PLASMA D-DIMER LEVELS IN ACUTE ISCHEMIC STROKE: ASSOCIATION WITH MORTALITY, STROKE TYPE AND PROGNOSIS

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ABSTRACT

• ***Objective:*** *The purpose of this study is to examine the correlation between mortality, stroke sub-types, neurological disability and D-Dimer values measured before a specific treatment is given to patients in the emergency department.*

• ***Material and Method:*** *In the first 24 hours after stroke symptoms started and before anticoagulant treatment started, the serum D-Dimer levels of every patient were examined. The stroke sub-type of every patient was determined according to TOAST criteria and clinical classification was made according to the Oxfordshire Community Stroke Project (OCSP). The Rankin scale was used to determine the neurological disability of the surviving patients.*

• ***Results:*** *Ninety one patients were included in the study. There was a significant difference between the D-Dimer levels of patients who died and who survived (4.50+2.80 and 1.39+1.36 ng/ml respectively, p=0.003). According to the TOAST criteria, average D-dimer levels of cardio-embolic and atherothrombotic stroke patients were higher than the control group. (4.35±3.03/ 3.11±1.69 and 0.43±0.26 respectively, p=0.000). According to OCSP classification, average D-dimer levels of patients with total anterior circulation infract (TOCI) and partial anterior circulation infract (PACI) were higher than the control group. (3.67±2.14, 4±3.03 and 0.43±0.26, respectively, p=0.000). The evaluation of surviving stroke patients in terms of neurological disability revealed that average D-dimer levels of patients with serious neurological disability (Rankin score=3-5) were higher than patients with slight neurological disability (Rankin score=0 and Rankin score=1-2), (2.85±1.69; 0.79±0.56; 0.81±0.44 respectively, p=0.000).*

• ***Conclusion:*** *We reached the conclusion that D-dimer levels in the acute period can be a leading factor for clinicians in predicting the direct results of cerebral infarct and deciding the type of treatment.*

• ***Key Words:*** *Stroke, D-dimer, mortality, neurological disability.* ***Nobel Med 2010; 6(2): 37-42***

ÖZET

AKUT İSKEMİK STROKTA PLAZMA D-DİMER DÜZEYLERİ: MORTALİTE, STROK TİPİ VE PROGNOZLA İLİŞKİSİ

• **Amaç:** Bu çalışmanın amacı; acil departmanına başvuran hastalarda spesifik tedavi verilmeden önce ölçülen plazma D-dimer değerleriyle mortalite, strok tipleri ve nörolojik yeti yıkımı arasındaki korelasyonu incelemektir.

• **Materyal ve Metod:** Strok semptomlarının başlangıcından sonraki ilk 24 saatte ve antikoagülan tedavi başlanmadan önce her hastanın serum D-dimer düzeyleri çalışıldı. TOAST kriterlerine göre her hastanın strok tipi belirlendi ve Oxfordshire Community Stroke Project (OCSP)'e göre klinik sınıflandırılması yapıldı. Yaşayan hastalardaki nörolojik yeti yitimini belirlemede rankin ölçeği kullanıldı.

• **Bulgular:** Çalışmaya 91 hasta dahil edildi. Ölen ve yaşayan hastaların ortalama D-dimer düzeyleri arasında anlamlı fark vardı (4,50+2,80 ve 1,39+1,36 ng/ml, p=0,003). TOAST kriterlerine göre kardioembolik ve atherotrombotik strok hastalarının ortalama D-dimer düzeyleri kontrol grubundan daha yüksekti (4,35+3,03/3,11+1,69 ve 0,43+0,26, p=0,000). OCSP klasifikasyonuna göre total anterior bölge infarktı (TOCI) ve parsiyel anterior bölge infarktı (PACI) olan hastaların ortalama D-dimer düzeyleri kontrol grubundan daha yüksekti (3,67+2,14/4,00+3,03 ve 0,43+0,26, p=0,000). Yaşayan hastalar nörolojik yeti yitimi açısından değerlendirildiğinde ciddi nörolojik yeti yitimi (Rankin skoru=3-5) bulunanların hafif nörolojik yeti yitimi (Rankin skoru=0 ve rankin skoru=1-2) bulunanlara göre ortalama D-dimer düzeyleri daha yüksekti (2,85+1,69 ve 0,79+0,56/0,81+0,44, p=0,000).

• **Sonuç:** Böylece akut dönemde ölçülen D-dimer düzeylerinin serebral enfarktın direkt sonuçlarını öngörmede ve tedavi şekline karar vermede klinisyenler için yol gösterici olabileceği sonucuna varılmıştır.

• **Anahtar Kelimeler:** Strok, D-dimer, mortalite, nörolojik yeti yitimi. **Nobel Med 2010; 6(2): 37-42**

INTRODUCTION

Ischemic stroke occurs when an artery which feeds the brain is occluded, resulting in a reduction in the blood flow going towards the area fed by that artery.[1] Stroke is a medical emergency and ranks third (after heart disease and cancer) among the diseases causing death and long term disability in developed countries.[2] Immediate prognosis of the various presentations of ischemic stroke is very difficult even for the most experienced neurologists.

All acute occlusions occur because of the occlusion of an artery either by local atherosclerotic/atherothrombotic or by a thrombus stemming from a distant artery or the heart. When coagulation occurs in an artery or vein, D-dimer levels increase. D-dimer is a reaction product of intravascular thrombus formation, and thrombolysis can be a clue for hypercoagulation in the patient.[3,4] For patients considered as having ischemic stroke, the threshold value of D-dimer is an important diagnostic issue.[1]

In the last ten years, important advances and developments have been achieved in thrombolytic treatments for restoring the cerebral blood flow in ischemic stroke. Giving intravenous tissue plasminogen activator (TPA) to patients with ischemic stroke in the first 3 hours has shown considerably good results in outcome.[5] Having biological plasma markers besides cranial CT and cranial MR within the first hours of the beginning of symptoms in different stroke sub-types is very useful for choosing appropriate patients who will benefit.

Because of the varying nature of thrombolysis and coagulation in various subtypes of ischemic stroke, D-dimer measurements might be beneficial to determine stroke subtypes and treatment. Thus, lacunar infarcts together with lipohyalinosis are related to occlusion affecting small penetrating arteries of 40-200 microns diameter. Atherothrombotic infarcts are those which affect 3-6 branches of the middle cerebral artery. In addition, infract which occurs as a result of complete occlusion of the cerebral artery and stems from cardio-embolic causes are cardio-embolic stroke.[1] The purpose of this study is to examine the correlation between mortality, stroke sub-types, neurological disability and D-Dimer values measured before a specific treatment is given to patients in the emergency department in the first 24 hours after the onset of stroke.

MATERIAL and METHOD

Study Population and D-Dimer Measurement This study was carried out on 91 patients who were admitted to our emergency department because of acute ischemic stroke between February 2007 and December 2007, following approval from the Ethical Committee of Dicle University Faculty of Medicine. Blood samples were→

taken from each patient within the first 24 hours of the onset of stroke symptoms and before the anticoagulant treatment were started. Patients who were admitted later than 24 hours after the beginning of stroke symptoms, those who were under the age of 18, had epileptic attacks, or had already started anticoagulant treatment previously, and those who did not have laboratory and monitoring data were excluded the study. Cerebral CT or MRI scanning was carried out on all patients in order to eliminate hemorrhagic stroke or other intracerebral diseases, and to classify the stroke subtype.[6,7]

Sub-extremity Doppler was applied to all patients for the diagnosis of deep venous thrombosis and venous thromboembolism along with echocardiography, abdominal ultrasonography, transesophageal echocardiography, carotid ultrasonography. The medical records and demographic, clinical, laboratory and radiological records of each patient were examined. Radiological findings of cerebral ischemia were recorded according to cerebral maps described by Tatu et al.[8]

The classification of each patient according to OCSP classification and TOAST criteria were done by the same neurologist. All patients were examined by the same neurologist on the 30th day and the score of each patient on the Rankin Scale was determined[9] with the purpose of determining neurological disability in vital patients.

The control group was formed from patients above 55 years of age who did not have a familial history of stroke or coagulopathy. The researchers who studied D-dimer levels in the blood samples were blind to diagnosis of patients and control group. D-dimer concentrations were determined using a D-DIMER assay (ACL 200; Diamond Diagnostics, ITALY) with a reference level (0.0 -0.5 ng/ml.).

Statistical Analysis

Univariety statistical analysis was carried out using k square test for categorical variables and student t test for permanent variables. Oneway ANOVA and Post Hoc Dunnett tests were applied to determine the differences between stroke subtypes and the control group. Multivariate analysis was by step-wise binary logistic regression. Variables were included in this analysis, when significance levels in univariate analysis fell below $p<0.05$. For the statistical analysis, $p<0.05$ was accepted as reasonable.

RESULTS

Patient Characteristics

During the study period, a total of 91 acute ischemic stroke patients (46% male) were selected who fitted our inclusion criteria. Average age was 64.5±12.7 years and average referral time to hospital was 7.2±4.9 hours (range: 2-24). The average length of stay in the hospital was 3.6±2.0 days.

Table 1: Demographic and clinical differences between dead patients and surviving patients

Variable	Deceased patients n=29	Surviving patients n=62	p
Age (years; mean ± SD)	68.38±11.16	62.68±13.08	0.452
Gender			
Male	10 (34%)	32 (52%)	0.176
Female	19 (66%)	30 (48%)	
Preexisting medical condition			
Previous hypertension	17 (59%)	45 (73%)	0.229
Known diabetes	8 (28%)	24 (39%)	0.352
Chronic renal failure	0	3 (5%)	0.549
Ischemic heart disease	3 (10%)	5 (8%)	0.706
Admission ECG findings			
Normal	11 (38%)	47 (76%)	0.001
Sinus tachycardia	2 (7%)	8 (13%)	0.493
Atrial fibrillation	16 (55%)	7 (11%)	0.000
Admission echocardiography			
Normal	7 (24%)	23 (37%)	0.243
Left ventricular hypertrophy	9 (31%)	35 (57%)	0.027
Left atrial thrombus	13 (45%)	4 (6%)	0.000
TOAST classification			
Athero-thrombotic	10 (34%)	13 (21%)	0.199
Cardio-embolic	19 (66%)	7 (11%)	0.000
Lacunar	0	17 (27%)	0.001
TIA	0	25 (41%)	0.000
OCSP classification			
TACI	15 (52%)	8 (13%)	0.000
PACI	12 (41%)	11 (18%)	0.021
LACI	0	42 (68%)	0.000
POCI	2 (7%)	1(1%)	0.237
Admission time (hours; mean ± SD)	7.76±3.80	7.00±5.37	0.314
Length of stay in acute hospital (days; mean ± SD)	2.79±1.34	3.97+2.15	0.009
D-Dimer concentration (ng/ml; mean ± SD)	4.50±2.80	1.39±1.36	0.003
Fibrinogen concentration (ng/ml; mean ± SD)	617±155	473±157	0.839

*; TIA: Transient ischemic attack, TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, LACI: Lacunar infarct, POCI: Posterior circulation infarct.

Mortality and D-dimer Levels

Twenty-nine (31.8%) of the 91 patients who are included in the study died. Clinical and demographic differences between the surviving and death patients→

Table 2: Distribution of patients categorized according to D-dimer levels.

Characteristic	D-dimer<0.50 (ng/ml) n=19	D-dimer=0.51-1.50 (ng/ml) n=23	D-dimer>1.51 (ng/ml) n=49	p
Deceased patients	0	0	29	=0.000
Surviving patients	19	23	20	
TOAST classification				
Athero-thrombotic	0	3	20	<0.01
Cardio-embolic	0	1	25	
Lacunar	1	12	4	
TIA	18	7	0	
OCSP classification				
TACI	0	0	23	<0.01
PACI	0	4	19	
LACI	19	19	4	
POCI	0	0	3	
Neurological disability survivors				
Rankin score 0	8	10	1	<0.05
Rankin score 1-2	11	11	3	
Rankin score 3-5	0	2	16	

*; TIA: Transient ischemic attack, TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, LACI: Lacunar infarct, POCI: Posterior circulation infarct.

Table 3: Step-wise logistic regression model of predictors mortality of acute ischemic stroke

	B (SE)	95% confidence interval	Odds ratio	p
Constant	4.214 (0.901)			
Cardio-embolic	2.447 (0.798)	0.018-0.414	0.087	0.002
TACI	2.113 (0.799)	0.025-0.578	0.121	0.008
D-dimer	0.674 (0.227)	0.327-0.796	0.510	0.003

All variables with p<0.05 in univariate analysis were included in this model.

are given in Table 1. There were no significant differences between surviving and deceased patients in the context of age, gender, preexisting medical condition, referral time to hospital and serum fibrinogen concentrations. The patients who had atrial fibrillation and left atrial thrombus at the time of admission to our hospital had higher mortality rates than those without (p=0.000). The mortality rate of patients with cardio embolic infract according to TOAST classification was higher than the patients with other diagnosis (atherothrombotic, lacunar and transient ischemic attack (p=0.000). The mortality rate of patients with anterior and partial circulation infarct (TACI and PACI) according to OCSP classification was higher than those with lacunar infarct (LACI) and posterior circulation infarct (POCI). (p=0.000 and p=0.021 respectively).

There was a significant difference between average serum D-dimer concentrations of surviving and death patients. (1.39±1.36 ng/ml and 4.50±2.80, respectively; p=0.003). Furthermore, when the patients were divided into three groups according to their D-dimer concentrations (<0.50, 0.51-1.50, >1.51), it was observed that the serum D-dimer concentrations of all deceased patients were above 1.51 ng/ml. (p=0.000) (Table 2). In other words, serum D-dimer concentration of all dead patients was more than three times the normal value. The results of a logistic regression model of predictors mortality of acute ischemic stroke are shown in Table 3. Of all demographic and clinical variables, only cardioembolic stroke, TACI and D-dimer were independently associated with mortality.

Stroke Category and D-dimer Levels

D-dimer levels showed variations according to different stroke types. When considered according to TOAST classification, an important difference was observed between D dimer levels in cardio-embolic stroke (4.35+3.03 ng/mL; p=0.000), atherothrombotic stroke (3.11+1.69 ng/mL; p=0.000) and the control group. However, no important difference was observed between lacunar stroke (1.28+0.32 ng/mL; p=0.306), TIA (0.43+0.25 ng/mL; p=1.000) and the control group (Table 4). In a similar way, when the patients were categorized according to their D-dimer levels, in 25 (96.2%) of 26 cardio-embolic stroke patients and in 20 (87%) of 23 atherothrombotic stroke patients, D-Dimer levels were more than 3 times the normal level (p<0.001) (Table 2).

When considered according to OCSP classification, there was an important difference between D-dimer levels of patients with TACI (3.67+2.14 ng/ml; p=0.000) and PACI (4.00+3.03 ng/ml; p=0.000) and the control group. But there was no significant difference in D-dimer levels between patients with LACI (0.77+0.50 ng/ml; p=0.858), those with POCI (2.76+1.25 ng/ml; p=0.930 and the control group (Table 4). D-dimer levels of all 23 patients with TACI and 19 (82.6%) of the 23 patients with PACI were more than 3 times normal levels (p<0.001) (Table 2).

Neurological Disability and D-dimer Levels

When surviving patients were evaluated on the Rankin scale in terms of neurological disability, the score of 19 patients was 0 (no disability), the score of 25 patients was 1-2 (slight disability) and the score of 18 patients was 3-5 (moderate to severe disability). D-Dimer levels showed variations according to the different neurological disability types. There was a considerable difference between the average D-dimer levels of patients with a Rankin score of 3 to5 (2.85±1.69 ng/ml; p=0.000)→

and the control group (Table 4). Furthermore, D-dimer levels of 16 patients (89%) out of 18 with a Rankin score of 3-5 was more than 3 times the normal level at the time of admission to the hospital (p<0.05)(Table 2).

DISCUSSION

We confirmed that there was a strong relationship between increased D-dimer levels measured in the acute phase of ischemic stroke and short term mortality, stroke category and neurological disability. In previous studies, significant findings were obtained showing that D-dimer values in patients with acute stroke were a precursor to early activation of the coagulation system. These values were compared to the control groups without stroke and were found to be high.[10-14] The data published in previous studies about plasma D-dimer levels and mortality in ischemic stroke is contradictory. In some studies, high plasma D-Dimer levels were found to be related to increased stroke risk in the general population and increased mortality rates in ischemic stroke patients.[15,16] However, other studies could not explain the relation between D-dimer levels and survival in stroke patients.[17,18] Feinberg et al., following 70 acute ischemic stroke patients for 1.22 years, found a high D-dimer level to be an independent predictor for mortality.[16] On the contrary, Lip et al were not able to show plasma D-dimer as an independent predictor in 86 vital acute stroke patients.[17] In our study, serum D-dimer levels increased more than 3 times of normal at the time of admission and average serum D-dimer concentrations of deceased patients were higher than the surviving patients. Unlike previous studies, we did not follow the patients for a long period. Our purpose was to investigate the relationship between short term results (first 30 days) and serum D-dimer levels. Thus, we eliminated cases with comorbid physical disorders that could have a direct effect on mortality in stroke patients over a long period and elder patients that could cause an age-related increase in mortality rates.

D-dimer is one of the acute phase reactants of haemostatic function. Thus, high D-dimer levels are a simple marker showing the degree and severity of stroke. Stroke severity is directly related to stroke sub-type. Therefore, different D-dimer levels are expected for different stroke sub-types.[19] In recent studies on this topic, there have been results confirming this aspect.[1,20] As stated in these studies, the difference of D-dimer levels between stroke subtypes is possibly a reflection of different mechanisms underlying acute ischemic stroke.[20] In atherothrombotic stroke, 3-6 branches of the middle cerebral artery were affected, in cardio-embolic stroke there was a complete occlusion of the middle cerebral artery. In lacunar strokes, there

Table 4: Plasma D-dimer level differences between patient group and control group.

Stroke/ neurological disability category	n	D-Dimer concentration (ng/ml; mean ± SD)	p
TOAST classification			
Athero-thrombotic	23	3.11±1.69	0.000
Cardio-embolic	26	4.35±3.03	0.000
Lacunar	17	1.28±0.32	0.306
TIA	25	0.43±0.25	1.000
Control	24	0.43±0.26	
OCSP classification			
TACI	23	3.67±2.14	0.000
PACI	23	4.00±3.03	0.000
LACI	42	0.77±0.50	0.858
POCI	3	2.76±1.25	0.930
Control	24	0.43±0.26	
Neurological disability survivors			
Rankin score 0	19	0.81±0.44	0.854
Rankin score 1-2	25	0.79±0.56	0.851
Rankin score 3-5	18	2.85±1.69	0.000
Control	24	0.43±0.26	

*: TIA: Transient ischemic attack, TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, LACI: Lacunar infarct, POCI: Posterior circulation infarct.

was an obliteration of 40-200 micron diameter small penetrating arteries.[1] Koch et al confirmed in a study carried out on 59 patients that there was a strong relationship between stroke subtypes and D-dimer levels, and stated that the average D-dimer level of cardio embolic and atherothrombotic stroke patients was considerably higher than the control group. On the other hand, they found no difference between the D-dimer levels of the control group and the lacunar stroke and TIA patients.[1] In a similar way, there is data showing that in total anterior circulation infarct, D-dimer levels increase considerably in relation to stroke severity and subtype.[21] Our data confirms the information reported in this last study. In our study also, D-dimer levels showed variations according to different stroke types. Especially, in all patients with TACI and in 96.2% of cardioembolic stroke patients, serum D-dimer levels increased more than 3 times the normal level. But we found no difference between the D-dimer levels of the control group and lacunar stroke and TIA or LACI and POCI patients. There was a strong correlation between D-dimer levels and neurological disability. We found higher D-dimer levels in patients with severe neurological disability than in others. Alessandro Squizzato et al reported similar results in a study carried out on 96 patients .[22] Thus, we came to the conclusion that we could predict the severity of disability in stroke patients by means of D-dimer levels. We found the relationship between plasma D-dimer→

levels examined before starting any stroke treatment and mortality, stroke subtypes and neurological disability. Thus we came to the conclusion that D-dimer levels measured in the acute period may be a leading factor for clinicians in predicting the direct results of cerebral infarct and in deciding on the type of treatment.

Our study's limitations are the number of patients in each group. Studies carried out in the future with a wider population range will define the place of D-dimer levels in ischemic stroke patients in predicting short term results.

CONCLUSION

In conclusion, we do not know for certain all the mechanisms that are responsible for the extreme increase in D-dimer in the acute phase of ischemic stroke. Dimensions of local arterial thrombosis and bionecrosis may play an important role. Other systemic factors may also contribute to D-dimer increase. Measurement of D-dimer is widespread and cheap. It may be helpful in intervention to improve the condition of certain patients after stroke. In particular, beneficial effects may be realized by manipulating the coagulation system.

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