Value of Platelet Indices in Identifying Complete Resolution of Thrombus in Deep Venous Thrombosis Patients

Utkan Sevuk · Rojhat Altindag ·
Mehmet Veysi Bahadir · Nurettin Ay ·
Ertan Demirtas · Firat Ayaz

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Abstract We aimed to evaluate whether mean platelet volume (MPV) and platelet distribution width (PDW) are helpful to identify complete thrombus resolution (CTR) after acute deep venous thrombosis (DVT). Patients who had first-time episode of acute proximal DVT were included in this retrospective study. 100 patients with DVT were divided into two groups according to absence (group 1; $n = 68$) or presence (group 2; $n = 32$) of CTR on doppler ultrasonography at month 6. There were no significant difference in admission MPV and PDW levels between group 1 and group 2. MPV ($p = 0.03$) and PDW ($p < 0.001$) levels at month 6 were significantly higher in group 1 than in group 2. CTR

showed a moderate negative correlation with PDW at month 6 ($\rho = -0.47$) and a weak negative correlation with MPV at month 6 ($\rho = -0.26$). Logistic regression analysis showed that PDW (OR, 2.2; $p = 0.004$) at month 6 was an independent risk factor for the presence of residual venous thrombosis in DVT patients. Receiver operating characteristics analysis revealed that a 8.4 % decrease in admission MPV at month 6 provided 62 % sensitivity and 62 % specificity (AUC: 0.64) and a 15.4 % decrease in admission PDW at month 6 provided 87 % sensitivity and 94 % specificity (AUC: 0.89) for prediction of CTR in DVT patients. Percent change in admission MPV and PDW levels at month 6 may be used to identify the patients with CTR after a first episode of acute proximal DVT.

U. Sevuk (✉) · F. Ayaz
Department of Cardiovascular Surgery, Diyarbakir Education
and Research Hospital, Diyarbakir, Turkey
e-mail: utkansevuk@gmail.com

F. Ayaz
e-mail: drfirat21@gmail.com

R. Altindag
Department of Cardiology, Diyarbakir Education and Research
Hospital, Diyarbakir, Turkey
e-mail: rojhataltindag@hotmail.com

M. V. Bahadir
Department of General Surgery, Dicle University,
Diyarbakir, Turkey
e-mail: mvbahadir@yahoo.com

N. Ay
Department of General Surgery, Diyarbakir Education and
Research Hospital, Diyarbakir, Turkey
e-mail: nurettinay77@hotmail.com

E. Demirtas
Department of Cardiovascular Surgery, Akay Hospital,
Ankara, Turkey
e-mail: edi2@mynet.com

Keywords Deep venous thrombosis · Complete thrombus resolution · Mean platelet volume · Platelet distribution width

Abbreviations

Rho	Spearman's correlation coefficient
WBC	White blood cell count
MPV6	MPV levels at 6 month follow-up
PDW6	PDW levels at 6 month follow-up
$\Delta\%$ MPV	Percent change for mean platelet volume values
$\Delta\%$ PDW	Percent change for platelet distribution width values

Introduction

Venous thromboembolism (VTE), which comprises deep venous thrombosis (DVT) and pulmonary embolism (PE), is an important cause of mortality and morbidity. Anticoagulant therapy remains the mainstay of medical therapy for

VTE. Patients who have residual venous thrombosis (RVT) after completion of oral anticoagulant therapy have been shown to have higher rates of recurrent VTE [1, 2]. RVT has been reported to be an independent risk factor for recurrent thromboembolic event and is generally considered a marker of hypercoagulability. Thus, RVT can be used for the risk stratification of patients with DVT and plays a vital role in determining the duration of anticoagulation [1, 3–5]. Therefore, it is of high clinical importance to distinguish patients with RVT from those who fully recovered.

Compression doppler ultrasonography (CUS) is regarded as the non-invasive gold-standard to detect complete thrombus resolution (CTR) in patients with DVT [6]. To date, no validated biomarkers have been established for diagnosis of CTR in patients with DVT.

Previous studies have shown platelet reactivity in patients with PE and DVT [7–12]. Mean platelet volume (MPV) is a measure of average platelet size [13, 14]. Platelet distribution width (PDW) measures the variability in platelet size and can be a sign of active platelet release. Platelet indices including MPV and PDW are markers of platelet activation [10, 15–17]. PDW is thought to be a more specific marker of platelet activation than MPV [18].

The purpose of this study was to examine whether MPV and PDW are helpful to identify CTR after a first episode of acute proximal DVT. As far as we know, this is the first study to examine the value of MPV and PDW in identifying CTR after an episode of DVT.

Patients and Methods

Study Population

Records of acute DVT patients who were admitted to Diyarbakir Education and Research Hospital between January 2008 and December 2012 were reviewed retrospectively. Patients who had first-time episode of acute proximal DVT were included in the study. Patients with conditions that have been considered to influence platelet indices were excluded from the study. Exclusion criteria were: (1) previous thromboembolism, (2) known malignancy, (3) immobilization, (4) inability to attend follow-up visits, (5) pregnancy, (6) ventricular systolic dysfunction, (7) trauma, (8) a new previous surgical operation, (9) atrial fibrillation, (10) obesity, (11) arterial stroke, (12) peripheral vascular disease, (13) infection, (14) acute coronary syndromes, (15) chronic renal or hepatic diseases, (16) diabetes mellitus, (17) acute and chronic PE and (18) recurrent episode of DVT. Control group consisted of

patients with uncomplicated primary varicose veins of the lower limbs.

Proximal DVT was defined as thrombosis of the popliteal, femoral, deep femoral, common femoral, iliac veins, and inferior vena cava. Initial diagnosis of DVT was based on direct visualization of the thrombus and lack of compressibility on gray scale and identification of either a persisting filling defect or thrombus in the color column of the vessel lumen or absence of flow on Doppler Ultrasonography (US). Patients underwent CUS after 6 months of oral anticoagulant therapy with warfarin sodium (target INR:2–3) prior to the withdrawal of anticoagulant therapy. RVT was defined as lack of complete recanalization on ultrasonographic examination at 6 month follow-up. Thrombus was said to be present in the vein by the partial or complete incompressibility of the vein or by visualization of thrombus within the vein. All testing was performed by radiologists with considerable experience in doppler ultrasonography who were blinded to the prothrombotic risk of the patients as well as the peripheral blood analysis.

Obesity was defined as a body mass index (BMI) of 30 or higher. Hypertension (HT) was defined as systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or use of an antihypertensive medication. Hyperlipidemia (HL) was defined as total serum cholesterol $\geq$ 200 mg/dl and/or low-density lipoprotein cholesterol (LDL) $\geq$ 130 mg/dl and/or history of current use of lipid-lowering regiment.

Blood Sampling

In all cases venous peripheral blood samples were drawn on admission before the treatment and after 6 months of oral anticoagulant therapy with warfarin sodium (target INR: 2–3) prior to the withdrawal of anticoagulant therapy. Blood samples were drawn from the antecubital vein by venipuncture using a 21 gauge needle and collected in Becton–Dickinson Vacutainer tubes containing 3.6 mg of K2EDTA (dipotassium ethylenediaminetetraacetic acid).

Normal range for MPV in our laboratory is 6.5–11.6 fl, normal range for PDW in our laboratory is 9–5 fl and normal range for PC in our laboratory is $150\text{--}400 \times 10^3/\text{microlitre}$. Glucose, creatinine and lipid profiles were determined by standard methods. An automatic blood counter (Sysmex XT 2000i Hematology Analyzer; Sysmex, Kobe, Japan) was used for whole blood counts. The medical records of our study population did not comprise any information about the processing time. However, our institutional policy dictates that collected bloods should be processed within 1 h after collection. The present study was approved by the local Ethics Committee and complies with the requirements of the Declaration of Helsinki.

Table 1 The baseline characteristics of the groups and laboratory findings for both groups at 6 month follow-up

	Group 1 ^a (<i>n</i> = 68)	Group 2 ^b (<i>n</i> = 32)	Control group (<i>n</i> = 50)	<i>p</i> value
Age (years), mean $\pm$ SD	38.18 $\pm$ 10.38	43.56 $\pm$ 10.9	39.76 $\pm$ 12.47	0.08
Sex (M), <i>n</i> (%)	35 (51.5)	14 (43.8)	27 (54)	0.65
BMI (kg/m ²), mean $\pm$ SD	25.42 $\pm$ 3.09	25.17 $\pm$ 1.81	25.31 $\pm$ 2.78	0.66
BMI body mass index, HT hypertension, HL hyperlipidemia, Glu glucose, Cre creatinine, WBC white blood cell count, Hb haemoglobin, PC platelet count				
HT, <i>n</i> (%)	34 (50)	19 (59.4)	25 (50)	0.51
Smoking, <i>n</i> (%)	18 (26.5)	12 (37.5)	19 (38)	0.002
HL <i>n</i> (%)	19 (27.9)	8 (25)	11 (22)	0.63
Glu, mg/dl, median (IQR)	97 (87.2–101.7)	91 (88–102.2)	94 (88.7–100.5)	0.89
Cre, mg/dl, mean $\pm$ SD	0.8 $\pm$ 0.19	0.9 $\pm$ 0.15	0.91 $\pm$ 0.11	0.67
^a Patients with residual venous thrombosis				
WBC (10 ⁹ /l), median (IQR)	9.2 (6.8–13)	8.7 (7–11.8)	7 (5.8–8)	<0.001
Hb (g/dl), median (IQR)	12.9 (12.1–13.5)	12.5 (11.9–13.5)	12.9 (12.1–13.5)	0.65
^b Patients with complete resolution of thrombus				
PC (10 ⁹ /l), mean $\pm$ SD	273.5 $\pm$ 47.1	319.6 $\pm$ 43.4	306.1 $\pm$ 47.9	<0.001

Statistical Analysis

Statistical analysis was performed using SPSS software version 17 for Windows. All variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov–Smirnov test) to determine whether or not they are normally distributed. Continuous variables were reported as means and standard deviation for normally distributed variables and as medians and interquartile range (IQR) for the non-normally distributed variables. Categorical variables were presented using numbers and percentages. The differences between groups were analyzed with the Kruskal–Wallis test for qualitative variables. Groups were compared by one-way analysis of variance (ANOVA) test for normally distributed continuous variables and by Kruskal–Wallis test for non-normally distributed continuous variables. When a significant difference between groups was observed using one-way ANOVA test, posthoc TUKEY HSD test was used to examine the differences. The percent change in admission MPV ($\Delta\%$ MPV) and PDW ($\Delta\%$ PDW) levels at 6 month follow-up were also calculated and compared between groups. Correlations were examined by Spearman's test. The logistic regression test was used to define independent predictors of residual venous thrombus in DVT patients. The capacity of percent changes in admission MPV and PDW levels in predicting complete DVT resolution were analyzed using receiver operating characteristics (ROC) curve analysis. Areas under the curve (AUC) were calculated as measures of accuracy of the tests. When a significant cut-off value was observed, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were presented. A *p* value <0.05 was considered significant.

Results

100 patients who had first-time episode of acute proximal DVT were included in the study (49 males, 51 females;

mean age 39.9 ± 10.8). Patients were divided into two groups according to the absence (group 1, *n* = 68; 35 males, 33 females; mean age 38.2 ± 10.4) or presence (group 2, *n* = 32; 14 males, 18 females; mean age 43.6 ± 10.9) of complete resolution of thrombus on CUS. Control group consisted of 50 patients with uncomplicated primary varicose veins of the lower limbs (27 male 23 females; mean age 39.76 ± 12.47).

The baseline characteristics of the groups and laboratory findings for both groups at 6 month follow-up are presented in Table 1. WBC levels at month 6 were significantly higher in group 1 than in group 2 and control group (*p* < 0.001). Platelet count at month 6 was significantly lower among group 1 patients when compared with group 2 and control group (*p* < 0.001) (Table 1). Table 2 presents a comparison of platelet indices and percent change in platelet indices between groups. On admission, MPV and PDW levels were significantly higher in group 1 and group 2 than control group (*p* < 0.001). There were no significant difference in admission MPV (*p* = 0.68) and PDW levels (*p* = 0.54) between group 1 and group 2. MPV (*p* = 0.03) and PDW (*p* < 0.001) levels at month 6 were significantly higher in group 1 than in group 2 and control group. There were no significant difference in MPV (*p* = 0.85) and PDW (*p* = 0.23) levels at month 6 between group 2 and control group. Percent change for MPV levels ($\Delta\%$ MPV) and percent change for PDW levels ($\Delta\%$ PDW) were significantly higher in group 2 than in group 1 and control group (*p* < 0.001) (Table 2).

The correlation between the complete DVT resolution and evaluated parameters is shown in Table 3. Complete DVT resolution showed a moderate negative correlation with PDW at month 6 ($\rho = -0.47$, *p* < 0.001) and a weak negative correlation with MPV at month 6 ($\rho = -0.26$, *p* = 0.008). Also, there was a strong positive correlation between complete DVT resolution and $\Delta\%$ PDW ($\rho = 0.63$, *p* < 0.001) and a weak positive correlation with $\Delta\%$ MPV ($\rho = 0.23$, *p* = 0.02).

Table 2 Comparison of platelet indices and percent change in platelet indices between groups

	Group 1 ^a (n = 68)	Group 2 ^b (n = 32)	Control group (n = 50)	p value
MPV (fl), mean $\pm$ SD	8.9 $\pm$ 1	8.7 $\pm$ 1.1	8.0 $\pm$ 1.1	<0.001
PDW (fl), median (IQR)	13.7 (12–14.7)	13.7 (12.8–14.8)	11.2 (9.9–13.1)	<0.001
MPV6 (fl), median (IQR)	8.1 (7.8–8.7)	7.8 (7.6–8.3)	7.7 (7–8.6)	0.03
PDW6 (fl), median (IQR)	12.6 (11.4–13.8)	10.6 (10–11.2)	11 (9.8–12.8)	<0.001
$\Delta\%$ MPV, mean $\pm$ SD	7 $\pm$ 4.9	10.1 $\pm$ 6	1.11 $\pm$ 5.6	<0.001
$\Delta\%$ PDW, median (IQR)	5.74 (3.4–8)	22.3 (17.1–25.9)	1.9 (–0.2–2.3)	<0.001

MPV admission mean platelet volume levels, PDW admission platelet distribution width levels, MPV6 mean platelet volume levels at 6 month follow-up, PDW6 platelet distribution width levels at 6 month follow-up, $\Delta\%$ MPV percent change for mean platelet volume levels, $\Delta\%$ PDW percent change for platelet distribution width levels

^a Patients with residual venous thrombosis

^b Patients with complete resolution of thrombus

Table 3 Correlation of complete thrombus resolution with patient characteristics and laboratory findings at 6 month follow-up

	p value	ρ
Age	0.03	0.21
Sex (M)	0.47	0.07
Body mass index	0.86	–0.02
Hypertension	0.4	0.09
Smoking	<0.001	–0.35
Hyperlipidemia	0.76	–0.03
Glucose	0.6	–0.05
Creatinine	0.71	0.01
WBC	0.7	–0.04
Hemoglobin	0.49	–0.07
Platelet count	<0.001	0.57
MPV6	0.008	–0.26
PDW6	<0.001	–0.47
$\Delta\%$ MPV	0.02	0.23
$\Delta\%$ PDW	<0.001	0.63

Rho Spearman's correlation coefficient, WBC white blood cell count, MPV6 MPV levels at 6 month follow-up, PDW6 PDW levels at 6 month follow-up, $\Delta\%$ MPV percent change for mean platelet volume values, $\Delta\%$ PDW percent change for platelet distribution width values
Correlation is significant at the 0.05 level

Logistic regression analysis showed that PDW (OR 2.2; 95 % CI 1.3–3.7; $p = 0.004$) at 6 month follow-up was an independent risk factor for the presence of RVT in patients with DVT.

ROC analysis revealed that a 8.4 % decrease in admission MPV at 6 month follow-up provided 62 % sensitivity and 62 % specificity (AUC 0.64; 95 % CI 0.53–0.75; PPV 43.5 %; NPV77.8 %) and a 15.4 % decrease in admission PDW at 6 month follow-up provided 87 % sensitivity and 94 % specificity (AUC 0.89; 95 % CI 0.79–0.98; PPV 87;

NPV 94) for prediction of complete resolution of thrombus in patients with DVT. The ROC curves of $\Delta\%$ MPV and $\Delta\%$ PDW are shown in Fig. 1.

Discussion

In the present study, we have demonstrated that the MPV and PDW levels were significantly lower in patients with complete DVT resolution than in patients with RVT at 6 month follow-up. We detected a significant association between MPV and PDW levels and complete DVT resolution. PDW at 6 month follow-up was an independent risk factor for the presence of RVT in patients with DVT. We have found that $\Delta\%$ PDW and $\Delta\%$ MPV were accurate markers in distinguishing the patients with CTR from the patients with RVT in DVT patients. The AUC for $\Delta\%$ PDW was higher than the AUC for $\Delta\%$ MPV. In addition, $\Delta\%$ PDW showed a strong positive correlation with complete DVT resolution, while $\Delta\%$ MPV showed a weak positive correlation with complete DVT resolution.

It has been previously shown that a considerable number of recurrences can be seen in the opposite leg or present as PE [1, 3, 5]. Young et al. [5] suggested that residual thrombus in DVT may be a marker for a generalized procoagulant diathesis. Higher thrombogenic state of the patients may be the possible mechanism responsible for platelet activation and MPV and PDW elevation in patients with RVT [19–21]. Large platelets are metabolically and enzymatically more active than small platelets. They aggregate more rapidly and release greater amounts of mediators such as thromboxane A₂, serotonin and ATP [13, 22]. Elevated MPV and PDW levels and low platelet count status in patients with RVT may also be a result of increased platelet consumption during the evolution of thrombosis. There is usually an inverse relationship between MPV and PC [23–25].

Fig. 1 The ROC curves of $\Delta\%$ MPV and $\Delta\%$ PDW for detection of complete resolution of thrombus in patients with deep venous thrombosis

There are limited studies investigating biomarkers in RVT after DVT. Biomarkers associated with coagulation and inflammation may play a role in the resolution of thrombosis [26, 27]. Cosmi et al. [28] demonstrated that repeated D-dimer testing after cessation of anticoagulant therapy for the first episode of unprovoked VTE could help determine the duration of the treatment. Montes-Worboys et al. showed that elevated levels of D-dimer after 3 months had a negative correlation with improvement of popliteal residual thrombosis. They also suggested that there was a correlation between IL-8 cytokine levels at baseline and the baseline diameter of femoral thrombi. According to their results, resolution of thrombosis at 1 month was associated with severe inflammatory reactions, as measured by plasma markers (higher TNF- α levels) [29]. Spiezia et al. [4] found that after an episode of proximal DVT, the thrombus persists over a longer period of time in carriers of thrombophilia than in non-carriers. They suggested that persistent residual thrombosis could be a marker of hypercoagulability.

In our study, smoking was found to be significantly less in group 1 than group 2 and control group. Smoking is a well-established risk factor for atherosclerotic disease, but its role as an independent risk factor for VTE remains controversial [30–32]. According to our study there is no positive relationship between smoking and RVT.

This study has several limitations. One of the main limitations of our study is its retrospective design. It was previously shown that blood collected in EDTA tubes should be analyzed within 1 h after collection to prevent platelet swelling [33]. The medical records of our study population did not comprise any information about the processing time. However, our institutional policy dictates that collected bloods should be processed within 1 h after collection. Moreover, small number of patients were included into the study due to numerous exclusion criteria.

Conclusions

MPV and PDW are simple, inexpensive tests and may provide practical data in selected patients. Percent change in admission MPV and PDW levels at 6 month follow-up may be used to identify the patients with complete DVT resolution after a first episode of acute proximal DVT. Reference ranges for MPV, PDW and PC may differ between laboratories. Therefore, percent change in admission MPV and PDW levels at 6 month follow-up may be more accurate to identify patients with complete DVT resolution than PDW and MPV levels at month 6 alone. Further prospective studies are needed to clarify the relationship between RVT and markers of platelet activation and aggregation.

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