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Platelet Indices may be Correlated with Severity of Vasospastic Disorders

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Background: Vasospastic disorders are common worldwide. In daily practice, routine blood samples are used for several investigations. In this study we aimed to determine the possible correlations between lymphocyte count, platelet indices, and the severity of vasospastic disorders.

Material/Methods: Data of 102 patients admitted to our department with vasospastic disorder symptomatology were retrospectively collected. Demographic data, symptoms, and blood test results were recorded. Patients were divided into 2 groups according to their rewarming time, which is determined by the cold stimulation test. Group 1 consisted of patients with rewarming time below 20 min and Group 2 consisted of patients with rewarming time above 21 min. Demographic data and blood test results were compared between groups. Results were analyzed with the SPSS for Mac 20.0 package program.

Results: There was no statistically significant difference between the groups in demographic variables and symptomatology. In Group 2, mean platelet volume (MPV) and platelet distribution width (PDW) were higher than in Group 1, which was statistically significant (8.87 ± 0.74 vs. 8.38 ± 0.78 , $p=0.001$ and 15.91 ± 1.92 vs. 14.7 ± 1.99 , $p=0.002$, respectively). Similar to MPV and PDW, lymphocyte count was also higher in Group 2 than in Group 1 (2.28 ± 0.65 vs. 1.90 ± 0.68 , $p=0.002$).

Conclusions: Diagnosis and grading the severity of VD is challenging, but it can be supported by the presence of increased PDW, MPV, and lymphocyte count.

MeSH Keywords: **Blood Cell Count • Cold Temperature • Mean Platelet Volume • Peripheral Vascular Diseases**

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Background

Vasospastic disorders (VD) are common, with a prevalence of 3.3% to 22% in the general population [1]. This group of disorders can be classified into 2 subgroups according to etiologic factors. If there is an underlying etiologic systematic disorder, it is called secondary form, which is uncommon. The other form of this disorder, without any underlying etiologic factors, is called primary form, and is much more common [1,2].

Several studies described many diagnostic tools and screening tests for this disorder. Unfortunately, an objective, quantitative diagnostic method has not been defined yet. Most vasospastic disorder diagnosis still depends on the physical examination and several screening tests such as observation of triphasic color changes, measurement of finger systolic blood pressure, or finger-brachial index, plethysmography, and capillaroscopy [3]. In our institution, we use the cold stimulation test (CST), and we described our application technique in a previous paper [3]. In daily practice, several simple routine blood samples are analyzed in such group of patients, especially for distinguishing the primary and secondary forms.

Mean platelet volume (MPV) and platelet distribution width (PDW) are some of the blood analysis markers. These parameters are closely correlated with shapes, volumes, and functions of platelets. In the literature there are many studies about the associations between these parameters in various systemic disorders, which will be discussed below.

In this study we aimed to determine the possible correlations between lymphocyte count, platelet indices, and the severity of vasospastic disorders.

Material and Methods

In this retrospective study, we aimed to compare the blood results of these 2 groups, which were defined according to the presence of vasospastic disorder. Our local ethics committee approved the study.

Patient's selection

Between August 2012 and April 2014 data were collected from files of 102 patients admitted to our department with vasospastic disorder symptomatology.

After data collection, patients were divided into 2 groups according to their CST results. Group 1 consisted of 51 patients with rewarming time below 20 min (20-min included). Group 2 consisted of 51 patients who had rewarming time above 21 min. Systemic evaluation, including blood examinations, capillaroscopy, and Doppler ultrasonography, are routinely performed in our clinic to exclude secondary etiologic factors. Therefore, in this study we only included the patients with primary vasospastic disorders. Demographic data of patients and type and duration of symptoms were recorded.

We recently defined an assessment scale of CST in a previous paper [3]. The assessment scale for CST results is given in Table 1. According to this scale, the cut-off value was determined as 20 min, so in this paper we divided the patients into subgroups according to this cut-off value.

Cold stimulation test

In our clinic, CST is routinely performed to all patients with vasospastic disorders due to our national and military regulations. This test is performed after patients have rested in a room at approximately 26°C temperature for at least 30 min. Above the waist, patients wore only their shirts, without additional jackets or coats. All measurements were performed with the patient's hands at the level of the heart. Patients are classified according to their smoking habits, but a standardized protocol about time refraining from tobacco prior to testing was not used. A Sonatemp™ 400/700 Monitor (Sheridan Catheter Corp. Argyle, NY, USA) device was used for temperature measurements. According to our protocol, application of the CST is as follows: 1). Hand temperatures of the patients are measured with a probe inserted between the pulp of the first and second distal phalanges. 2). The most affected hands are immersed into the ice-water at +4°C for 20 s. 3). After drying the hands, the temperature is measured again at 5, 10,

Table 1. Assessment scale for cold stimulation test.

Stage	Rewarming time (minute)	Assessment	Potential diagnosis
0	0–10	Normal	Healthy person
I	11–15	Mild disturbed	Otherwise healthy person
II	16–20	Moderate disturbed	Mild vasospastic disorder
III	21–30	Serious disturbed	Moderate vasospastic disorder
IV	≥31	Serious disturbed	Serious vasospastic disorder

Table 2. Patients' demographic data.

	Group I (n=51)	Group II (n=51)	p value
Age (year)	23.92±7.402	23.29±4.43	>0.05
Gender (male/female)	46/5	48/3	>0.05
Smoking (n)	33	29	>0.05
Duration (year)	3.86±2.89	4.52±2.95	>0.05
Symptoms			
Cyanosis (n,%)	48/3	48/3	>0.05
Numbness (n,%)	36/15	32/19	>0.05
Hyperhidrosis (n,%)	32/19	30/21	>0.05
Hand swelling (n,%)	24/27	24/27	>0.05
Pain (n,%)	21/30	29/22	>0.05
Rewarming time (Min)	10.25±2.74	30.12±5.81	<0.001

Table 3. Analysis of blood results.

	Group I	Group II	p value
WBC	6.37±1.69	6.96±2.00	>0.05
Lymph	1.90±0.68	2.28±0.65	0.002
HCT	44.57±3.16	45.02±3.49	>0.05
PLT	248.49±55.85	243.64±64.23	>0.05
MPV	8.38±0.78	8.87±0.74	<0.001
PDW	14.7±1.99	15.91±1.92	0.002
LDH	199.21±57.94	240.96±108.44	>0.05
Sedimentation	7.47±6.59	7.68±6.99	>0.05

WBC – white blood cells; Lymph – lymphocyte count; HCT – hematocrit level; PLT – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; LDH – lactate dehydrogenase level.

15, and 20 min, with the same technique detailed above. 4). The rewarming time to initial temperature is also recorded.

Blood samples

As mentioned previously, we routinely analyze the blood samples of patients derived from a peripheral vein for excluding possible secondary etiologic mechanisms. In these examinations, standardized routine blood parameters, including blood cell counts, biochemical analysis (such as SGOT, SGPT, urea, creatinine, LDH, and several electrolytes), and sedimentation rates are analyzed. In our study, we compared the existing blood test results between the 2 groups.

Statistical analysis

SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL) was used for statistical evaluation. Descriptive results are expressed as mean ± standard deviation for normally distributed continuous variables and median values for abnormally distributed continuous variables. Categorical variables are reported as numbers and percentages. Before analyses, the Kolmogorov-Smirnov test was used for analyzing the distribution pattern of data. Comparisons of the parametric values were performed with the t test for normally distributed groups and with Mann-Whitney U test and Wilcoxon signed ranks test with abnormally distributed groups. Pearson's chi-square test, Fisher's exact test, and McNemar-Bowker test were used for the comparisons of categorical variables.

A p value of <0.05 was considered as statistically significant with a 95% confidence interval.

Results

Patient characteristics

Because this study was performed in a military hospital, most of the patients were young males. Sixty-two of the patients (60.8%) were smokers. None of the patients had any other comorbid disorders. The most common complaints were cold-aggravated cyanosis (96 patients, 94.1%) and numbness (68 patients, 66.7%). The other complaints were: hyperhidrosis (52 patients, 50.9%), cold-aggravated pain (50 patients, 49.1%), and cold-aggravated swelling (38 patients, 37.3%). Mean duration of symptoms from onset was 4.19 ± 2.93 years. Demographic data of patients are given in Table 2.

Blood analysis

There were statistically significant differences in MPV, PDW, and lymphocyte count between the 2 groups. However, there were no significant differences in other blood markers between the groups. Analysis of the blood results are given in Table 3.

Discussion

In this study, we demonstrated the relationship between MPV, PDW, lymphocyte count, and the severity of VD. To our knowledge, to date, the relationship between VD and these parameters has not been evaluated previously. Thus, this is the first study on this subject. We found that patients in Group 2 had significantly higher MPV, PDW, and lymphocyte count than patients in Group 1.

As a component of complete blood count examination, platelet markers have no additional cost and do not require further invasive interventions. Although clinical validity of these markers has not been established, most authors have focused on the other unknown functions of platelets in recent studies. Today, many authors agree with that platelets have roles not only in the coagulation pathway, but also in several other processes such as inflammation, immunity, neoangiogenesis, and tumor metastasis [4,5].

MPV is a marker of platelet activation and is correlated with platelet function. It is also a more sensitive index than platelet counts itself, and may be used as a marker for various disorders in daily practice [4]. It is associated with various inflammatory conditions and may be used as an indicator of platelet activation and severity of inflammation [6,7]. Some studies

conclude that MPV has an important role as a marker of inflammation, disease activity, and efficacy of anti-inflammatory treatment in several disorders such as rheumatoid arthritis, ankylosing spondylarthritis, ulcerative colitis, and Crohn's disease [8,9–11].

Increased levels of MPV can be observed in diabetes mellitus, cardiovascular diseases, and peripheral arterial and venous disorders [7,8]. Conversely, MPV is decreased in several high-grade inflammatory disorders such as active rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and inflammatory bowel diseases [4,10]. Increased MPV levels may be secondary to low-grade inflammatory disorders and various disorders, which are associated with concomitant thrombotic processes [8]. Reduced MPV could be due to the consumption or sequestration of the large activated platelets from circulation by the spleen [4,8]. However, the exact mechanisms of these changes are still unclear [8].

In general, newly-generated platelets are smaller and have lower MPV levels, while the older platelets are larger with higher MPV levels [8]. Thrombopoietin and several inflammatory lymphocyte-derived cytokines such as interleukins (IL), interferons (IFN), and TNF- α were the most important factors of the regulation of thrombopoiesis [4,8]. From this point, there may be a positive correlation between lymphocyte counts and platelet indices. In our study, lymphocyte counts and MPV levels were both significantly higher in patients in Group 2. We consider that the previous correlation may be an explanation of the differences in MPV levels and lymphocyte counts between our study groups.

Yilmaz et al. concluded that the sympathetic activation causes a rapid shift in MPV values. They speculated that some older platelets, which are sequestered from the spleen, are released back into circulation with sympathetic activation [12]. Therefore, we consider that sympathetic activation, which has an important role on VD pathogenesis, was another cause of the increased MPV levels in our study.

Another marker of the platelet activation is PDW, which directly measures the variability in platelet sizes [6]. Its high values may suggest a greater production of larger platelets with increased MPV. In daily clinical practice it is used for differential diagnosis of platelet disorders, for example, to distinguish essential thrombocythemia from reactive thrombocytosis [5,7].

In a recent study, Liu et al. conclude that PDW is a more specific marker for platelet activation and is associated with vascular damage [4]. Based on our results, we consider that the positive correlation between high PDW values and the severity of VD could be further evidence supporting the previous hypothesis.

In our study, beside this quantitative laboratory data, there was a statistically significant difference between groups in smoking habits, which were higher in Group 2. Although there is no measurable and quantitative data, we also consider that smoking is an independent risk factor for vasospastic disorder course.

Conclusions

Ours is the first study to demonstrate the relationship between severity of VD and MPV, PDW, and lymphocyte counts. We conclude that grading the severity of VD is challenging, but it can be supported by the presence of increased PDW, MPV,

and lymphocyte count. Moreover, whole blood cell count is a simple and useful test, and does not need any advanced, complex, or expensive technology. Further larger studies are needed to determine the pathophysiologic mechanism of this correlation between VD and MPV, PDW, and lymphocyte count.

Study limitations

This study was performed in a military hospital; therefore, all of the patients were male. For this reason, it may be difficult to make a generalized conclusion for both sexes based on our results. There is a need to perform similar studies in a wider population.

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