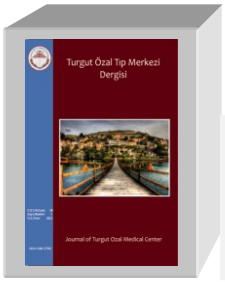

ORİJİNAL MAKALE/ORIGINAL ARTICLE
J Turgut Ozal Med Cent 2013;20(4):295-9.

Journal Of Turgut Ozal Medical Center
www.jtomc.org

Mean Platelet Volume in Remitter Patients with Inflammatory Bowel Disease

Erhan Alkan[1], Mustafa Serkan Karakaş[2], Bülent Yıldırım[1]

[1]Akdeniz University School of Medicine, Department of Gastroenteroloji, Antalya, Turkey
[2]Niğde State Hospital, Department of Cardiology, Niğde, Turkey

Abstract

Aim: Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases of the gastrointestinal tract. An increase in thromboembolic complications has been observed among patients with IBD. Platelet activation and aggregation play an important role in the pathophysiology of atherothrombosis. Mean platelet volume (MPV), a determinant of platelet activation, is one of the newly identified risk factors for atherothrombosis. In this study, we investigated the possible relationship between IBD and MPV.

Material and Methods: The study enrolled 17 CD and 23 UC patients who were in remission for at least 6 months and a control group of 40 healthy subjects. Patients with established atherosclerosis, diabetes, hypertension, hyperlipidemia, renal failure, smokers, patients aged over 45, patients diagnosed within less than 6 months and non-remitters were excluded from the study. MPV values were obtained.

Results: Comparison of IBD and control groups with respect to demographic data did not yield statistically significant differences. However,statistically significant higher MPV values were observed for IBD patients versus control group (8.17±0.71 vs.7.76±0.48 fl; p=0.004). Comparison of UC and CD individually did not show any differences in MPV values (8.26±0.82 vs.8.05±0.52 fl; p=0.3).

Conclusions: Our results show increased platelet activation in IBD and an increased risk for atherothrombosis in IBD patients.

Key Words: Atherothrombotic Risk; Mean Platelet Volume; Inflammatory Bowel Disease; Platelet Activation.

İnflamatuvar Barsak Hastalığı Olan Remisyondaki Hastalarda Ortalama Trombosit Hacminin Değerlendirilmesi

Özet

Amaç: Ülseratif kolit ve Chron hastalığını içeren inflamatuvar barsak hastalıkları gastrointestinal sistemin kronik inflamatuvar bir hastalığıdır. İnflamatuvar barsak hastalıkları olan hastalarda tromboembolik komplikasyonlarda önemli oranda artışlar saptanmıştır. Trombosit aktivasyon ve agregasyonu, aterotromboz patofizyolojisinde önemli bir rol oynamaktadır. Trombosit aktivasyonunun bir diğer göstergesi olan ortalama trombosit hacmi, aterotromboz için yeni keşfedilmiş ve giderek yaygın kullanılan bir laboratuar parametresidir. Bu çalışmada inflamatuvar barsak hastalıkları ile ortalama trombosit hacmi arasındaki ilişkiyi araştırdık.

Gereç ve Yöntemler: Çalışmaya en az 6 aydır remisyonda olan 17 Chron hastası ve 23 ülseratif kolit hastası ile 40 sağlıklı birey alındı. Bilinen aterosklerozu, diabeti, hipertansiyonu, hiperlipidemisi, böbrek yetmezliği olanlar, sigara içenler, 45 yaşın üzerindeki hastalar ile 6 aydan daha önce tanı almış hastalar ile remisyonda olmayanlar çalışmadan çıkarıldı. Hastalar ve kontrol grubunda ortalama trombosit hacmi değerleri karşılaştırıldı.

Bulgular: İBH ve kontrol grubunun demografik değerlerinde farklılık saptanmadı. İBH olanlarda kontrol grubuna kıyasla ortalama trombosit hacmi değerlerinin daha yüksek olduğu görüldü (8.17±0.71 vs.7.76±0.48 fl; p=0.004). ülseratif kolit ve chron hastaları ı ortalama trombosit hacmi değerleri açısından karşılaştırıldığında fark saptanmadı (8.26±0.82 vs.8.05±0.52 fl; p=0.3).

Sonuç: Çalışmamızın sonuçları inflamatuvar barsak hastalıklarında trombosit aktivasyonunda artış olduğunu ve İBH'da aterotromboz riskinde artış olduğunu göstermektedir.

Anahtar Kelimeler: Aterotrombotik Risk; Ortalama Trombosit Hacmi; Inflamatuvar Bağırsak Hastalığı; Trombosit Aktivasyonu.

INTRODUCTION

Inflammatory bowel diseases (IBD) including ulcerative colitis and Crohn's disease are chronic inflammatory diseases of the gastrointestinal tract. IBD is a group of inflammatory conditions which occurs in genetically susceptible individuals as a result of an exaggerated immune response to several antigens or environmental factors, with no clearly defined cause. It has a chronic course with remission and activation phases. Etiology and pathopyhsiology of IBD are not fully elucidated (1,2). An increased incidence of thromboembolic complications was observed among IBD patients. Studies reported that the incidence of arterial and venous thromboembolism ranged between 1 to 8% in IBH. However, an increased rate, up to 39%, was reported in post-mortem series (3). It was demonstrated that all elements of coagulation system were affected in IBD, with development of a hypercoagulable state (4-6). Exact etiology and pathogenesis of the hypercoagulable state seen in IBD are unknown; nevertheless, procoagulant effect of proinflammatory cytokines and acquired or genetic disorders of coagulation systems were implicated (3).

Increased platelet activation was shown to play an important role in development of cardiovascular

complications (7). Platelet volume increases as platelet activation is increased. Large platelets have greater thrombotic potential compared to small platelets and they contain more dense granules, metabolically and enzymatically more active than small platelets (8-10). Mean platelet volume (MPV) is an indicator of platelet activation and has an important role in the pathophysiology of cardiovascular complications (7,11). Increased MPV values have been shown in hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction and atherosclerotic heart diseases (12).

Increased platelet number and abnormal platelet function were reported to be a predisposing factor for systemic thromboembolisms in IBD and an important parameter for detection of hypercoagulable state. Also, it was stated that platelets are directly associated with inflammatory response and could be used as a marker for demonstrating disease activity (13). Atherosclerotic heart diseases including myocardial infarction, unstable angina pectoris have been reported to occur during IBD (14). Consistent with this, mean platelet volume (MPV) values were shown in studies to increase in myocardial infarction and atherosclerotic heart diseases (15). Contradicting results were obtained from studies that assessed the association between IBD and MPV, with some studies reporting decreased MPV values in IBD while others reported no change (13,16,17).

The purpose of our study was to evaluate the association between inflammatory bowel disease and MPV and to investigate whether there were any differences between MPV values measured in Crohn's disease (CD) and ulcerative colitis (UC) in non-smoking patients without any conditions which would increase MPV values such as hypertension, hyperlipidemia or diabetes mellitus who were in the inactive phase of the disease.

MATERIAL AND METHODS

The study enrolled 23 ulcerative colitis patients and 17 patients with Crohn's disease who were in remission for at least 6 months and being followed in Department of Internal Medicine, Division of Gastroenterology outpatient clinics between June 2009 and February 2010 due to the diagnosis of inflammatory bowel disease. UC patients were assessed by using Truelove-Witts activity index and CD patients with Crohn's Disease Activity Index. Those who were found to be remitters were enrolled. Forty healthy subjects were included as control group. The study was approved by the local ethics committee. Each patient was informed about the study and all patients read and signed informed consent.

Cardiovascular system examinations were performed for enrolled patients after 10-minute rest. Blood pressures were obtained from both arms while sitting using a mercury sphygomanometer with an appropriate cuff, based on Korotkoff phase I and phase V sounds. Body weight, height, waist and hip circumference measurements were performed for patients. Body mass index (BMI) was calculated by dividing the body weight (in kg) by height in meters squared, using Quetlet index.

Biochemical analysis and blood counts were conducted on venous blood samples obtained from patients in all groups between 08:00 am and 13:00 pm after 8 hours of fasting.

Patient with known coronary artery disease or peripheral artery disease (with atherosclerosis detected by coronary-peripheral angiography and Doppler ultrasonography), patients with known diabetes or who were diagnosed as diabetic during study (patients receiving antidiabetic therapy with a diagnosis of diabetes and fasting blood glucose level 126 mg/dl or above), hypertensive patients (those who were previosly diagnosed, receiving antihiypertensive drugs or those who are not on antihipertensive therapy, with blood measure recordings over 140/90 mmHg during previous examinations and follow-up charts), hyperlipidemic patients (those diagnosed as hyperlipidemic, receiving antihyperlipidemic therapy with fasting plasma levels of LDL above 130 mg/dl and Triglycerides above 200 mg/dl), smoking patients, patients with valvular heart disease, congenital heart disease, left ventricular systolic dysfunction (EF<50%), acute heart failure and cases of acute coronary syndromes, patients with cerebrovascular diseases, arrhythmias, hepatic or renal failure, malignancies, concomitant endocrinologic disorders (hypothyroidism, hyperthyroidism, Cushing syndrome, pheochromocytoma, acromegaly), patients with a disease duration of less than 6 months, patients aged over 45 and non-remitters were excluded. Additionally, patients with angina or similar symptoms detected during pre-study examinations or patients with findings suggestive of ischemia as observed during echocardiography, electrocardiography (resting/exercise) and nuclear medicine studies were also excluded.

Study data were analyzed using SPSS 18.0 software package. Continuous variables were expressed as mean±standard deviation, whereas frequency data were expressed as percentage. Based on distribution features of variables, continuous variables showing normal or non-normal distribution were analyzed using unpaired t test and Mann-Whitney U test respectively, for comparison of two independent groups. Normality analysis was done using Kolmogorov Simirnov test. Pearson's Correlation analysis was used for determining linear association between two variables. All tests were structured as two-sided and critical alpha level was considered as 0.05.

RESULTS

A total of 40 patients including 22 males (55%) and 18 females (45%) diagnosed with IBD (age range, 22–45 years). Control group consisted of 40 healthy subjects including 22 males (55%) and 18 females (45%) with an age range between 23 and 45 years. IBD patients included 23 UC patients and 17 patients with Crohn's disease. Among UC patients, 1 had ulcerative proctitis, 10 had UC with distal involvement, 7 left-sided UC and 5 had UC with pancolitis.

Mean age of IBD patients was 38.4±6.5 years. Mean age of control group was 38.2±6.4 years. Mean duration of

disease was 52.2±48.7 months. A review for comparison of IBD and control groups with respect to age, gender, body mass index, systolic and diastolic blood pressure, serum creatinine, ALT, total cholesterol, LDL, HDL, triglycerides and sedimentation rate showed similar results and statistical analysis did not yield any significant differences. White blood cells, platelet counts and CRP levels were higher in IBD group compared to control group and a significant difference was found in statistical analysis. However, hemoglobin values were lower in IBD group compared to control group and the difference was statistically significant (Table 1). Comparison of MPV values showed statistically significantly higher MPV values in IBD groups versus control group (8.17±0.71 vs.7.76±0.48 fl; p=0.004) (Figure 1). No difference was observed in MPV values when UC and CD were compared individually (8.26±0.82 vs.8.05±0.52 fl; p=0.3) (Figure 2). Correlation analysis did not yield any correlations between MPV and sedimentation rate, CRP and white blood cells.

Table 1. Baseline characteristcs in patients and control group.

	IBD (mean±sd) (n= 40)	Control group (mean±sd) (n=40)	p Value
Age (years)	38.4±6.5	38.25±6.4	0.97
Creatinine (mg/dl)	0.78±0.12	0.79±0.14	0.76
ALT (U/l)	17.5±7.8	19.8±7.6	0.07
Total cholesterol (mg/dl)	178.2±20.6	170.1±21.8	0.10
LDL (mg/dl)	107.5±21.4	99.0±20.3	0.06
HDL (mg/dl)	52.2±12.0	49.5±10.6	0.41
Triglyceride (mg/dl)	109.4±48.5	117.2±50.0	0.53
Systolic blood pressure (mmHg)	117.6±10.0	116.9±10.0	0.80
Diastolic blood pressure (mmHg)	74.0±7.6	71.2±7.2	0.16
Hemoglobin (g/dl)	12.7±1.2	13.9±1.3	0.001
Leukocyte ($x10^9$/L)	7742±1803	6635±1640	0.01
Platelet count ($x10^9$/L)	287.9±91.3	237.0±48.4	0.003
MPV (fl)	8.17±0.71	7.76±0.48	0.004
Sedimentation (mm/h)	21.4±12.4	16.1±3.0	0.18
CRP (mg/L)	0.44±0.37	0.23±0.07	0.002
Fasting blood glucose (mg/dl)	88.3±8.1	84.8±8.4	0.62
BMI (kg / m2)	23.74±1.94	23.75±1.56	0.76

Abbreviations: IBD:Inflammatory bowel disease, mean ± sd: mean ± standart deviation, ALT: alanine transaminase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, MPV:Mean platelet volume, CRP:C-reactive protein, BMI: Body mass index

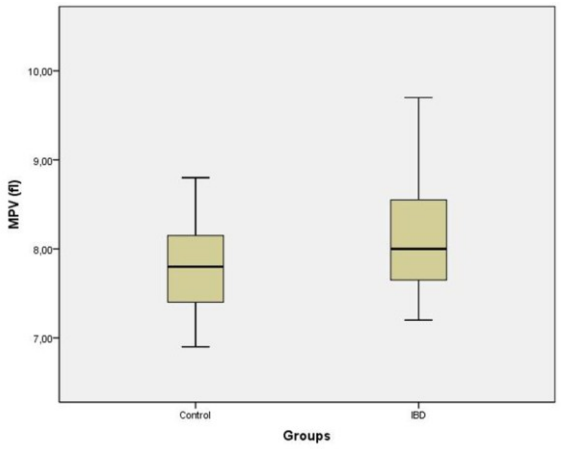

Figure 1. Comparision of inflammatory bowel disease patients and control values for mean platelet volume (MPV)

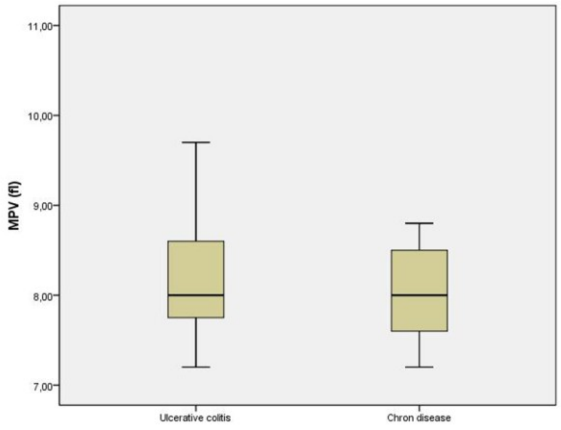

Figure 2. Comparision of ulcerative colitis and chron patients values for mean platelet volume (MPV)

DISCUSSION

IBD is a systemic disorder with extraintestinal symptoms and complications. The incidence of extraintestinal symptoms varies between 6 to 47%. While cardiac diseases less commonly occur in IBD, early atherosclerosis and thromboembolic events increase cardiovascular mortality among these patients (16).

MPV is a cardiovascular risk marker which has recently drawn much attention. MPV was shown to increase in conditions such as hypertension, hyperlipidemia, diabetes mellitus, obesity, metabolic syndrome, acute myocardial infarction and acute ischemic stroke (12). A limited number of studies are available which assessed the relationship between IBD and MPV, giving contradicting results. In a study conducted by Yuksel et al. in UC patients, lower MPV values were found for these patients compared to control group. In that study, MPV values were lower among patients with active UC compared to those found in patients with inactive UC. However, no comparison was made between patients

with inactive UC and control group. In the same study, CRP level was higher in UC patients compared to control group, while no difference was found in sedimentation rate and white blood cell counts (17). In a study by Kapsoritakis et al., MPV values were lower in patients with active IBD versus control group but no difference was found in MPV values between patients with inactive IBD and control group (18). In Dogan et al.'s study, no difference was found in MPV values between IBD and control groups; similarly, there was no difference in MPV values when UC and CD were compared individually. However, no information was given in that study regarding whether the patients were in active or inactive phase of the disease (16). On the other hand, MPV values were lower among patients with active UC versus control group and inactive UC patients but there was no difference between inactive UC patients and control group with respect to MPV values (13). In all of these studies investigating the relationship between IBD and MPV, MPV values were found to be significantly higher in IBDs in active phase and comparison with control group showed lower MPV values versus control group but the difference was not statistically significant. Among those studies, Dogan et al.'s study lacked information regarding whether the patients were in active or inactive phase of the disease and in other studies, there was no information about how long the disease had been inactive. Additionally, while some factors affecting MPV values were excluded in these studies, factors like hyperlipidemia, diabetes or hypertension were not excluded. In our study, statistically significantly higher MPV values were found among IBD patients compared to control group. Possible explanations for the higher MPV values versus control group found in our study as opposed to other studies include the enrollment of patients who had inactive disease for a minimum of 6 months and the exclusion of all clinical conditions other than IBD such as hypertension, diabetes, hyperlipidemia or smoking that could affect MPV values. In studies, it was reported that a hypercoagulable state developed in IBD with an increase in thromboembolic events (19). Apart from active phase of IBD, increased MPV values are observed in all diseases where thromboembolic events frequently occur (20-22). While thromboembolic events were commonly observed in IBD in studies investigating MPV values during IBD, it was reported that MPV values did not increase and even decreased in the active phase of IBD. Also, it was stated that the exact cause of reduced MPV values is not exactly known and that the most plausible explanation for this would be consumption or sequestration of large active platelets inside the blood vessels of intestinal system or a defect that occurs during regulation of thrombopoesis in IBD (13,17,23). The findings of studies including higher MPV values in the inactive phase of IBD compared to MPV values in the active phase and a statistical difference versus control group suggest that MPV values could increase with increased duration of inactive phase of the disease. Enrollment of patients with inactive IBD for at least 6 months in the present study and higher MPV values obtained in those patients versus control group supports our argument.

In this study, we found significantly higher MPV values in IBD patients compared to control group. Our results show an increase in platelet activation during inactive phase of IBD in the absence of risk factors for cardiovascular disease. Increased platelet activity may contribute to an increased risk for atherothrombotic events during inactive phase of IBD. While we believe that the remarkable findings obtained from this assessment might have repercussions for clinical outcomes, our results need to be clinically confirmed by prospective cohort studies.

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Received/Başvuru: 13.05.2013, Accepted/Kabul: 19.06.2013

Correspondence/İletişim

Mustafa Serkan KARAKAŞ
Niğde State Hospital, Department of Cardiology, NİĞDE, TURKEY
E-mail: mserkan19@hotmail.com

For citing/Atıf için

Alkan E, Karakas MS, Yildirim B. Mean platelet volume in remitter patients with inflammatory bowel disease. J Turgut Ozal Med Cent 2013;20:295-9. DOI: 10.7247/jtomc.2013.830