 58% patients. Only 3 (6%) patients had history of diabetes and 5 (10%) patients had valvular heart disease. About 62% patients had habit of smoking (Table-IV).

Table-IV

Risk factors in the studied subjects

Variables	Ischemic stroke group n=50 (%)
Hypertension	29 (58)
Diabetes	3 (6)
Valvular heart disease	5 (10)
Family H/O Stroke	15 (30)
Smoking	31 (62)

Glasgow Coma Scale (GCS) score was observed in all patients. A score of 9-15 was found in 88% patients and a score <8 was found in 12% patients. A variety of speech involvement found in the studied group. Dysarthria and motor dysphasia occurred in 40% patients each. Global dysphasia was found only in 6% patients. However, speech was normal in 14% patients. Cranial nerve lesion was found in 82% patients (Table-V).

Table-V

Neurological findings in the studied subjects

Variables	Ischemic stroke group n=50 (%)
GCS Score	
Score 9-15	44 (88)
Score > 8	6 (12)
Speech involvement	
Normal	7 (14)
Motor dysphasia	20 (40)
Global dysphasia	3 (6)
Dysarthria	20 (40)
Cranial nerve involvement	41 (82)

Hematological and biochemical findings of the studied subjects are shown in Table-6. The mean values of serum cholesterol, triglyceride, LDL and HDL were 219±50, 181±70, 133±32 and 41±9 respectively (Table-VI).

Table-VI

Hematological findings in the studied subjects

Variables	Ischemic stroke group n=50
Hematological values	
Total count of WBC	9243±2478
Polymorph (%)	70±9
RBC (million/mm^3)	4.4±0.64
Platelet count (per mm^3)	2,46,780±56,000
Hemoglobin (gm/dl)	12.6±1.4
ESR mm in 1st hour	32±18
Plasma glucose (mmol/L)	7.9±3.6
Serum creatinine (mg/dl)	1.07±0.18
Lipid profile	
Serum triglyceride (mg/dl)	181±70
Serum LDL (mg/dl)	133±32
Serum cholesterol (mg/dl)	219±50
Serum HDL (mg/dl)	41±9

Values are expressed in mean±SD

CT scan of brain was performed in all patients; and the site and volume of the lesion was measured. The study shows, both cortical and subcortical lesion, were found in 56% patients, whereas subcortical lesion was found in 34% patients and cortical lesion in 10% patients only. CT volume (mean±SD) of the involved brain lesion was 19.95±4.92 cm^3 (Table-VII).

Table-VII

Findings of CT scan of the brain in the studied subjects

Variables	Ischemic stroke group n=50 (%)
Site of the lesion	
Cortical	5 (10)
Cortical and subcortical	28 (56)
Subcortical	17 (34)
Volume of the lesion (cm^3)	19.95±4.92

Qualitative and quantitative measurement of plasma D-Dimer was made in both studied subjects and control groups. Qualitative analysis of plasma D-Dimer reveals 76% positive and 24% negative in the ischemic stroke group. On the other hand, plasma D-Dimer value was only 6% positive and 94% negative in the control group. Qualitative analysis of plasma D-Dimer differs significantly (χ^2=50.64, p=0.001) between the two groups. The analysis also reveals 76% sensitivity and 94% specificity of the Plasma D-Dimer test. Quantitative measurement of plasma D-Dimer (p=0.001) was 804±120 ηg/ml and 126±16 ηg/ml in ischemic and control groups respectively. The plasma concentration of D-Dimer between the two groups was statistically highly significant (t=31.21, p=0.001) (Table-VIII).

There were 24% lacunar infarcts, 40% atherothrombotic and 36% embolic infarcts in the studied group. Mean plasma D-Dimer level was highest in embolic infarct (1700±964 ηg/ml) followed by atherothrombotic (536±234 ηg/ml) and lowest in lacunar (100±00 ηg/ml) subtype. A significant difference (F=31.16, p=0.001) observed in the mean plasma D-Dimer level in the subtypes of stroke (Table-IX).

Table-VIII

Qualitative and quantitative analysis of Plasma D-Dimer

Variables	Ischemic stroke group	Control group n=50 (%)	Sensitivity	Specificity	χ^2/t	p value
D-Dimer	n=50 (%)					
Positive	38 (76)	3 (6)	76%	94%	50.64	0.001
Negative	12 (24)	47 (94)				
Total	50 (100)	50 (100)				
Quantitative assay (ηg/ml)	804±120	126±16			31.21	0.001

Table-IX

Mean value of Plasma D-Dimer in etiological subtypes of acute ischemic stroke

Subtypes of Acute ischemic stroke	Number of patients n=50 (%)	Plasma D-Dimer (ηg/ml)	F	p value
Lacunar	12 (24)	100±00		
Atherothrombotic	20 (40)	536±234	31.16	0.001
Embolic	18 (36)	1700±964		

Discussion

Rapid diagnosis of stroke remains a major challenge for patient management and therapeutic interventions. Diagnosis of acute ischemic stroke is difficult because CT scan results may appear normal in the early stage or in patients with minor symptoms, and MRI is not always possible in the early hours of the disease. Therefore, the first objective in the management with patients of ischemic stroke is the diagnosis of subtypes as thrombolytic agents have been shown to improve outcome when therapeutic intervention is taken timely. Objective of the present study was to assess the potential diagnostic utility of blood borne protein biomarker in predicting stroke. Plasma D-Dimer level was measured in 50 acute ischemic stroke patients and was compared with the age and sex matched healthy control groups. The results of the present study demonstrate that D-Dimer level significantly differ among the stroke subtypes after an acute ischemic event and the measurement of D-Dimer levels can be reliable in the early diagnosis of the mechanism of underlying cause. The mean age of first stroke in male is 68.6 years and 72.9 years in female; and male incidence of stroke rate is 33% higher in comparison to female in Western population[17] but in a series of 291 consecutive stroke patients in Bangladesh revealed mean age was 57.9 years and incidence of stroke was 80% in male patients[18]. This study reveals mean age of stroke as 58.36±14.80 years and frequency of stroke in male and female patients are 68% and 32% respectively. A study from Chittagong Medical College, Bangladesh demonstrates that middle class group has the highest risk of ischemic strokes and housewives are most commonly affected group[19]. Our study also demonstrates higher incidence of stroke in middle socioeconomic class (34%) and the commonest in housewives occupation (32%). Habit of smoking (62%) was higher in this study comparison to Hossain's study from Bangladesh[20].

Hemostatic abnormalities after cerebral ischemia apparently are not related to the extent of the neurological damage in terms of severity and duration of symptoms but to the mechanism responsible for cerebral ischemia.[21] In our study analysis of symptoms reveal that hemiplegia (98%), speech involvement (86%), cranial nerve involvement (82%) correlate with the findings of Walter his colleagues.[21] In a study of Aydin et al., found 74% of patients with GCS >13 and 11% with

GCS <7[22]. In our study 88% patients were with GCS score 9-15 and 12% were with score <8. In a study in Australia by Kawn& Hand in 2006, did not find significant correlation on clinical characteristics of stroke on admission with blood glucose, serum creatinine, and platelet counts, but had significant association with hemoglobin and leukocyte count[23]. This study has similar relationship with the above parameters except blood glucose level and platelet count and also significant association with other variables, as for example, lipid profile, ESR, total and differential count of leukocytes.

At present non-contrast CT scan is the standard of care in the evaluation of acute stroke, although CT changes associated with ischemia are often absent or quite subtle[24]. In this study patients were categorized into stroke subtypes on the basis of clinical history, examination and CT findings. Cerebral infarction was categorized anatomically into 3 groups: cortical, subcortical and both cortical and subcortical; and our study reveals both cortical and subcortical 56%; subcortical 34% and cortical only 10% cases which is similar to several studies [25, 26].

Several studies have found that an increased concentration of plasma D-Dimer level in acute ischemic stroke patients[27,28,29]. This D-Dimer value showed weak to moderate correlation, supports a link between inflammation, hypercoagubility and fibrin turnover in ischemic stroke patients[27]. On the other hand, Alvarez-Perez and Montaner, in their separate study found significant correlation of plasma D-Dimer with a mean value ranging from 500-218 ηg/ml in different subtypes with the lowest concentration in atherothrombotic group[14, 25]. Park et al., found mean plasma D-Dimer level on admission as 215.3 ηg/ml in patients with focal infarction and 385.7 ηg/ml in patients with multiple embolic infarctions[16]. He also observed that plasma D-Dimer value was 566 ηg/ml in patients with 1-19 cc infarctions, 668 ηg/ml in patients with 20-49 cc infarctions, 702 ηg/ml in 50-199 cc infarctions, 844 ηg/ml in >200 cc infarctions[16]. These findings are also similar with a study from a medical university from Japan[30]. Although the volumetric measurement of CT scan of the brain and Plasma D-Dimer value correlated on admission but the D-Dimer value was insignificant with the stroke volume at 7 days after stroke[16]. In this study the average CT volume of lesion was 19.95±4.92 cm^3 and Plasma D-Dimer measured within 33.49±28.71 hours after the event of stroke. Our study reveals that mean concentration of plasma D-Dimer was 804±120 ηg/ml in all ischemic stroke patients irrespective of subtypes and a value 126±16 η g/ml in control group. Furthermore, the plasma D-Dimer (ηg/ml) concentration was 1700±964, 536±234 and 100±0 in embolic, athero-thrombotic and lacunar group respectively. Values of plasma D-Dimer varied significantly in different subtypes of stroke in this study although we found lowest concentration in lacunar group which is contrary to the other studies[14, 25] but similar to Ageno's study[21]. Some authors have shown that plasma D-Dimer has a specificity of 68% to 96% and a sensitivity of 61% to 72% when tested by ELISA method[10, 21]. This study reveals that plasma D-Dimer has a specificity of 94% and a sensitivity of 76% in ischemic stroke patients.

This study suggests that plasma D-Dimer level is a potential biomarker in acute ischemic stroke and also helpful in categorizing the subtypes. Estimation of plasma D-Dimer level and adjunct to CT scan will strengthen the diagnosis of acute ischemic stroke which will help in therapeutic management.

Conclusion

This study indicates that raised plasma D-Dimer is a constant finding in acute phase of ischemic stroke. Plasma D-Dimer has statistical significance with neurological involvement and also with the changes of CT scan diameter or thickness of lesion. Its sensitivity and specificity are higher in ischemic stroke group. Measurement of plasma D-Dimer is simple and can be an adjunct to diagnosis of acute ischemic stroke.

Thus measuring plasma D-Dimer level will further strengthen the clinical diagnosis of ischemic stroke particularly where CT scan could not be done.

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