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ORIGINAL ARTICLE **ARAŞTIRMA YAZISI**

ERYTHROCYTE SEDIMENTATION RATE: CAN BE A PROGNOSTIC MARKER IN ACUTE ISCHEMIC STROKE?

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ABSTRACT

OBJECTIVE: The aim of this study is to investigate the relationship between the erythrocyte sedimentation rate (ESR) values and the severity of neurological findings on admission, short- term prognosis, risk factors and etiology of the patients with acute ischemic stroke.
MATERIAL and METHODS: One hundred and fifty-eight consecutive patients who admitted to the hospital within 24 hours of stroke onset were retrospectively analyzed. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores on admission and mRS scores at discharge, brain imaging findings, stroke etiology and risk factors of the patients were recorded. Patients were classified into three groups according to ESR values on admission and compared in terms of severity of clinical symptoms on admission, short-term prognosis, risk factors and etiology of stroke.
RESULTS: A total 158 patients with acute ischemic stroke including 89 women and 69 men were enrolled in the study. Patients with ESR≤10 mm/h were included in group 1 (n=49), ESR levels between 11-25 mm/h were included in group 2 (n=69) and ESR≥26 mm/h were included in group 3 (n=40). No significant difference was determined between the groups in terms of NIHSS and mRS scores on admission and mRS scores at discharge and etiology of stroke. While coronary artery disease was found more frequently in group 1 and 2 than group 3 (p=0.018), valvular heart disease was more frequently in group 2 than group 1 (p=0.037).
CONCLUSION: The results of our study revealed that ESR levels on admission do not reflect the severity of stroke and can not be accepted as a useful predictor of short-term prognosis in patients with acute ischemic stroke.
Key Words: Erythrocyte sedimentation rate, ischemic stroke, prognosis, cerebrovascular disease, inflammatory markers, inflammation.

ERİTROSİT SEDİMENTASYON HIZI: AKUT İSKEMİK İNMEDE PROGNOSTİK BİR GÖSTERGE OLABİLİR Mİ?

ÖZET

AMAÇ: Bu çalışmada akut iskemik inmeli hastaların başvuru sırasındaki nörolojik bulgularının şiddeti, kısa dönem prognozları, inme risk faktörleri ve etyolojisi ile eritrosit sedimentasyon hızı (ESH) arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.
GEREÇ ve YÖNTEM: İnme başlangıcından sonraki ilk 24 saatte hastaneye kabul edilen iskemik inmeli ardı sıra 158 hasta retrospektif olarak incelendi. Hastaların başvuru National Institutes of Health Stroke Skalası (NIHSS) ve modifiye Rankin Skalası (mRS) ve taburculuk modifiye Rankin Skalası (mRS) puanları, beyin görüntüleme bulguları, inme risk faktörleri ve etyolojileri kaydedildi. Hastaların başvuru sırasındaki ESH değerlerine göre 3 gruba ayrıldı ve bu 3 grupta yer alan hastalar başvuru nörolojik bulgularının şiddeti, kısa dönem prognozları, inme risk faktörleri ve etyolojileri açısından karşılaştırıldı.
BULGULAR: Seksen dokuz kadın, 69 erkek toplam 158 akut iskemik inmeli hasta çalışmaya alındı. ESH≤10 mm/s olan hastalar 1. grubu (n=49), ESH değerleri 11-25 mm/s olanlar 2. grubu (n=69), ESH≥26 mm/s olan hastalar ise 3. grubu (n=40) oluşturdu. Gruplar arasında başvuru NIHSS ve mRS puanları, taburculuk mRS puanları ve inme etyolojileri açısından istatistiksel olarak anlamlı bir farklılık saptanmadı. Koroner arter hastalığı 1 ve 2. gruplarda 3. gruba göre istatistiksel olarak anlamlı olacak şekilde daha sık bulunurken (p=0.018), kalp kapak hastalığı 2. grupta 1. gruba göre daha sıktı (p=0.037).
SONUÇ: Çalışmamızdan elde edilen bulgular, akut iskemik inmeli hastalarda ESH'nın başvuru klinik bulgularının şiddetini yansıtmadığını ve kısa-dönem prognozun öngörülmesinde bir belirteç olarak kullanılmasının yararlı olmadığını göstermiştir.
Anahtar Sözcükler: Eritrosit sedimentasyon hızı, iskemik inme, prognoz, serebrovasküler hastalık, inflamatuvar belirteçler, inflamasyon.

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INTRODUCTION

Inflammation plays an important role in the pathophysiology of the cerebral ischemia. Cerebral ischemia and consequential reperfusion initiate an inflammatory response in the brain which is associated with induction of several cytokines. Accompanying peripheral inflammatory response causes an increase in proinflammatory cytokines, leukocytes, platelets and acute-phase reactant proteins (1,2). Elevation of fibrinogen and other acute-phase reactant proteins causes an increase in plasma viscosity and erythrocyte aggregation, hence reduces microcirculatory blood flow and promotes ischemia and infarction (1). Among acute-phase proteins, fibrinogen has the greatest effect on erythrocyte aggregation (3,4). When blood flow is insufficient, increased erythrocyte aggregation and adhesiveness to the endothelium contribute vascular damage particularly in microcirculation (4,5). Increased erythrocyte aggregation may also have an indirect role in the formation of arterial thrombosis through its effects on the platelets (4).

Erythrocyte aggregation can be evaluated indirectly by erythrocyte sedimentation rate (ESR) (4,6). ESR is a simple, widely used and inexpensive laboratory test to assess an acute inflammatory response. Higher ESR values in acute phase of stroke may indicate a greater increase in fibrinogen concentration and blood viscosity, a more pronounced reduction in cerebral blood flow (7,8). Clinical studies suggested that increased ESR levels are associated with poor clinical outcome, early clinical worsening, and extent of brain damage (9).

The present study aimed to investigate the relationship between the ESR values and the severity of neurological findings on admission, short-term prognosis, risk factors and etiology of stroke in acute ischemic stroke patients.

MATERIAL AND METHODS

One hundred and fifty-eight consecutive patients admitted to hospital within 24 hours of stroke onset were enrolled in the study retrospectively. All of the patients were evaluated by computed tomography (CT) or diffusion-weighted magnetic resonance imaging (DWI).

Hematological and biochemical laboratory tests including ESR were performed in the first 24 hours. Electrocardiography, echocardiography and carotid-vertebral artery color Doppler ultrasonography were also performed. Risk factors for cerebrovascular disease such as hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, atrial fibrillation, valvular heart disease, prior transient ischemic attacks and/or stroke were recorded. Systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher or both, was diagnosed as hypertension. Total cholesterol values 200 mg/dl or higher than 200 mg/dl were considered as hypercholesterolemia. The diagnosis of diabetes mellitus was confirmed with the use of antidiabetic agents prior to stroke or fasting blood glucose higher than 120 mg/dl. The diagnosis of coronary artery disease, atrial fibrillation, valvular heart disease was confirmed with electrocardiography and echocardiography. Prior transient ischemic attacks and/or stroke were evaluated with brain CT and history of the patients. Patients were classified etiologically according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores on admission and mRS scores at discharge were recorded. Individuals with a history of infection on admission or within the last 7 days, having axillary body temperature higher than 37.5°C and accompanying acute coronary syndrome on admission were excluded from the trial.

In addition, patients with a history of malignancy, autoimmune and rheumatologic disease, recent operation or patients on steroid and regular anti-inflammatory agents were also excluded from the trial. Patients were divided into three groups according to their ESR values by using weighted averages. Severity of clinical symptoms on admission, short-term prognosis, risk factors and etiology of stroke were compared within groups.

Statistical analysis: Data analysis was performed using SPSS for Windows 11.5 packet program. Continuous variables were expressed as mean ± standard deviation, ordinal variables were expressed as the median (minimum-maximum) and nominal variables were expressed in the form of the

number of cases and percentage (%). The ESR levels were divided into 3 groups using weighted averages. The significance of the difference between the groups in terms of averages was analyzed by one-way ANOVA. The significance of the difference in terms of median values was evaluated by Kruskal Wallis test. In case Kruskal Wallis test revealed significant results, nonparametric multiple comparison test was used in order to determine which group or groups cause the difference. Nominal variables were evaluated by Pearson chi-square test or Fisher's exact chi-square test. The results were considered significant for p<0,05.

RESULTS

A total 158 patients with acute ischemic stroke including 89 women and 69 men were enrolled in the study. The mean duration of the patients' hospital stay was 8,96 days. The patients were divided into three groups according to ESR values. Patients with ESR≤10 mm/h were included in group 1 (n=49), ESR values between 11 and 25 mm/h were included in group 2 (n=69), and ESR≥26 mm/h were included in group 3 (n=40).

Demographic characteristics of the patients and risk factors for stroke according to ESR values are shown in Table-1. Except for coronary artery disease and valvular heart disease, there was no statistically significant difference in terms of stroke risk factors between the groups. Coronary artery disease was found more frequently in group 1 and 2 than group 3 (p=0.018) and valvular heart disease was more frequently in group 2 than group 1 (p=0.037).

Etiology of stroke, NIHSS and mRS scores on admission and mRS scores at discharge according to ESR values are shown in Table-2. Although large artery atherosclerosis is found to be more frequently than small vessel disease in higher ESR group, we couldn't detect any statistically significant differences between the groups in terms of stroke etiology. NIHSS and mRS scores on admission and mRS scores at discharge also showed no significant differences between the groups.

DISCUSSION

Higher ESR levels in the acute phase of stroke may indicate a greater increase in the concentration of fibrinogen and a more pronounced reduction in cerebral blood flow (7,8). It was also reported that high ESR levels are associated with a larger infarct volume (10-12) and a poor outcome (7,8,10,11,13-15). However, neither the NIHSS and mRS scores on admission nor the mRS scores at discharge had any association with the ESR levels in patients with acute stroke in our study. Also, there was no correlation between ESR levels and stroke etiology and risk factors except for coronary artery disease and valvular heart disease.

In the previous studies, ESR levels were found to be increased in the acute phase of stroke (4,8,11,12,16) and associated with short-term poor prognosis (7,11). It was also reported that high ESR levels in the acute phase of stroke are associated with long-term poor outcome, but not with short-

Table 1. Demographic characteristics of the patients and risk factors for stroke.

	Group I (n=49) ESR≤10 mm/hour	Group II (n=69) ESR=11-25 mm/hour	Group III (n=40) ESR≥26 mm/hour	p
Age	66.7±10.6	66.9±11.7	67.8±10.7	0.883*
Female gender	22(44.9%)	42(60.9%)	25(62.5%)	0.150†
HT	33(67.3%)	49(71.0%)	28(70.0%)	0.911†
DM	11(22.4%)	20(29.0%)	15(37.5%)	0.298†
HC	24(49.0%)	29(42.0%)	17(42.5%)	0.729†
Previous TIA¶ / stroke	15(30.6%)	19(27.5%)	14(35.0%)	0.716†
Coronary artery disease	21(42.9%)‡	23(33.3%)§	6(15.0%)‡§	0.018†
Valvular heart disease	1(2.0%)‖	10(14.5%)‖	5(12.5%)	0.037†
AF	10(20.4%)	16(23.2%)	4(10.0%)	0.228†

*One way ANOVA
†Pearson Chi-square test.
‡The difference between the Group I and Group III is statistically significant (p=0,004).
§The difference between the Group II and Group III is statistically significant (p=0,037).
‖ The difference between the Group I and Group II is statistically significant (p=0,025).
¶ Transient ischemic attack

Table 2. Etiology of stroke, NIHSS and mRS scores on admission and mRS scores at discharge.

	Group I (n=49) ESR≤10 mm/hour	Group II (n=69) ESR=11-25 mm/hour	Group III (n=40) ESR≥26 mm/hour	p
Etiology of stroke				
Large-artery atherosclerosis	12(24.5%)	18(26.1%)	14(35.0%)	0,497†
Small-vessel occlusion	13(26.5%)	18(26.1%)	7(17.5%)	0,532†
Cardio-embolism	18(36.7%)	26(37.7%)	12(30.0%)	0,703†
Other determined etiology	1(2.0%)	-	-	-
Undetermined etiology	5(10.2%)	7(10.1%)	7(17.5%)	0,468†
NIHSS scores on admission	4(1-17)	5(1-15)	5,5(1-13)	0,550**
mRS scores on admission	3(2-6)	3(1-6)	4(1-6)	0,535**
mRS scores at discharge	3(0-7)	3(0-6)	4(1-6)	0,889**

† Pearson Chi-square test
**Kruskal Wallis test

term outcome (10,13). Although a positive correlation was demostrated between higher ESR levels and 30-day mortality rates (14,15), others didn't found any relationship (17,18). Because of early clinical deteoriation and elevated D-dimer levels in acute stroke patients with high ESR levels, it was suggested that high ESR levels may be an indicator of ongoing thrombosis (7,19). In addition, high ESR levels were defined as a useful marker for identifying patients at risk for progression of atherosclerosis in ischemic stroke (20).

In the present study, high ESR levels were not found as a predictive marker for the prognosis of acute stroke patients. This may be related with the fact that ESR is a nonspecific marker of infection and inflammation (3). ESR is found to be elevated in many acute and chronic diseases characterized by tissue necrosis and inflammation (3,6). On the other hand, ESR is an indirect method to reveal red blood cell aggregation (21) and poorly correlates with erythrocyte aggregation because of the confounding effects of hematocrit, plasma albumin levels, temperature and hemodilution with anticoagulants (4). In a study using a simple slide test and image analysis for the direct measurement of erythrocyte adhesiveness/aggregation, highly significant difference was noted between patients with TIA or ischemic stroke and controls, although there was no significant difference for both ESR or fibrinogen concentrations (21). Besides, epidemiologic studies have also shown that there is a wide variation of inflammatory, haemostatic and rheologic variables within the general population.

Such variations in markers of low-grade inflammation are associated with genetic and familial influences, age, enviromental stresses, cardiovascular risk factors and vascular or non-vascular diseases (1). Another possible reason detecting ESR as a non-valuable marker in our study may be related to timing of either ESR measurement or assessment of prognosis. We focused on ESR values during admission; consecutive peak values following the insult might be even more informative. On the other hand, preferring relatively long-term outcome scores might influence our results instead of using discharge scores to evaluate the prognosis.

It has been found that markers of inflammation are associated with future coronary heart disease rates in the prospective population studies (1,6,22). It was interesting to observe that coronary artery disease had been detected less frequently in the higher ESR group as compared with other groups. This finding may be assumed as ESR is not a predictive marker for both coronary artery disease and ischemic stroke. On the other hand, valvular heart disease was found to be less frequently in the first group having lower ESR levels compared with group 2. It is consistent with the fact that valvular heart disease is characterized by ongoing inflammatory response (23).

Although it was observed that large artery disease occurs more frequently than small vessel disease in the higher ESR group, we couldn't found any statistically significant differences among ESR groups in terms of stroke etiology. In a study evaluating the association of subtypes of inflammatory markers with vascular disease in patients with acute ischemic stroke, no correlation was found between ESR levels and large or small vessel disease (24). However, it was reported that patients with atherothrombotic stroke showed raised fibrinogen and ESR, while cardioembolic stroke patients had increased D-dimer, fibrinogen and D-dimer/fibrinogen ratio. They suggested that the biochemical profile may be prothrombotic in patients with cardioembolism and inflammatory in those with atherothrombotic stroke (25).

The present study revealed that ESR levels are not specific enough to predict the prognosis of patients with acute ischemic stroke and using more specific inflammatory markers for early identification of prognosis in the acute phase of stroke may be even more informative.

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