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Increased Mean Platelet Volume in Deep Vein Thrombosis Patients With Cancer

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Abstract

Background: Patients who have malignancy have an increased risk of thromboembolism. Thromboembolic events occur in 4-20% of cancer patients. Mean platelet volume (MPV) is a machine-calculated measurement of platelet size from the blood that is usually reported in the blood tests as part of the CBC. In this study, we aimed to determine whether there is any relationship between MPV and DVT in cancer patients.

Methods: Outpatient oncology clinic records were searched between the period of 2006 and 2012 and 77 cancer patients with acute DVT were enrolled into the study.

Results: There were no statistically significant differences between the groups with regard to the age, gender, and laboratory parameters except MPV. MPV values were significantly higher in patients with DVT (8.6 ± 1.3 vs 7.7 ± 0.7, $P < 0.001$). The most common cancer types were colorectal, gynecologic and breast cancer in DVT patients. In the DVT group 46% of cancer was adenocarcinoma.

Conclusion: We have shown that MPV was significantly elevated in cancer patients with DVT compared to the cancer patients without DVT. Chemotherapy is one of the major risk factor for DVT in cancer patients. Chemotherapy regimens may increase MPV and so might trigger thromboembolism in cancer patients. Being metastatic or nonmetastatic is not a risk factor for increased MPV.

Keywords: Mean platelet volume; Deep vein thrombosis; Cancer

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Introduction

Patients who have malignancy have an increased risk of thromboembolism. Furthermore, thromboembolism can be the first manifestation of cancer and is associated with a high rate of morbidity and mortality. Thromboembolic events occur in 4-20% of cancer patients and 50% of cancer patients had thrombosis in autopsy series. It is the second cause of mortality in cancer patients after the infections [1-6]. Nearly 50% of the events have no obvious predisposing factors while surgery, hospitalization, immobilization, malignancy, trauma, pregnancy, medications, and inherited thrombophilia are the associated factors in the rest [7, 8].

Platelets in circulation differ greatly in size and hemostatic potential. Mean platelet volume (MPV) is a machine-calculated measurement of platelet size from the blood that is usually reported in the blood tests as part of the CBC. In addition, it has been shown that MPV is the most accurate measure of the size of platelets in stable conditions and inversely associated with platelet count. In comparison to smaller platelets, greater platelets contain more granules and produce greater amounts of prothrombotic factors, such as thromboxane A2 and serotonin, and they are aggregate rapidly under a stimulus and express a greater number of adhesion molecules, such as P-selectin and glycoprotein IIb/IIIa [9-15]. Increased MPV is associated with platelet reactivity and shortened bleeding time [7]. All of these findings guide us larger platelets have a greater risk for thrombosis and are more active than smaller platelets that are more frequently observed in stable conditions [16].

Venous thromboembolism (VTE) incidence rates in cancer patients differ remarkably, depending on tumor site, stage and treatment. Some of the studies focused on possible risk factors like co-morbidities, immobilization or treatment associated factors such as surgery, chemotherapy (CHT), hormone therapy and venous catheters. Having the large number of studies about the clinical risk factors, only limited data have been published for laboratory parameters with a predictive value for the risk of VTE in cancer patients [1, 17-20]. When we reviewed the lliterature, we could not find any single study about the relationship between MPV and Deep-

Table 1. Comparison of the General Characteristics of Patients With DTV and Controls

	DVT (n = 77) SD/IR	Control (n = 45) SD/IR	P Value
Age, years	60.7 ± 10.9	62.5 ± 12.0	0.3
BMI	23.3 ± 3	23.9 ± 3	0.3
Gender (Male/Female)	31/46	19/26	0.9
Smoking, %	30 (42%)	18 (40%)	0.8
WBC × 10^9 per L	9.7 ± (3-35)	7.9 ± 3.3	0.16
Hemoglobin, g/dL	11.7 ± 1.8	11.3 ± 2.4	0.4
Platelet count, × 10^9 per L	289 ± 110	273 ± 56	0.5
Glucose, mg/dL	85 ± 10	89 ± 15	0.6
Hypertension	15 (19%)	8 (17%)	0.8
Hyperlipidemia	8 (10%)	4 (9%)	0.8
MPV, fL	8.6 ± 1.3	7.7 ± 0.7	0.0002

BMI: Body mass index; WBC:White blood cell; MPV: Mean platelet volume.

Vein Thrombosis (DVT) in cancer patients. So we decided to conduct this study to determine whether there is any relationship between MPV and DVT in cancer patients.

Patients and Methods

This is a retrospective study and ethical approval was obtained from the local ethical committee of Karaelmas University, Zonguldak, Turkey. Outpatient oncology clinic medical records were searched between the period of 2006 and 2012 and patients with diagnosis of acute DVT were enrolled into the study. The study group consisted of 77 cancer patients with acute DVT (31 male and 46 female, mean age 60.7 ± 10.9 years), and the control group consisted of age and gender matched 45 cancer patients without DVT (19 males and 26 females, mean age 62.5 ± 12.0 years). All patients and controls had clinical examination, biochemical measurements, and ultrasonographic examination for DVT. Exclusion criterias were; using an anticoagulant agent for DVT prophylaxis, history of a recent surgery or hospitalization for palliative care, use of any medication for hyperlipidemia, and the presence of hypertension, diabetes mellitus, cerebrovascular event or coronary heart disease. In the control group DVT was excluded by physical examination and radiological investigations.

Biochemical measurements

Blood samples were taken from the antecubital vein with a 21 guage sterile needle at 8.00 - 10.00 am after an overnight fast. All samples were taken on the first day of diagnosis of DVT. MPV was measured in blood samples collected in dipotassium EDTA tube within 90 minutes following puncture.

Statistical analysis

All statistical analyses were conducted by using the SPSS 18.0 statistical software program (SPSS, Chicago, IL). Continuous variables were presented as mean ± standart deviation and categoric variables as percentages. Data with normal distribution were analyzed using unpaired t test. Mann-Whitney U test was used for analyzing nonnormally distributed data. Categorical variables were compared with the chi-square test. A cut off value of MPV was calculated with roc curve analysis. Correlations were studied using Pearson's correlation test. P values under the 0.05 were considered as statistically significant.

Results

Clinical and laboratory findings of the patients with DVT

Table 2. Etiology of the Study Groups

	DVT (n:77)	Control (n:45)	P
Colorectal cancer	14	11	0.408[1]
Gynecologic malignancy	11	8	0.608[1]
Breast	11	8	0.608[1]
Gastric	7	5	0.758[2]
Lung	7	6	0.547[2]
Pancreatic cancer	7	3	0.744[2]
Brain tumors	4	0	0.295[2]
Skin	4	2	1.000[2]
Occult primary	4	0	0.295[2]
Hepatobiliary tract	3	1	1.000[2]
Bladder	3	1	1.000[2]
Kidney	1	0	1.000[2]
Lymphoma	1	0	1.000[2]

[1] Pearson ki-kare testi (Pearson Chi-Square); [2]Fisher Kesin-Ki-kare testi (Fisher Exact Test).

and controls were presented in Table 1. There were no statistically significant differences between the groups with regard to age, gender, and laboratory parameters except MPV. MPV values were significantly higher in patients with DVT (8.6 ± 1.3 vs 7.7 ± 0.7, P < 0.001). White Blood Cell (WBC) counts were higher in the DVT group, but this was not statistically significant. Etiology of the groups was presented in Table 2. Most common cancer types were colorectal, gynecologic and breast cancer in DVT patients. In the DVT group 46% of cancer were adenocarcinomas, all of the breast cancers were invasive ductal carcinoma and 6 of 7 lung cancers were nonsmall cell carcinoma, 67 (87%) patients in the DVT group and 15 (33%) patients in the control group received cancer chemotherapy (P < 0.001). Twenty patients in the DVT group had received chemotherapy adjuvantly and 42 patients for metastasis. Most commonly used chemotherapeutic agents were gemcitabine, taxanes and platinums. There was no significant difference in MPV values between women and male patients (8.49 ± 1.3 vs 8.7 ± 1, P = 0.38, respectively). There was no significant difference with regard to MPV between metastatic and nonmetastatic patients with DVT (8.7 vs 8.45, P = 0.450). Correlation analysis indicated that MPV was significantly correlated with platelet counts and with the time interval from the diagnosis of cancer to the diagnosis of DVT (time of diagnosis DVT minus diagnosis C). Roc curve analysis showed that MPV levels over the 8.6 had an increased DVT risk in cancer patients (Area under the ROC curve 0,704, Sensitivity 50%, Specificity 95.5, CI 95%, P < 0.001). Regression analysis showed that platelet counts and the time interval from the diagnosis of cancer to the diagnosis of DVT had negative correlation with MPV (R^2 0.18 r = 0.42, P = 0.037 and 0.002 respectively).

Discussion

In this study, we showed that cancer patients with DVT had increased MPV levels compared to cancer patients without DVT and increased MPV levels can be a risk factor for thromboembolism in cancer patients independent of metastatic or nonmetastatic state. The most common histopathological type was adenocarcinoma in the DVT group. Colorectal, gynecologic, breast, pancreatic and lung cancers were the most common etiologies for DVT in cancer patients. Nonsmall cell lung cancer type had a higher risk for DVT compared to small cell lung cancer.

Chemotherapy is an independent risk factor for thromboembolism in cancer patients. Treatment with gemcitabine, cisplatin or carboplatin has a higher risk of thromboembolism [6, 21]. Some of the studies have demonstrated that cisplatin activates platelets and endothelial cells, which together may result in a prothrombotic state [22]; however, gemcitabine's role in the thrombosis is not known yet [23]. Case series and observational studies have suggested that gemcitabine may

increase the risk of thromboembolism, particularly when combined with cisplatin [24-26]. In our study chemotherapy was more common in the DVT group compared to the control group ($P < 0.001$) and the most commonly prescribed agents were gemcitabine, platinums and taxanes. So treatment with chemotherapy could be the possible reason of DVT and the higher MPV levels in our cancer patients. To the best of our knowledge, there is no study examining directly MPV changes with different chemotherapy regimens. Khorana et al had an impressive study. They demonstrated that the risk of VTE in cancer patients initiating chemotherapy can be predicted by a model simple risk assessment, based on 5 clinical and laboratory parameters. Parameters were site of cancer, prechemotherapy platelet count 350×10^9/L or more, hemoglobin level less than 100 g/L or use of red cell growth factors, prechemotherapy leukocyte count more than 11×10^9/L, and Body Mass Index (BMI) 35 kg/m^2 or more. In high-risk patients (3 or more risk factors) they found 7% or more VTE in cancer patients whose on chemotherapy [27]. Like this study, our study showed that DVT patients also have higher PLT and WBC counts but there were no significant differences between the groups. Red cell growth factors using were significantly higher in DVT group in our study ($P = 0.03$) as Khorana and et al study. We propose that MPV may be added to these risk factors as a predictive factor for DVT in cancer patients. Mean platelet volume is calculated by dividing the plateletcrit (PCT) by the total number of platelets [28]. There are a lot of concerns about the technological limitations and variations in the measurement of the MPV. In our study, we used a centralized laboratory to prevent variability of measurements and also all measurements were done in 90 minutes following the venopuncture.

Large platelets have a higher thrombotic risk and express higher levels of platelet activation markers such as P-selectin [29, 30]. Chirinos et al showed that VTE patients have increased P-selectin levels and Kyrle et al found that levels were also higher in the recurrent VTE [31, 32]. Elevated levels of the cell adhesion molecule such as soluble P-selectin (sP-selectin) were associated with a 2.6-fold increased risk of future VTE [33]. This can be one of the reasons of elevated levels of MPV in cancer patients with DVT, but we were not able to test P selectin levels.

Braekkan et al demonstrated that MPV is a risk factor for thromboembolism in 445 patients [7]. Their study had 103 cancer patients, and they found a negative correlation with MPV and PLT as in our study. But they didn't report and compare MPV values in cancer and noncancer patients at the same time. Our study revealed that increased MPV values may be a risk factor for DVT in cancer patients and treatment with chemotherapy may increase MPV.

There are some limitations of this study such as it has limited patient numbers. Furthermore, this is a retrospective study, but we revealed our nearly 10 years experience.

Conclusion, we have shown that MPV was significantly elevated in cancer patients with DVT compared to the cancer patients without DVT. Chemotherapy is one of the major risk factors for DVT in cancer patients. Chemotherapy regimens may increase MPV and therefore, might trigger thromboembolism in cancer patients. Being metastatic or nonmetastatic is not a risk factor for increased MPV.

Declaration

The authors declare no conflict of interest. We did not receive any financial support fort his study.

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