

The relationship of the mean platelet volume and C-reactive protein levels with mortality in ischemic stroke patients

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Abstract. – BACKGROUND AND OBJECTIVES: The relationship of the mean platelet volume (MPV) and C-reactive protein (CRP) values with mortality in patients with ischemic stroke is not clear. Besides, the correlation between CRP and MPV in patients with ischemic stroke has not been adequately studied yet. In the present study, our aim is to investigate the interrelationship of the CRP and MPV parameters together with their influence on mortality in patients with acute ischemic stroke.

PATIENTS AND METHODS: Sixty-three patients with acute ischemic stroke have been enrolled in the study. The stroke patients were divided into 2 groups as those who died within the first 10 days and those who survived. The MPV and CRP in both groups have been compared. Also, the MPV obtained from the ischemic stroke patients were compared with the MPV of the healthy volunteers.

RESULTS: A statistically significant difference ($p = 0.027$) was observed between the MPV of the stroke patients (8.6 ± 1.95 fL) and the control group (7.93 ± 0.82 fL). The MPV (9.24 ± 1.98 fL) and CRP (10.8 ± 7.0 mg/l) of those ischemic stroke patients who died were statistically significantly higher ($p < 0.05$) than the MPV (8.09 ± 1.75 fL) and CRP (3.2 ± 3.5 mg/l) of the patients who survived. There was also a positive correlation between the MPV and CRP of the ischemic stroke patients ($r = 0.31, p = 0.029$).

CONCLUSIONS: The fact that there is a relationship between the MPV and CRP in ischemic stroke patients and that the CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived may be an indication of the roles these markers play in the mortality of stroke patients.

Key Words:

Stroke, Mean platelet volume, C-reactive protein, Mortality.

defined as a risk factor for myocardial infarction in patients with coronary heart disease². Also in patients with risk factors for stroke, like diabetes mellitus or hypercholesterolemia, the MPV values were found to be higher than the control groups^{3,4}. Although a relationship between the MPV values and the severity and prognosis of the ischemic stroke has been observed in some reports, other studies did not reveal such an interrelation⁵⁻⁸. In atherosclerotic vascular disease, the C-reactive protein (CRP) levels in the systemic circulation are increased due to the underlying chronic inflammation⁹. Although this increase in CRP has been pointed out as an important prognostic marker in stroke, it has also been claimed that CRP does not shed a light at the prognosis in cerebrovascular disease¹⁰⁻¹². Therefore, the relationship between inflammation and thrombosis still continues to be complicated: While the inflammation contributes to thrombogenesis, the thrombosis in return increases inflammation¹³. It has already been specified that the CRP has prothrombotic properties and increases platelet activity¹⁴. On the other hand, the CRP and platelet activation were suggested as two strong risk factors influencing the severity and incidence of cardiovascular disease¹⁵. However, the relationship between CRP and MPV, of which the latter is a marker of platelet activation, has not been adequately studied in patients with ischemic stroke.

In the present study, our aim is to investigate the interrelationship of the CRP and MPV parameters together with their influence on mortality in patients with acute ischemic stroke.

Patients and Methods

For the purposes of this study, the clinical data, complete blood count (CBC) test results, CRP values and erythrocyte sedimentation rates (ESR) of 72 patients admitted with the diagnosis of acute ischemic stroke to the Dicle University School of Medicine, Neurology Department between January 2010 and November 2011 have been studied in a retrospective

Introduction

The mean platelet volume (MPV), a parameter of platelet function, is an important marker of platelet-related activities like platelet aggregation, thromboxane A₂ generation, and platelet factor 4 and thromboglobulin secretion¹. High MPV-levels have been

manner following the obtainment of the approval of the local Ethics Committee. The age and sex data of the patients together with any history involving hypertension, diabetes mellitus, previous strokes as well as their cigarette and alcohol consumption have been recorded. The aetiological factors have been classified as atherothrombotic, cardioembolic, lacunar and cryptogenic according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Forty-six healthy individuals in matching age and sex groups and with no history of strokes or any present haematological or infectious conditions have also been enrolled as the control group. The enrolled patients were chosen from among those who were not on any thrombolytic treatments or did not receive any anticoagulant therapy before the event. The patients who presented with high fever or in which infection developed within the first five days following the stroke, those with renal or hepatic insufficiency and the patients who had undergone a surgical procedure or had myocardial infarction within the last 3 weeks were excluded. The remaining sixty-three patients with ischemic stroke were divided into two groups as those who died in the first 10 days and those who survived. The venous count blood cells (CBC), CRP and erythrocyte sedimentation rate (ESR) values of these patients obtained from the blood collected in EDTA tubes within the first 24 hours as of their post-stroke hospital admittance were recorded. The CRP, MPV and ESR values as well as the leukocyte and platelet counts were compared between the groups. Also, the MPV values of the ischemic stroke patients were compared to the values of the control group.

Statistical Analysis

The results have been calculated as mean \pm standard deviation (SD). The statistical analysis was carried out using the SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). The comparison of the MPV values of the ischemic stroke patients and the control group was made through the Student's *t*-test. The MPV and CRP levels of the ischemic patients who died or survived were also compared using the Student's *t*-test. The relationship between the MPV and CRP values were further evaluated by means of the Pearson's correlation analysis. An inter-group difference of $p < 0.05$ is statistically significant.

Results

The group of stroke patients consisted of 32 females and 31 males, while the healthy controls comprised 24 females and 22 males ($p > 0.05$).

The mean ages of the stroke patients (64.0 ± 15.3) and the controls (60.4 ± 7.9) were similar ($p > 0.05$). A statistically significant difference ($p = 0.027$) was observed between the MPV values of the stroke patients (8.6 ± 1.95 fl) and the MPV values of the control group (7.93 ± 0.82 fl). The comparison of the MPV values, platelet count, CRP levels, ESR and leukocyte counts is presented in Table I. The MPV (9.24 ± 1.98 fL) and CRP (10.8 ± 7.0 mg/l) values of the ischemic stroke patients who died were statistically significantly higher ($p < 0.05$) than the MPV (8.09 ± 1.75 fl) and CRP (3.2 ± 3.5 mg/l) values of those who survived. There was a positive correlation between the MPV and CRP values of the ischemic stroke patients ($r = 0.31$, $p = 0.029$). No statistically significant difference ($p > 0.05$) was detected between the MPV values of the subgroups of ischemic stroke patients evaluated according to the TOAST classification. The platelet counts of the ischemic stroke patients who died ($246.3 \pm 73.6 \times 10^3/\text{mL}$) were statistically significantly lower ($p = 0.026$) than the platelet counts of those who survived ($342.8 \pm 162.3 \times 10^3/\text{mL}$). There was no statistically significant difference ($p > 0.05$) between the leukocyte and ESR values of those ischemic stroke patients who died and those who survived.

Discussion

The mean platelet volume is related to platelet activation and it has been suggested as a marker of haemostasis¹. Larger platelets are more densely granulated and they are metabolically more active than smaller ones. Increases in MPV levels lead to increased secretions of the prothrombotic agents thromboxane A₂, serotonin, β -thromboglobulin, the procoagulant surface protein P-selectin and glycoprotein-IIIa^{16,17}. It has already been demonstrated that larger platelets constitute a risk factor for myocardial infarction and death¹⁸. The relationship between MPV and the outcome of ischemic stroke is controversial in the literature. Guldiken et al⁸ compared the MPV levels and platelet counts of 102 acute ischemic stroke patients with a group of healthy controls and did not detect any statistically significant difference. Ntaios et al⁷ have also claimed that no relationship exists between the MPV values in the early phase of acute ischemic stroke, and the severity and prognosis of the stroke. In our study, we have found higher MPV values in the acute ischemic stroke patients in comparison to the control group. Besides, the MPV levels of the patients who died in the first 10 days were statistically significantly higher than the patients

Table I. The comparison of the MPV values, platelet and leukocyte count, CRP levels, ESR counts of ischemic stroke patients who died and survived.

	Ischemic stroke patients		<i>p</i>
	Died	Survived	
MPV (fL)	9.24 ± 1.98	8.09 ± 1.75	0.023
Platelet count (× 10 ³ /mL)	246.3 ± 73.6	342.8 ± 162.3	0.026
CRP(mg/l)	10.8 ± 7.0	3.2 ± 3.5	0.001
Leukocyte count (× 10 ³ /mL)	12.8 ± 6.28	11.9 ± 3.9	NS
ESR (mm)	35.8 ± 24.1	24.1 ± 22.9	NS

Abbreviation: MPV: Mean Platelet Volume; CRP: C - reactive protein; ESR: Erythrocyte Sedimentation Rate; NS: Not Significant.

who survived. However, we did not observe any significant difference in the MPV levels between the subgroups classified according to the TOAST criteria. The increases in the MPV levels were also found to correlate with the severity of the ischemic stroke in other investigations conducted in parallel to our^{5,6}. These variances between the studies may stem from the differences in the number of the patient groups and the different criteria used in the classification of the subgroups. The MPV levels and the platelet count are inversely correlated: as the MPV increases, the platelet count decreases and, thus, the total platelet volume stays more or less constant¹⁹. In our study, we have observed that the platelet count in the patients who died was statistically significantly lower than the patients who survived. In their report conducted on 384 acute ischemic stroke patients, Mayda et al⁶ suggested that higher MPV levels are a predictor of the prognosis independently from other risk factors; and that MPV, as a marker of increased platelet reactivity, becomes apparent before the ischemic stroke and contributes to the development of the disease. Since in our work the MPV values we obtained indicate the levels during the first 24 hours following the patients' admittance to the hospital and since the platelets have a lifespan of 8 to 10 days, these findings may point to a disorder in platelet function present before the occurrence of the stroke. Also, as the size of the platelets is determined during the progenitor cell phase and as they later enter the circulation with this size unchanged, increased MPV levels and prothrombotic conditions before the ischemic stroke may reflect a proinflammatory environment⁵. The increase detected in MPV in the ischemic stroke patients compared to the controls, and the higher MPV levels in the patients who died compared to those who survived in our study might indicate the role MPV plays in the pathogenesis and mortality in stroke.

Research is continuing on the role of the inflammatory elements accompanying the ischemia and the tissue damage caused by the inflammation in is-

chemic stroke. It is thought that the CRP activates the classical complement pathway and, thus, increases tissue damage through the end products of the complement system²⁰. Following a stroke, the plasma CRP levels may increase rapidly and may stay stable up to 28 days²¹. Higher CRP levels have been demonstrated in stroke patients in several researches^{11,22}. Purfoy et al²³ suggested that the higher CRP levels observed in patients who experienced transient ischemic attacks may be used as markers in order to predict the more severe ischemic events that may occur in the future. Several Authors^{24,25} have even suggested that CRP plays a direct role in the pathogenesis of atherosclerosis. Folsam et al²⁶ claimed after a study they conducted on a large group of patients that higher levels of CRP are a strong predictor of thrombotic events rather than the severity of atherosclerosis. There is also a report¹⁴ stating that administering CRP to a person increases coagulation and fibrinolysis in the blood. It has been claimed²⁷ that the CRP may cause thrombus formation by triggering platelet adhesion to the surface of the endothelial cells over the P-selectin stored in platelets. Also in our study, the CRP levels during the first 24 hours were statistically significantly higher in the patients who died compared to those who survived. However, we have not detected any significant difference between the leukocyte and ESR values.

Conclusions

These results support the view that the increase in CRP does not depend on an infectious origin and that CRP is a strong predictor of thrombotic events. A research conducted measuring the monocyte-platelet aggregates, which are a marker of platelet activation, demonstrated the relationship between CRP and platelet activation. Thus, the connection between thrombosis and inflammation has been suggested to be mediated through the high CRP levels¹⁵. The connection we observed between the

MPV and CRP levels in the stroke patients supports the view that CRP increases platelet activation.

The fact that in our paper both the CRP and the MPV levels were found higher in the patients who died, compared to the patients who survived points out that these predictors may light the way in the follow-up and prognosis of stroke patients. Also, the correlation observed between MPV and CRP may indicate that the increase in CRP and MPV levels plays a role in the mortality of stroke patients. However, since our study was conducted on a limited number of patients, there is a need for further investigations on larger groups of patients in order to support these results.

Conflict of Interest

None to declared.

References

- BATH PM, BUTTERWORTH RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis* 1996; 7: 157-161.
- ENDLER G, KLIMESCH A, SUNDER-PLOSSMANN H, SCHILLINGER M, EXNER M, MANNHALTER C, JORDANOVA N, CHRIST G, THALHAMMER R, HUBER K, SUNDER-PLOSSMANN R. Mean platelet volume is an independent risk factor for myocardial infarction but for coronary artery disease. *Br J Haematol* 2002; 117: 399-404.
- KURABAYASHI H, TAMURA J, NARUSE T, KUBOTA K. Possible existence of platelet activation before onset of cerebral infarction. *Atherosclerosis* 2000; 153: 203-207.
- TSCHOEPE D, ROESEN P, ESSER J, SCHWIPPERT B, NIEUWENHUIS HK, KEHREL B, GRIES FA. Large platelets circulate in an activated state in diabetes mellitus. *Semin Thromb Hemost* 1991; 17: 433-438.
- GREISENEGGER S, ENDLER G, HSIEH K, TENTSCHERT S, MANNHALTER C, LALOUSCHEK W. Is elevated mean platelet volume associated with a worse outcome in patients with acute ischemic cerebrovascular events? *Stroke* 2004; 35: 1688-1691.
- MAYDA-DOMAÇ F, MISIRLI H, AND YILMAZ M. Prognostic role of mean platelet volume and platelet count in ischemic and hemorrhagic stroke. *J Stroke Cerebrovasc Dis* 2010; 19: 66-72.
- NTAIOS G, GURER O, FAOUZI M, AUBERT C, MICHEL P. Mean platelet volume in the early phase of acute ischemic stroke is not associated with severity or functional outcome. *Cerebrovasc Dis* 2010; 29: 484-489.
- GÜLDIKEN B, ÖZKAN H, KABAYEL L. Mean platelet volume and peripheral blood count response in acute ischemic stroke. *Balkan Med J* 2008; 25: 130-135.
- DIRNAGL U, IADECOLA C, MOSKOWITZ MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci* 1999; 22: 391-397.
- SHANTIKUMAR S, GRANT PJ, CATTO AJ, BAMFORD JM, CARTER AM. Elevated C-reactive protein and long-term mortality after ischaemic stroke: relationship with markers of endothelial cell and platelet activation. *Stroke* 2009; 40: 977-979.
- CORSO G, BOTTACCHI E, BRUSA A, DI BENEDETTO M, GIARDINI G, LIA C, REGGIANI M, VERONESE MOROSINI M. Is there a prognostic role for C-reactive protein in ischemic stroke? *Acta Neurol Scand* 2010; 122: 209-216.
- CANOVA CR, COURTIN C, REINHART WH. C-reactive protein in cerebrovascular events. *Atherosclerosis* 1999; 147: 49-53.
- LIBBY P, SIMON DI. Inflammation and thrombosis: the clot thickens. *Circulation* 2001; 103: 1718-1720.
- BISOENDIAL RJ, KASTELEIN JJ, LEVELS JH, ZWAGINGA JJ, VAN DEN BOGAARD, B REITSMA, PH MEIJERS, JC, HARTMAN D, LEVI M, STROES, ES. Activation of inflammation and coagulation after infusion of C-reactive protein in humans. *Circulation Res* 2005; 96: 714-716.
- DANENBERG HD, KANTAK N, GRAD E, SWAMINATHAN RV, LOTAN C, EDELMAN ER. C-reactive protein promotes monocyte-platelet aggregation: an additional link to the inflammatory-thrombotic intricacy. *Eur J Haematol* 2007; 78: 246-252.
- MARTIN JF, SHAW T, HEGGIE J, PENINGTON DG. Measurement of the density of platelets and its relationship to volume. *Br J Haematol* 1983; 54: 337-352.
- KRISTENSEN SD. The platelets vessel wall interaction in experimental atherosclerosis and ischemic heart disease with special reference to thrombopoiesis. *Dan Med Bull* 1992; 39: 110-127.
- MARTIN JF, BATH PM, BURR ML. Mean platelet volume and myocardial infarction. *Lancet* 1992; 339: 1409-1411.
- BILJAK VR, PANCIROV D, CEPELAK I, POPOVIC-GRLE S, STJEPANOVIC G, GRUBISIC TZ. Platelet count, mean platelet volume and smoking status in stable chronic obstructive pulmonary disease. *Platelets* 2011; 22: 466-470.
- BARTOSIK-PSUJEK H, BELNIAK E, STELMAIAK Z. Markers of inflammation in cerebral ischemia. *Neurol Sci* 2003; 24: 279-280.
- ELKIND MS, COATES K, TAI W, PAIK MC, BODEN-ALBALA B, SACCO RL. Levels of acute phase proteins remain stable after ischemic stroke. *BMC Neurol* 2006; 16: 37.
- DI NAPOLI M, PAPA F, BOCOLA V. Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke. *Stroke* 2001; 32: 133-138.
- PURROY F, MONTANER J, MOLINA CA DELGADO P, ARENILLAS JF, CHACON P, QUINTANA M, ALVAREZ-SABIN J. C-reactive protein predicts further ischemic events in transient ischemic attack patients. *Acta Neurol Scand* 2007; 115: 60-66.
- VAN DER MEER IM, DE MAAT MP, HAK AE, KILIAAN AJ, DEL SOL AI, VAN DER KUIP DA, NUHUIS RL, HOFMAN A, WITTEMAN JC. C-reactive protein predicts progression of atherosclerosis measure at various sites in the arterial tree: the Rotterdam Study. *Stroke* 2002; 33: 2750-2755.
- WANG TJ, NAM BH, WILSON PW, WOLF PA, LEVY D, POLAK JF, D'AGOSTINO RB, O'DONNELL CJ. Association of C-reactive protein with carotid atherosclerosis in men and women: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2002; 22: 1662-1667.
- FOLSOM AR, PANKOW JS, TRACY RP, ARNETT DK, PEACOCK JM, HONG Y, DJOUSSÉ L, ECKFELDT JH. Association of C-reactive protein with markers of prevalent atherosclerotic disease. *Am J Cardiol* 2001; 88: 112-117.
- GRAD E, PACHINO RM, DANENBERG HD. Endothelial C-reactive protein increases platelet adhesion under flow conditions. *Am J Physiol Heart Circ Physiol* 2011; 301: 730-736.