Serum Level Of The Soluble CD 40 Lıgand And Mean Corpuscular Volume, Mean Platellet Volume In Patıents Wıth Ischemıc And Hemorrhagıc Cerebrovascular Dısease

İskemik ve Hemorajik Serebrovasküler Hastalarda Ortalama Eritrosit Hacmi, Ortalama Trombosit Hacmi ve çözünür CD 40 ligand seviyesi

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ÖZET

GİRİŞ ve AMAÇ: Serebrovasküler hastalık (SVH) tanısı ve prognozunun tayininde görüntüleme yöntemlerinin yanı sıra, her geçen gün yenisi eklenen biyokimyasal belirteçlerin de klinik önemi artmaktadır. Çalışmamızda iskemik ve hemorajik SVH'larda soluble-CD40 ligand (sCD40L), ortalama trombosit (MPV) ve ortalama eritrosit hacmi (MCV) düzeylerinin erken prognoz ve mortalite ile ilişkisinin tespit edilmesi amaçlanmıştır

YÖNTEM ve GEREÇLER: Çalışmaya 100 iskemik ve 80 hemorajik inme olan hastalar ve 50 sağlıklı gönüllü kontrol grubundan oluşan 230 birey dahil edildi. Her hastanın demografik verileri ve Glasgow Koma skalaları, intraserebral kanamalı hastalarda İSK skoru ve iskemik inmeli hastalarda NIHSS puanları, kan MPV, MCV, sCD40L düzeyleri kaydedildi

BULGULAR: sCD40L ve MCV düzeyleri açısından hasta grupları ile kontrol grubu arasında anlamlı bir farka rastlanmadı. MPV düzeyinin iskemik ve hemorajik inme geçiren hastalarda kontrol grubuna göre anlamlı oranda yüksek olduğu gözlendi. İnme geçiren hastaların % 22,2'si, ilk hafta içerisinde yaşamını yitirdi. Ölen hastalarda sCD40L değerlerinin, yaşayan hastaların sCD40L değerine göre anlamlı oranda düşük olduğu gözlendi. MCV ve MPV düzeyleri açısından yaşayan ve ölen hastalar arasında anlamlı bir fark tespit edilmedi.

TARTIŞMA ve SONUÇ: MPV düzeyleri akut inme ile başvuran hastalarda anlamlı oranda yükselmektedir. İlk tanı anındaki düşük serum sCD40L düzeyleri akut inme geçiren hastalarda erken prognozun daha kötü olacağına işaret edebilir.

Anahtar Kelimeler: Serebrovasküler hastalıklar, Ortalama eritrosit volümü, Ortalama trombosit volümü, Çözünmüş CD40 Ligand düzeyi

ABSTRACT

INTRODUCTION: The clinical importance of biochemical indicators as well as imaging methods in diagnosis and prognosis of cerebrovascular disorder increase continuously. The aim of the present study is to determine the relationship among soluble-CD40 ligand, mean platelet volume (MPV), mean red blood cell volume (MCV) levels and early prognosis in ischemic and hemorrhagic stroke.

METHODS: 100 ischemic and 80 hemorrhagic stroke patients and 50 healthy volunteers were included in the study. Demographic data, Glasgow Coma Scale, intraserebral hemorrhage scale and NIH Stroke Scale/Score results for stroke, hemoglobin, MPV, MCV and sCD40L measurement results were enrolled.

RESULTS: MPV levels for patients with ischemic and hemorrhagic stroke were significantly higher than the control group. There was no a significant correlation between blood MCV/serum sCD40L levels and strokes. sCD40L levels for exitus patients was statistically significantly lower when compared to sCD40L levels in living patients.

DISCUSSION AND CONCLUSION: MPV levels in patients with stroke increase considerably. The low level of sCD40L may be a parameter associated with early unfavorable prognosis and mortality.

Keywords: Cerebrovascular disease, mean platelet volume, mean corpuscular volume, soluble CD40 ligand.

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Introduction

Cerebrovascular disease (CVD) is the second most common reason for mortality following cardiovascular diseases in individuals aged greater than 60 years; CVD is also the primary reason for disability and loss of workforce in the world. Age, sex, race, family history, hypertension (HT), heart diseases, diabetes mellitus (DM),hyperlipidaemia, smoking, alcohol use and atherosclerosis are risk factors for cerebrovascular diseases. The long-term activation of endothelium cells is believed to play a role in atheropathogenesis [1].

Endothelial surface damage associated with inflammation increases adhesion molecules. Migration of inflammatory cells, monocytes and T lymphocytes and adhesion of lipids provides a prothrombotic characteristic to plaques on the endothelial surface [2]. Inflammation increases the blood flow in the cerebral endothelium, thereby increasing the risk of intraluminal thrombosis and stroke [3].

It has been reported that CRP level, an indicator of inflammation, increases the risk of stroke by 2-3 folds [4, 5]. The relationship of increased levels of serum soluble sCD40-ligand with vascular diseases, thrombosis, acute coronary syndrome and acute cerebral ischaemia has been emphasised [6-7]; CD40 ligand is produced in active CD4+ T lymphocytes. Its soluble form (sCD40L) is produced in platelets present in the circulation; sCD40L is important in the activation of endothelium cells. Serum sCD40L binds with CD40 in the endothelial cells and synthesises a tissue factor, which is important in the inflammatory response [8].

The association of mean platelet volume (MPV) with idiopathic and ischaemic cardiomyopathy [9], acute myocardial infarction [10, 11], coronary artery disease [12] and CVD [13-14] has been reported. Further, mean corpuscular volume (MCV) may be a prognostic factor for the mortality and morbidity of early stage acute ischaemic stroke [14).

Our study aimed to detect soluble CD40 ligand levels, MPV and MCV in ischaemic and haemorrhagic patients with acute stroke. The study also aimed to investigate the relationship between the above mentioned parameters and the early mortality of patients with stroke.

Methods

Our study included a total of 180 patients who were admitted to the emergency service (ES) department of the FıratUniversity, Faculty of Medicine (FUTF), and diagnosed with ischaemic and haemorrhagic stroke; further, 50 healthy controls were also included. The study was approved by the ethics committee of the said institution. The criteria for inclusion were as follows: at least 18 years old, admission to the ES within the first 24 hours (from symptom onset to presentation) and consent to participate in the study. Patients aged less than 18 years, pregnant women, patientsreceiving steroids and patients with pulmonary emboli, acute coronary syndrome, acute kidney failure and chronic kidney failure were excluded from the study. Patients with TIA were also excluded from this study. The diagnosis was made from the patient's symptoms was confirmed by radiologic imaging.

Demographic data, such as age, sex, chief complaints, comorbidities (DM, HT, kidney failure, ischaemic heart disease, arrhythmia and hyperlipidaemia), electrocardiography (ECG), physical examination findings, such as neurological findings, respiratory rate, body temperature, blood pressure, pulse rate and oxygen saturation of patients were recorded. The National Institute of Health Stroke Scale/Score (NIHSS) was used to grade the severity of a stroke, the Glasgow Coma Scale (GCS) was used to detect the severity of brain damage in patients on admission and the intracerebral haemorrhage (ICH) score was used for grading severity in haemorrhagic stroke.

For assessing the values of MPV, MCV and sCD40L, 3 ml of blood from the antecubital vessel was obtained. Similarly, blood samples were also obtained from the 50 healthy controls who voluntarily participated in the study. The obtained blood samples were transferred to gelbased serum separating tubes and were centrifuged at 4°C for 10 minutes at 1600 *g*. The samples were then stored at −80°C for further use.

Serum sCD40L levels were measured using the Human sCD40L ELISA kit (eBioscience; Bender MedSystems, GmbH, Vienna, Austria), in accordance with manufacturer instructions.

Serum MPV and MCV levels were measured using thiazole orange dye with the

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Automated haematology analyser ABX Pentra DX120 (MicromedTıbbiMalzeme, Ind. Trade. Co., Ltd.).

The patients with ischaemic and haemorrhagic stroke were classified according to their aetiologies as ischemic and hemorrhagic CVD groups.They were further separated into subgroups based on their GCS at the time of admission; patients with haemorrhagic stroke were separated into subgroups based on their ICH scores.

Patients were followed after emergency department discharge, for a further 5 to7 days in other departments.

Statistics

After all data were obtained, statistical analyses were performed using the SPSS 21 software. Numerical data were expressed as mean ± standard deviation, whereas qualitative data were expressed as percentages. For numerical values, *t*-test was used for comparing two independent groups. Continuous variables were compared with the Mann-Whitney *U* test.Chisquare test was used for analysing categorical data. Linear relation between two continuous biochemical variables was evaluated by Spearman correlation analysis. $p < 0.05$ was considered statistically significant.

Results

The current study included 100 patients with ischaemic stroke, 80 with haemorrhagic stroke and 50 control group participants. Of the patients with stroke, 50.6% were males and 49.4% were females. There was no statistically significant difference between the ischaemic stroke and the control groups in terms of the average age ($p = 0.08$) and sex ($p = 0.25$). There was also no statistically significant difference between the haemorrhagic stroke and the control groups in terms of the average age ($p = 0.84$) and sex ($p = 0.80$). However, a statistically significant difference was observed between the ischaemic and haemorrhagic CVD patient groups in terms of the age ($p = 0.001$). Patients in the ischaemic group were older(Table 1).

The most commonly observed concomitant diseases in our patients with stroke were DM, HT and atrial fibrillation. No other concomitant diseases were observed in 42% of the ischaemic stroke patients and 38.8% of the haemorrhagic patients.

Table 1. Demographics of the groups

By contrast, the GCS of the ischaemic CVD patients was significantly higher than that of the haemorrhagic stroke patients (13.17 ± 2.48 vs. 11.38 ± 3.85, $p < 0.001$) (Table 1).

The values of MPV in patients with ischaemic stroke were significantly higher than those of the control group patients (Table 2). There was no difference among three groups in terms of the presence of anemia($p > 0.05$).The values of MCV and MPV in patients with haemorrhagic stroke were statistically significant higher than those of the control group patients; however, no statistically significant differences were detected between control groups and the two diseases groups in terms of sCD40L levels (Table 3). No significant difference was detected between the haemorrhagic and ischaemic stroke groups in terms of hemoglobin, mean corpuscular hemoglobinconcentration (MCHC), MCV, MPV and sCD40L values (Table 4). No significant correlations were detected for the association of the GCS with sCD40L, MPV and MCV.

According to the results of the Pearson correlation analysis conducted to detect the correlations between the soluble CD40L, MPV and MCV levels and the used neurologic rating scales, a significant negative correlation ($r = -0.305$, $p = 0.042$) was observed only between the MCV and ICH scores. Further, no significant correlations between the sCD40L and MPV levels and the Hunt–Hess scale, ICH and NIH Stroke Score (NIHSS) scale were observed in both ischaemic and haemorrhagic stroke groups (Table 5). Out of the 180 patients with stroke included in the study, 40 (22.2%) died in the ES or in other services where they were being monitored. (37 patients died in the emergency department and 3 patients died in the neurology intensive care unit). Patient mortality were higher in hemorrhagic stroke group (28 of 80 patients) than in ischemic stroke group (12 of 100 patients).

The serum sCD40L levels of the 40 patients with an in-hospital mortal course was 3.56 ± 2.11 ng/ml, whereas the average serum SCD40L levels of those who died was statistically significant lower than that of those who survived. (3.56 ± 2.11 ng/ml vs 5.01 ± 4.03 ng/ml, $p = 0.001$).

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	Control (n=50)	Ischemic CVD (n=100)	Hemorrhagic CVD (n=80)
Age (years)	68.1 ± 10.7	71.4 ± 11.2	64 ± 15.8
Male Gender	23 (46%)	56 (56%)	35 (44%)
SBP (mmHg)	113 ± 22.5	135.6 ± 31.2	152 ± 37.9
DBP(mmHg)	75 ± 9	80.7 ± 21.9	88.5 ± 21.9
MRS	0 ± 0	3.1 ± 1.2	3.5 ± 1.4
GCS	15 ± 00	13.17 ± 2.48	11.38 ± 3.85

CVD: cerebrovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure,MRS: Modified Rankin Scale, GCS: Glasgow coma score, SD: Standard deviation.

Table 2. Comparison of mean MPV, MCV sCD40L values between patients with ischemic CVD and healthy control group individuals

	Control (Mean□□SD)	Ischemic CVD (Mean□□SD)	P
MCV (fl)	84 ± 6.2	85.2 ± 10.6	0.463
MPV (fl)	8.3 ± 0.8	9 ± 0.9	0.000
sCD40L*	5.6 ± 4.7	22.2 ± 174	0.269

CVD: cerebrovascular disease, MCV: mean erythrocyte volume, MPV: mean platelet volume, fl: femtaliter, sCD40L: soluble CD40 ligand, SD: standard deviation. (*) sCD40L unit: ng / ml.

Table 3. Comparison of mean MPV, MCV sCD40L values between patients with hemorrhagic CVD and healthy control group individuals

	Control (Mean□□SD)	Hemorrhagic CVD (Mean□□SD)	P
MCV (fl)	84 ± 6.2	86.8 ± 6.8	0.020
MPV (fl)	8.3 ± 0.8	8.8 ± 1.2	0.009
sCD40L*	5.6 ± 4.7	4.4 ± 3.1	0.089

CVD: cerebrovascular disease, MCV: mean erythrocyte volume, MPV: mean thrombocyte volume, fl: femtaliter, sCD40L: soluble CD40 ligand, SD: standard deviation (*) sCD40L unit: ng / ml.

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Table 4. Comparison of mean MPV, MCV and sCD40L values between patients with hemorrhagic and ischemic CVD

	Ischemic CVD (Mean□ □SD)	Hemorrhagic CVD (Mean□ □SD)	p
Hb (g/dl)	13.4 ± 1.6	13.4 ± 1.8	0.987
MCHC (g/dl)	32.8 ± 1,5	32.9 ± 1,5	0.625
MCV (fl)	92.7 ± 74.9	86.8 ± 6.8	0.240
MPV (fl)	9 ± 0.9	8.8 ± 1.2	0.354
sCD40L*	22.2 ± 174	4.4 ± 3.1	0.534

CVD: cerebrovascular disease, MCV: mean erythrocyte volume, MPV: mean platelet volume, fl: femtaliter, sCD40L: soluble CD40 ligand, SD: standard deviation. (*) SCD40L unit: ng / ml.

Table 5. The correlation between sCD40L, MPV and MCV levels and neurological scales

Scales	Parameters	R value	P value
Hunt–Hess	MPV (fl)	−0.171	0.470
	MCV (fl)	0.195	0.411
	sCD40L (ng/ml)	0.013	0.956
ICH	MPV (fl)	0.000	0.999
	MCV (fl)	−0.305	0.042
	sCD40L (ng/ml)	0.091	0.553
NIHSS	MPV (fl)	−0.27	0.792
	MCV (fl)	−0.45	0.654
	sCD40L (ng/ml)	−0.023	0.817

*MCV: mean erythrocyte volume, MPV: mean platelet volume, sCD40L: soluble CD40 ligand, fl: femtaliter, ICH: intracerebral hemorrhage **scale**, NIHSS: National Institute of Health Stroke Score*

Discussion

The average age of the patients with cerebrovascular stroke included in the study was 68.1 ±10.7 years, which was lower than that reported in studies conducted in the west [15-16]. We believe that the average age in our study is lower owing to the relatively young population in Turkey compared with the other western countries; another possible reason for this could be the small number of patients included in our study.

Only a limited number of studies examine the correlation between MCV and stroke. Aksoy et al. reported that MCV and a few biochemical indicators may be prognostic indicators for the mortality and morbidity of early stage acute ischaemic stroke [14]. In

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another study which had 98 participants, MCV was highlighted as a prognostic indicator of the first-week mortality of ischaemic stroke [17]. In our study, no correlation was observed between ischaemic stroke and MCV. But, a statistically significant increase in the average MCV values was observed between the haemorrhagic stroke and control group patients.

Several studies have examined the correlation between MPV and ischaemic stroke and between ischaemic and haemorrhagic CVD; however, the results are very different from each other. In a study, a positive correlation between the stroke risk and MPV was observed in high-risk patients with stoke history, and it was reported that every 1-femtoliter increase in MPV increases the stroke risk independently from other risk factors by 12% [13]. Butterworth et al. reported that an increased MPV was associated with poor prognosis in patients with stroke [18]. Tohgi et al. [19] reported that the platelet volume was lesser in patients with acute ischaemic strokes than in control group patients. They also explained that this result is caused by the immediate consumption of large platelets during cerebral thrombosis. However the study only included a small number of cases (22 patients, 29 controls). In one study with ischaemic stroke sub-grouping, no difference was observed between the lacunar infarction group and the control group in terms of MPV; however, MPV was found to be significantly higher in cortical infarction associated with large vessel disease group [20]. In another study was reported no significant difference between patients with prior ischaemic stroke and control group patients in terms of MPV values; however, MPV was increased in the patients with acute ischaemic stroke. No difference was observed between the stroke sub-types of the lacunar infarction group and the large vessel groups [21]. McCabe et al. reported no significant difference between MPV levels in the early stage of CVD and those at six months after the event. They also reported that the risk factors had no influence on MPV [22]. In another article involving ischaemic and haemorrhagic stroke patients, no correlation was observed between mortality and platelets and MPV. In that study, no significant difference was observed between the acute stroke subgroups and MPV [23]. Mayda et al. also reported no significant difference in the comparison of MPV of 208 ICH patients with the control group patients [24]. In terms of MPV values of both the ischaemic and hemorrhagic CVD patients and the MPV values of the control group patients, we detected no statistically significant in our study population. We believed that the increased MPV values in the stroke patients, reported in other studies could be caused by the increase in MPV because of HT, DM, atherosclerosis, vascular impairments or other previously-existing diseases, such as platelet function impairment.

In the current study, no significant difference was observed in terms of sCD40L levels, neither compared with the healthy control group nor between the haemorrhagic and ischaemic groups. In a large-scale cohort study involving patients with acute coronary syndrome, no correlation was observed between the cardiovascular findings and sCD40L [25]. Garlichs et al. [6] reported that sCD40L levels were increased in the acute cerebral ischaemia patients, and Ferro et al. reported that sCD40L levels are an indicator of vascular events [26]. Wang et al. reported that sCD40 levels were correlated with the severity of acute cerebral ischaemia and neurological dysfunction and that this correlation was higher particularly in patients with acute cerebral strokes associated with atherosclerosis [27]. In our study, the sCD40L levels were not found to be higher in the CVD group, though the results are not statistically significant. In a previous article was reported that plasma sCD40L levels in adults admitted to the ES were not useful as a diagnostic indicator for ischaemic stroke or thromboembolic events; they also reported that there was a significant correlation between the platelet count and sCD40L levels and that sCD40L could be associated with active platelets [7]. Tanne et al. reported no correlation between stroke and high sCD40L [28]. sCD40L being useless in the diagnosis of these diseases can also be attributed to the high prevalence of procoagulation activity impairments and/or inflammation in the ES patients.

sCD40L levels of the patients with an in-hospital mortal course in our study being lower than those of patients who were discharged with partial or complete recovery suggests that this indicator may be associated with inflammation or another pathologic process.

Neurologic rating scales, such as the Glasgow Coma Scale, Hunt–Hess, ICH and

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NIHSS, are scales that have been proven in the determination of disease prognosis with clinical findings; these scales are prevalently used for this purpose worldwide [29]. There are very few studies examining the correlation between these clinical scales and the MCV, MPV and serum sCD40L levels analysed in our study. In the stroke severity evaluation by Muscari et al., it was stated that there was no significant correlation between MPV and neurological scores [20]. Contrarily, in another study was stated that MPV is correlated with the severity of stroke and that platelet activity is increased in parallel with the severity of stroke [30]. However, the platelet lifespan being approximately 8–10 days suggests that this correlation observed with the blood samples obtained during hospitalisation may be associated with an acute phase reaction and with the need for a platelet function disorder to exist prior to the stroke. In our study, no significant correlation was observed between sCD40L and MPV levels and the Hunt–Hess scale, ICB and NIHSS scale in both ischaemic and haemorrhagic CVD groups. However, in patients with haemorrhagic cerebrovascular events, a significant but weak negative correlation was observed between the MCV levels and ICH. None of these three biochemical parameters checked were associated with the clinical severity of the patients at the time. This indicated that the prognosis or mortality could not be foreseen using these parameters.

In conclusion, we could not detect a significant correlation between blood MCV and serum sCD40L levels and ischemic or hemorrhagic stroke. Although MPV values significantly increased in ischemic and hemorrhagic stroke patients compared to the control group, they did not correlate with NIH, HH nor GCS scores. Only ICH affected negatively with MCV and sCD40L values were significantly lower in stroke patients who died in hospital. Furthermore, we also did not observe any effects of increased MPV on early prognosis and mortality. The level of sCD40L in patients who had stroke and died in the ES or in other services where they were being monitored was significantly lower than that in the survivors. Thus, serum sCD40L may be a parameter associated with early prognosis and mortality.

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