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The decisive role of red cell distribution width in carotid endarterectomy patients

Kırmızı hücre dağılım genişliğinin karotis endarterektomi hastalarında belirleyici rolü

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ABSTRACT

Background: This study aims to investigate whether the red cell distribution width is an independent cardiovascular risk factor for carotid artery disease.

Methods: The study enrolled 113 symptomatic patients who had carotid artery stenosis ≥50% according to the North American Symptomatic Carotid Endarterectomy Trial criteria with a history of a recent transient ischemic attack or partially recovered cerebrovascular accidents between June 2011 and June 2014. The patients were able to carry on with their daily activities on their own. The control group consisted of 114 patients who did not meet these criteria. All blood samples were obtained after 12 hours of fasting. The red cell distribution width values of the study group and the controls were compared. The red cell distribution width values were also assessed in terms of the possible relation with cardiovascular risk factors and clinical features in the study group.

Results: There was no significant association between the red cell distribution width values and carotid artery stenosis in the study group. The red cell distribution width did not reach significance among the study patients with respect to the preoperative and postoperative clinical features.

Conclusion: Although increased red cell distribution width values may be considered as an epiphenomenon due to an underlying biological or metabolic imbalance, it still necessitates further comprehensive studies to conclude that it is an independent cardiovascular risk factor for carotid artery disease.

Keywords: Carotid artery stenosis; carotid endarterectomy; red cell distribution width.

ÖZ

Amaç: Bu çalışmada, kırmızı hücre dağılım genişliğinin karotis arter hastalığında bağımsız bir kardiyovasküler risk faktörü olup olmadığı araştırıldı.

Çalışma planı: Çalışmaya Haziran 2011 - Haziran 2014 tarihleri arasında Kuzey Amerika Semptomatik Karotis Endarterektomi Çalışması kriterlerine göre ≥%50 karotis arter darlığı olan ve yakın zamanda geçici iskemik atak veya kısmen iyileşmiş serebrovasküler olay öyküsü olan 113 semptomatik hasta alındı. Hastalar tek başına günlük aktivitelerini yerine getirebiliyordu. Kontrol grubu bu kriterleri taşımayan 114 hastadan oluşuyordu. Tüm kan örnekleri, 12 saatlik açlığı takiben alındı. Çalışma grubu ve kontrollerin kırmızı hücre dağılım genişliği değerleri karşılaştırıldı. Ayrıca, çalışma grubunda kırmızı hücre dağılım genişliği değerlerinin kardiyovasküler risk faktörleri ve klinik özellikler açısından ilişkisi de değerlendirildi.

Bulgular: Çalışma grubunda kırmızı hücre dağılım genişliği değerleri ve karotis arter darlığı arasında anlamlı bir fark bulunamadı. Çalışma grubunda kırmızı hücre dağılım genişliği değerleri, ameliyat öncesi ve ameliyat sonrası klinik özellikler açısından anlamlılığa ulaşmadı.

Sonuç: Yüksek kırmızı hücre dağılım genişliği değerleri altta yatan biyolojik veya metabolik dengesizlik nedeniyle ikinci semptom olarak düşünülebilmesine karşın, bağımsız bir kardiyovasküler risk faktörü olduğu sonucuna varmak için daha kapsamlı çalışmalara gereksinim vardır.

Anahtar sözcükler: Karotis arter darlığı; karotis endarterektomi; kırmızı hücre dağılım genişliği.

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Red cell distribution width (RDW), which normally determines macrocytic or microcytic anemia, can be considered as a biomarker which reflects the proinflammatory state in the presence of cardiovascular diseases (CVD).[1] There are numerous comprehensive studies denoting the importance of increased RDW values being the deterministic factor for death in healthy and high-risk individuals in terms of myocardial infarction (MI) and heart failure (HF), as well as in the development, severity, and outcome of stroke, and even for all-cause mortality.[2-8] In the developing cardiac pathologies, the relationship between the coronary heart diseases (CHD) and RDW values have been put forward, while the relation with the intima-media thickness of the common carotid arteries (CCA-IMT), carotid plaques (CPs), and RDW values have been established for carotid arterial diseases.[5,8-10] Therefore, these variables are effective in predicting stroke independently from the carotid arterial stenosis (CAS).[11,12] The majority of the strokes due to atherosclerotic CAS usually occur in the presence of ≥50%.[13] Strokes ensue in 80% of asymptomatic patients; therefore, being aware and estimating an approximate time before its onset in patients with CAS is of utmost importance. Cardiovascular risk factors, the structure of the plaque, the degree of stenosis, and the complaints of the patient all help to an estimation of the surgery time.[13] Thus, finding of new risk factors will help us further with the timing in the diagnosis and treatment of CAS.

In this study, we aimed to investigate whether the RDW is an independent cardiovascular risk factor for CAS in patients undergoing carotid endarterectomy (CEA).

PATIENTS AND METHODS

The institutional ethics committee approval was obtained for this study (Date 11 June, 2015, Decision No: 171). The study was conducted in accordance with the principles of the Declaration of Helsinki.

This study included a total of 113 patients who were operated either unilaterally or bilaterally between June 2011 and June 2014 with ≥50% stenosis in their unilateral or bilateral carotid arteries according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. The patients referred from the neurology department were those who had a history of a transient ischemic attack (TIA) or partially irreversible neurological deficits (IND) recovered from a cerebrovascular event, but who were able to carry on with their daily activities on their own. The preliminary examination was performed by Doppler ultrasonography, while the definitive diagnosis was made by cervical computed tomography or magnetic resonance angiographies. There were a total of 114 patients in the control group who did not have any neurological problems either clinically or radiologically with no stenosis or plaques in their carotid arteries, and whose peak systolic velocities were <100 cm/sec. The patients with a blood pressure of >140/90 mmHg, those receiving oral anti-hypertensive drugs or those who were diagnosed with a high blood pressure by the treating physician were accepted as hypertensives. The patients who were diagnosed with a high blood glucose level using oral anti-diabetic drugs or insulin with a hemoglobin A1c levels of 6.5% were accepted as diabetics. The patients with a total serum cholesterol level of 240 mg/dL receiving anti-lipidemic drugs were accepted as hyperlipidemics. The patients with a body mass index (BMI) of 30 were accepted as obese patients. As preparations for the CEA operations were carried out, all patients were routinely investigated in terms of CHD. A coronary angiography was undertaken when necessary. A written informed consent was obtained from each patient.

All operations were accomplished under general anesthesia with the patients heparinized without the use of a shunt by the surgeon who carries out more than 30 CEA operations annually. All patients had a saphenous vein patch for the closure of the arteriotomy following CEA. Following surgery, they were all examined by a neurologist for any newly developed neurological deficits. We operated all patients within one month following the cerebrovascular events. The patients who had bilateral carotid stenoses were operated in separate sessions. The patients who had hepatic, renal or cardiac failures, those with a diagnosis of malignancy, those with inflammatory diseases, and undergoing simultaneous CEA and coronary artery bypass grafting were excluded. All data including demographic and clinical characteristics and complete blood count test results were obtained from the hospital database.

Blood samples were obtained from the study patients during the preoperative preparation period following a 12 hours fasting period, while blood samples for the controls were taken at the outpatient ward at 08.00 AM after the same fasting period. All biochemical variables were studied from the serum of the blood samples by using the Abbott Architect C8000 analyzer (Abbott Laboratories, Abbott Park, IL, USA), and hematological parameters were studied from the blood samples taken into the tubes containing ethylenediaminetetraacetic acid (EDTA) using an automatic blood counter (System

XT-2000i, Roche Diagnostics, Indianapolis, IN, USA). Based on the institutional laboratory reference ranges (11.6% to 14.8%), we reported red blood cell volume as a coefficient of variation (percentage).

Statistical analysis

Statistical analysis was performed using the MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) and PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) software. Categorical variables were presented in percentages and frequencies, while the odds ratios were expressed at their significance level. Parametric methods were used due to the large sample size. Descriptive statistics were given in mean and standard deviation. Independent sample t tests were used to compare the means of dependent groups. Despite small sample size, an intragroup analysis was also performed for the patients only with CAS and the patients with coexistent CHD, bilateral carotid stenosis, bleeding or hematoma. As a result, the number of this subgroup was balanced with the mere carotid group by increasing the group count 1.5 fold.

RESULTS

The demographic and clinical data of the study and control groups are shown in Table 1. The number of hyperlipidemics and smokers was higher in the surgery group; however, there was no significant difference in other clinical variables and RDW values between the groups. The BMI of our patients was less than 30. A total of 23.9% of the patients had IND, but were able to manage their daily lives on their own. Nearly 61.9% patients were on an antiaggregant (AA) therapy. Ten patients (8.8%) had had coronary stenting or underwent coronary artery bypass grafting. The degree of stenosis in patients whom we operated unilaterally were 70-89% in 60 and 90% or greater in 40. Bilateral CAS was existed in 13 patients (11.5%) and the degree of stenosis in contralateral lesions were 70-89% in four, 90% or greater in six and totally occluded in three. The RDW values of coexistent CHD, bilateral CAS, ensuing hematoma or bleeding after CEA did not show any relation in the study group. No major symptoms such as death, MI, or stroke were seen in the operated patients. Of the eight patients who experienced complications, three (7.1%) developed bleeding and hematoma which necessitated a surgical intervention. Four patients had peripheral nerve injuries. All four patients completely recovered at the end of six months.

DISCUSSION

For the past couple of years, it has been considered that RDW is an important prognostic marker in predicting the mortality and morbidity in CVD.[2-8] A prospective study conducted by the National Health and Nutrition Examination Surveys (NHANES) reported that RDW is an independent atherosclerotic risk factor, apart from the conventional risk factors and nutritional deficiencies in patients who did not have CVD.[2] Comprehensive prospective and randomized studies on CHD, MI, HF, and stroke showed that RDW was a strong predictor of the mortality in the middle or older ages.[3-6] Studies associated with stroke and RDW usually demonstrate the results related with the severity of stroke, outcome and the course of disease,[14-17] the relationship between the RDW, CCA-IMT, and CP has been mostly investigated in carotid artery disease studies.[5,8] However, CCA and IMT are subclinical atherosclerotic markers;[9,10] and it seems it would be beneficial, if the relationship

Table 1. Baseline characteristics of participants

Groups	Study			Control			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			67.7±9.6			66.1±8.6	0.179
Gender							
Male	78	69.0		83	72.8		0.531
Hypertension	40	35.4		27	23.7		0.053
Diabetes mellitus	26	23.0		18	15.8		0.169
Hyperlipidemia	47	41.6		28	24.6		0.006
Smoking	57	50.4		40	35.1		0.019
Antiaggregan therapy	70	61.9		71	62.3		0.959
Hemoglobin (mg/dL)			14.4±3.5			13.4±0.8	0.424
Platelet count (x10^3/L)			273.6±26.1			275.2±25.9	0.650
Red cell distribution width			13.9±1.4			13.8±1.9	0.641

SD: Standard deviation.

between the RDW and atherosclerotic CAS, which increases stroke, is investigated in patients undergoing CEA. The presence of ≥50% stenosis is critical in most of the strokes associated with carotid artery disease that is why we also investigated the possible relationship between the RDW and stenosis. On the other hand, we found no correlation between the RDW values and clinical variables of the operated patients. Due to the relatively small sample size and other risk factors, significant positive results were able to be only obtained from the smoking ratio (p=0.019) and lipid levels (p=0.006) in terms of CAS (Table 1). Our study group consisted of patients who experienced TIA or a neurological attack but who were able to manage their daily lives in a decent way. They were previously operated for the protection of further infarction development and to lower the risk of death. The RDW values were usually found to be higher in patients with serious cerebral infarctions in most of the studies.[15-17]

Therefore, the lack of a decisive value of RDW in our study can be explained by the mild ischemic attacks in our study population. On the other hand, some studies showing the relationship between the RDW and risk factors and atherosclerosis also yielded conflicting results. In the literature, significantly higher RDW values were found in the study groups of reports showing the close relationship between the RDW and atherosclerotic risk factors.[2,4,6] However, Chen at al.[18] reported that they were unable to establish a definite correlation between the RDW and CHD, despite significantly high atherosclerotic risk factors in their study group. In another study reporting controversial results between the RDW, stroke severity, and functional termination of the stroke, the authors also showed no correlation between other risk factors and atherosclerotic risk factors.[19] Altogether, we can conclude that the correlation between the RDW values, atherosclerosis, and other risk factors is not evident.

On the other hand, our study has some limitations. The relatively small sample of study subjects may have affected the results. In addition, large-scale prospective randomized studies are required to establish a definite conclusion.

In conclusion, although increased red cell distribution width values may be considered as an epiphenomenon due to an underlying biological or metabolic imbalance, it still necessitates further comprehensive studies to conclude that it is an independent cardiovascular risk factor for carotid artery disease.

Declaration of conflicting interests

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