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ORIGINAL ARTICLE

Are Mean Platelet Volume and Platelet Distribution Width Useful Parameters in Children With Acute Rheumatic Carditis?

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Abstract Rheumatic fever (RF) is an inflammatory disease caused by autoimmune response to a preceding group A streptococcal infection. Mean platelet volume (MPV) reflects the platelet size and the rate of platelet production in bone marrow, and it may be used as an indicator of platelet activation and severity of inflammation. Fifty-three consecutive patients diagnosed with acute rheumatic carditis and 53 control subjects were enrolled into this study. Leukocyte and platelet counts were significantly higher in patients with acute carditis before treatment compared with controls, whereas MPV and platelet distribution width (PDW) values were not significantly different between groups. Platelet counts, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were decreased significantly in patients with RF after treatment. There was not a significant difference in terms of platelet count between the controls and the patient group after treatment. ESR was found to be correlated with CRP in patients before and after treatment. In conclusion, the results of our study showed that MPV and PDW levels do not change during acute rheumatic carditis before and after treatment.

Keywords Mean platelet volume · Platelet distribution width · Rheumatic fever · Rheumatic carditis

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Introduction

Rheumatic fever (RF) is an inflammatory disease caused by an autoimmune response to a preceding group A streptococcal (GAS) infection. It is an important public health problem associated with poor living conditions and decreased access to appropriate health care services throughout developing countries [13]. It is the leading cause of acquired heart disease in children and young adults worldwide. Carditis is the most important manifestation of RF and may result in significant morbidity and mortality [5]. Recently it was found that inflammatory cytokines played a significant role in the pathogenesis of RF. In addition, significantly increased cytokine, nitrite, and adrenomedullin levels were detected in the sera of RF patients. Lymphocyte accumulation, overexpression of adhesion molecules, and complement deposition in heart tissues have also been shown [3, 9, 17].

In numerous clinical studies, platelets have been proven as an important component of the inflammatory response. Chemokines, cytokines, and other inflammatory mediators are secreted by activated platelets [4]. Mean platelet volume (MPV) reflects the platelet size and the rate of platelet production in the bone marrow, and it may be used as an indicator of platelet activation and the severity of inflammation [14]. Another marker of the platelet activation, platelet distribution width (PDW), shows the variability in platelet sizes [11]. MPV values have previously been studied in various conditions with inflammatory pathogenesis, such as familial Mediterranean fever (FMF), rheumatoid arthritis, asthma, hypertension, diabetes mellitus, myocardial infarction, secondary pulmonary hypertension, and acute rheumatic fever [7, 16].

In this study, we aimed to evaluate MPV and PDW in patients with acute rheumatic carditis during the acute

phase and after anti-inflammatory therapy and compare them with those obtained in healthy control subjects. According to our knowledge, MPV and PDW together have not been studied previously in patients with rheumatic carditis.

Material and Methods

At the beginning of the study, the sample size required for the detection of any existing difference between the groups with a statistical power of 80 %, and type α error of ≤0.05 was calculated as 41 by comparing with datasets of previous studies with similar means and SDs [16]. After power analysis, 53 consecutive patients, diagnosed with acute rheumatic carditis at Izmir Dr. Behcet Uz Children's Hospital's Department of Pediatric Cardiology between the years 2006 and 2012, were enrolled into the study. The diagnosis of RF was established when the Jones criteria were fulfilled for acute cases [8]. All of the participants underwent echocardiographic examination performed by a pediatric cardiologist experienced in rheumatic heart disease. Demographic features of the patients were extracted from the patient data system. Complete blood count—including white blood cell (WBC) and platelet counts, MPV, PDW, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) at the time of diagnosis and after 8 weeks of treatment for acute rheumatic carditis—were collected using a computerized patient database. The diagnosis of carditis was made by the presence of murmurs suggestive of valvular regurgitation and by echocardiographic examination. A Vivid 3 Pro Ultrasound System (GE Medical Systems, NE) with 3- and 5-MHz transducers were used for two-dimensional, M-mode, and colour flow Doppler imaging echocardiography. Any valvular incompetence, thickening, vegetation, prolapse or nodular appearance; annular and/or cordal pathologies, and pericardial effusion were recorded. Mitral and aortic valve regurgitation were assessed by colour Doppler echocardiography from apical and parasternal long-axis views. Echocardiographic criteria as suggested by the World Health Organization expert Committee in 2004 were used to differentiate pathological valve regurgitation from normal on echocardiographic examination. Pathological valve regurgitation was defined as a regurgitant jet >1 cm in length, seen in at least two planes, mosaic colour jet with a peak velocity of 2.5 m/s, and persisting throughout systole (for mitral valve regurgitation) or diastole (for aortic valve regurgitation) [15].

Patients who had history of drug ingestion within the last 8 weeks before blood sampling that may cause platelet dysfunction, such as aspirin, nonsteroidal anti-inflammatory drugs, and oral anticoagulants, were excluded from the study. All patients had moderate to severe carditis. Oral steroid therapy was started in patients without discriminating between moderate and severe carditis. Initially prednisolone (2 mg/kg/d) was given for 2 weeks, which was then tapered, and aspirin was started 80–100 mg/kg/d (maximum dose 3.5 g/d) to prevent rebound [18]. Complete blood count parameters of 53 sex- and age-matched healthy control subjects were recorded from the same computerized database. Complete blood count, CRP, and ESR analyses were performed in our institution's central laboratory. CRP levels <0.32 mg/dl were considered as increased. The study was approved by the Ethical Committee of our institution.

Data were analyzed and processed with SPSS 18.0 statistical package programme (SPSS, Chicago, IL). The distribution pattern of data was assessed by Shapiro–Wilk test. Quantitative variables are shown as mean ± SD for normally distributed data or as median and interquartile ranges for the others. The differences between quantitative groups with normal distribution were evaluated with Student *t* test. Mann–Whitney *U*-test was used for abnormally distributed data. The associations between parameters were assessed using Pearson's or Spearman's correlation test. A p-value < 0.05 was considered was statistically significant.

Results

A total of 53 patients (34 male, 19 female) diagnosed with rheumatic carditis and 53 sex- and age-matched healthy control subjects were enrolled into the study. The mean age of the patients was 10.8 ± 2.3 years. The groups were similar in terms of age and sex ($p > 0.05$). The characteristics of the patients before and after treatment and those of healthy control subjects are listed in Table 1. WBC and platelet counts were significantly higher in patients with acute carditis before treatment compared with controls ($p < 0.01$), whereas MPV and PDW values were not different between the groups ($p > 0.05$). Hemoglobin levels were significantly lower in patients with acute carditis before treatment compared with controls ($p < 0.01$). There was not a significant difference in terms of platelet count between the controls and the patient group after the treatment ($p > 0.05$).

The comparison of laboratory parameters of the patients at presentation and after treatment are listed in Table 2. There were no significant differences between the two groups in terms of WBC count and MPV and PDW values. Platelet counts, ESR values, and CRP values were significantly decreased and hemoglobin levels significantly increased in patients after the treatment compared with baseline (both p values < 0.01). ESR levels correlated with CRP levels in patients with rheumatic carditis during the

Table 1 Demographic and laboratory characteristics of patients with rheumatic carditis and healty controls

Characteristics	Healthy controls	Patients during the acute stage of RC	Patients with RC after treatment	*p*	
				Controls versus acute stage	Controls versus after treatment
Age (mean ± SD)	10.1 ± 2.1	10.8 ± 2.3			
Male/female	34/19	34/19			
Hemoglobin (mean ± SD)	12.7 ± 1	12 ± 1.3	12.7 ± 1.2	<0.01	
WBC (count/mm^3)[a]	7,000 (2,575)	10,100 (8,400)	9,600 (6,300)	<0.01	<0.01
ESR(mm/hour)[a]	–	44 (54)	16 (17)		
CRP(mg/dl)[a]	–	3.5 (5.9)	0.7 (0.3)		
PLT (count/mm^3) (mean ± SD)	304,000 ± 80,000	418,000 ± 120,000	330,000 ± 110,000	<0.01	0.09
MPV (fl) (mean ± SD)	9.3 ± 1.2	9 ± 1	8.9 ± 1.3	0.16	0.13
PDW (%) (mean ± SD)	12.3 ± 2.4	11.9 ± 2.4	11.9 ± 2.9	0.45	0.49

RC rheumatic carditis

[a] Data are expressed as median with range in parentheses

Table 2 Laboratory characteristics of patients with rheumatic carditis during the acute stage and after treatment

Characteristics	Patients during the acute stage of RC	Patients with RC after treatment	*p*
Hemoglobin (mean ± SD)	12 ± 1.3	12.7 ± 1.2	<0.01
WBC (count/mm^3)[a]	10,100 (8,400)	9,600 (6,300)	0.89
ESR (mm/h)[a]	44 (54)	16 (17)	<0.01
CRP(mg/dl)[a]	3.5 (5.9)	0.7 (0.3)	<0.01
PLT (count/mm^3) (mean ± SD)	418,000 ± 120,000	330,000 ± 110,000	<0.01
MPV (fl) (mean ± SD)	9 ± 1	8.9 ± 1.3	0.56
PDW (%) (mean ± SD)	11.9 ± 2.4	11.9 ± 2.9	0.98

RC rheumatic carditis

[a] Data are expressed as median with range in parentheses

acute stage and after treatment ($r = 0.7$, $p < 0.01$ and $r = 0.4$, $p < 0.01$, respectively).

Discussion

To our knowledge, MPV values were evaluated previously only in one study in children with acute RF that was reported by Sert et al. However, the relationship between acute rheumatic heart disease and MPV and PDW values has not been evaluated previously. This is the first study to investigate MPV and PDW in patients with rheumatic carditis. Our sample size was also greater than the one of Sert et al. [16]. In contrast to Sert et al. [16], we showed that MPV and PDW values before and after treatment did not differ significantly between each other and when compared with the healthy subjects.

Acute RF is an autoimmune disease that results in abnormal and overt immune response to preceding GAS infection and involves both humoral and cellular immune mechanisms. This abnormal immune response may be triggered by molecular mimicry between streptococcal antigens and some specific human tissues, most prominently the heart, joints, brain, skin, and subcutaneous tissues, in genetically susceptible individuals. Both genetic and environmental factors contribute to the development of acute RF. Cytokines produced by activated lymphocytes and macrophages after antigenic stimulation can play an important role in the pathogenesis of acute RF. Previously reported data showed high tumor-necrosis factor (TNF)-α and interleukin (IL)-1 levels in patients with RF and rheumatic heart disease. In addition, significant correlation was found between IL-6, TNF and ESR, and CRP levels [19]. Hafez et al. [10] suggested that IL-1a and IL-6, respectively, may be used as a minor criterion in carditis and arthritis, and anticytokine therapy, such as anti–IL-1a or anti–IL-6, has been recommended for preventing and decreasing valvular damage in rheumatic carditis.

MPV and PDW are simple and useful parameters detected in routine complete blood count analysis. However, clinicans usually do not pay attention to these parameters. In response to decreasing platelet count, production of platelets increases in the bone marrow. Newly produced platelets are larger and more reactive; thus, MPV values are higher. In recently reported data, MPV was used as a simple marker for reflecting the severity of

inflammation and was shown to be increased in cases of myocardial infarction, sepsis, chronic pulmonary disease, and FMF [1, 4, 6]. In contrast, Kisacik et al. [12] and Sert et al. [16] found lower platelet volumes in rheumatoid arthritis and acute RF patients, respectively. Similar to MPV, PDW, which represents variability in platelet sizes, can be used as a marker of platelet activation [2].

The previously reported study [16] showed increasing platelet count and decreasing MPV values in patients with RF during the acute phase of illness. The investigators hypothesized that decreased MPV values in conditions with elevated inflammatory markers might indicate the intensity of the inflammatory process. Excessive production of cytokines such as IL-6 and acute phase reactants may cause suppression of the size of platelets released from the bone marrow by affecting the megakaryopoiesis. They also speculated that low MPV values during acute attack of RF might be related to IL-6's effect and/or intensive consumption of larger platelets at the areas of inflammation.

In contrast to this study, we did not find any difference in MPV and PDW values in patients with acute rheumatic carditis before and after treatment. In addition, no difference was found between patients and healthy controls. However, the pretreatment platelet count was found to be significantly higher in our cases as described in other studies. This may be related to the effect of IL-6 [17]. Suppression of proinflammatory cytokines by steroids may cause decreased levels of CRP and ESR. In the present study, though, we observed a decrease in levels of CRP and ESR; however, WBC counts were persistently high due to the use of steroids.

In conclusion, our study showed that MPV and PDW values do not change during acute rheumatic carditis before and after treatment. However, because of the retrospective design of this study, prospective studies with greater number of patients are needed to assess MPV and PDW in patients with rheumatic carditis.

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