

Is Mean Platelet Volume a Useful Noninvasive Biomarker for Inflammatory Bowel Disease in Childhood?

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ABSTRACT

Introduction: The incidence of inflammatory bowel disease (IBD) has become a global disease in newly industrialised countries. Inflammation leads to a structural modification in platelets, and the secretion of cytokines results in a change of mean platelet volume (MPV).

Aim: To evaluate the relationship between IBD activity parameters and MPV.

Materials and methods: The study group included 26 patients [consisting of 18 ulcerative colitis (UC), 6 Crohn's disease (CD), and 2 indeterminate colitis patients] followed-up at Dr. Behçet Uz Children's Hospital between 2004–2016. The data of patients were screened retrospectively and the demographic, clinical and laboratory characteristics were evaluated. The changes in MPV during the activation, remission and relapse periods of the disease and correlation with other disease activity markers were investigated.

Results: The study group consisted 26 IBD patients (female/male: 11/15) and 71 healthy controls. We used the Pediatric Ulcerative Colitis Activity Index and the Pediatric Crohn Disease Activity Index to determine disease activity. The IBD group had statistically significantly higher leukocyte count and lower hemoglobin values compared with the control group ($p < 0.05$). The mean platelet count and MPV values were not correlated significantly with both the C-reactive protein level and erythrocyte sedimentation rate ($p > 0.05$).

Conclusion: We suggest that MPV is a simple and inexpensive method that can be useful in the diagnosis of IBD but does not provide significant results to determine the disease activity.

Keywords: Children, Inflammatory bowel diseases, Mean platelet volume.

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INTRODUCTION

Since the recognition of ulcerative colitis (UC) in 1875 and Crohn's disease (CD) in 1932, the incidence of inflammatory bowel disease (IBD) has increased to a level such that IBD has become a global disease in newly industrialized countries.¹ The disease is characterized by a chronic relapsing course of colonic mucosal inflammation due to several genetic, dietary, immune, and environmental risk factors. There is no "gold standard" diagnostic test or examination for the disease. Clinicians evaluate a combination of symptoms, laboratory markers, radiological findings, and endoscopy with histology to make the diagnosis to assess severity and to evaluate the activation of the disease.² Histological evaluation is used to demonstrate intestinal inflammation accurately, but clinicians prefer tests that are noninvasive, such as acute-phase determinants, fecal markers, serological tests, and novel genetic determinants, to establish the degree of activation of IBD.

Inflammation leads to a structural modification in platelets, and the secretion of cytokines results in a change in mean platelet volume (MPV).³ Mean platelet volume reflects the platelet size and has been studied as an inflammatory marker in several diseases. High-grade inflammatory diseases, such as rheumatoid arthritis activation or familial Mediterranean fever attacks, are known to present with decreased MPV. Mean platelet volume has also been reported to decrease in active IBD in adults,^{4,5} but the clinical course in both children and adolescents is different from that of adults,⁶ and the literature lacks information about MPV changes in IBD and disease activation in childhood.

The aim of this study is to evaluate the MPV levels in IBD in childhood and adolescence to determine whether platelet volume is a useful marker in predicting the status of the disease

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and examine the correlation with other parameters used for disease activity.

MATERIALS AND METHODS

The study group consisted of children and adolescents diagnosed and followed up with IBD between August 2004 and October 2016 at Department of Gastroenterology, Hepatology and Nutrition in the major tertiary hospital for pediatric-aged patients. The patients' medical records were evaluated retrospectively, and the periods of relapses and remissions were specified according to physician-based activity indexes; Pediatric Crohn's Disease Activity Index

(PCDAI) for Crohn's disease (CD), and the Pediatric Ulcerative Colitis Activity Index (PUCAI) for ulcerative colitis (UC) or indeterminate colitis (IC). Age, gender, disease subtype, symptoms at admission, hemoglobin (Hb), leukocyte (WBC) count, platelet (PLT) count, MPV values, erythrocyte sedimentation rate (ESR), C-reactive protein levels (CRP), albumin levels, PUCAI, and PCDAI scores were recorded. The first month controls were accepted as an early period evaluation, and the third month controls were recorded as late period evaluations. The control group consisted of children and adolescents admitted for preoperative routine screening, including blood count. Children with a history of acute/chronic liver-kidney diseases, anemia, leukocytosis/leukopenia, and consuming drugs such as nonsteroidal anti-inflammatory, aspirin, oral anticoagulant, and oral contraceptive that might cause thrombocytosis/thrombocytopenia were not enrolled in the control group.

In our hospital, for complete blood count (CBC) analysis, the blood samples are collected in standard tubes containing EDTA (%15 K₃EDTA, 0.054 mL/4.5 mL blood), and CBC analysis is performed within the first 2 hours on a Caldyn 3700, calibrated monthly by central laboratory. The laboratory reference values for MPV are 7.4–10.4 fL.

The data were evaluated with SPSS (Statistical Package for Social Sciences) for Windows 20.0 (SPSS Inc., Chicago, IL). Descriptive analysis was performed with percentage and mean \pm standard deviation values. Categorical variables were analyzed with Chi-square test and Fisher's exact, where appropriate. Mann-Whitney *U* test, a non-parametric test, was used to compare two independent means, whereas nonparametric Kruskal-Wallis test was used for comparison of more independent groups. Pearson and Spearman tests were used for correlation analysis. Comparisons where *p* values were < 0.05 were accepted as statistically significant.

The study was conducted following the approval of the Local Ethics Committee on June 23, 2016 (Protocol No:2016/93; Approval No:2016/10-04).

RESULTS

The patient group consisted of 26 children and adolescents [M/F:15/11; mean age: 14.2 ± 2.8 (min: 8 max:18)] diagnosed with IBD (18 patients with UC; 6 patients with CH and 2 patients with IC), while the control group consisted of 71 healthy children and adolescents [M/F: 47/24; mean age: 50 months (min: 3 max:147)]. Differences in gender and age were not statistically significant between the groups.

The most common symptoms of patients with UC were bloody diarrhea (72.2%) and abdominal pain (72.2%) in addition to rectal bleeding (38.8%), and the mean PUCAI score was 41.2 ± 17.7 on the first admission. All of the patients with CD had abdominal pain (100%), diarrhea (100%), and the mean PCAI score was 34.83 ± 6.6 at the time of diagnosis. The rate of moderate and severe disease was 72.2% and 66.7% in UC and CD, respectively. Table 1 shows the clinical properties of the study group.

In the patient group, the mean Hb level was 10.0 ± 2.0 g/dL, and the leukocyte count was $11.2 \pm 4.2 \times 10^3/\text{mL}$. The Hb level was significantly lower, whereas the leukocyte count was remarkably higher than the control group (11.6 ± 1.0 ; *p* value = 0.001 and 8.4 ± 2.3 ; *p* value < 0.05 , respectively). The platelet count at admission was $509.5 \pm 193.4 \times 10^3/\text{mL}$ in the patient group and $311.9 \pm 96.6 \times 10^3/\text{mL}$ in the control group, and the difference was statistically significant (*p* value = 0.001). Moreover, the mean MPV value of the patient group on admission was significantly lower than the control

Table 1: Findings of patients with inflammatory bowel disease at the time of diagnosis

Symptoms	Ulcerative colitis, n (%)	Crohn disease, n (%)	Indeterminate colitis, n (%)
Bloody diarrhea	13 (72.2)	6 (100)	2 (100)
Rectal bleeding	7 (38.8)	0 (0)	1 (50)
Abdominal pain	13 (72.2)	6 (100)	2 (100)
Weight loss	10 (55.5)	3 (50)	2 (100)

Table 2: The hematological parameters of patients with inflammatory bowel disease and control group

Variables	Patients (n = 26) (mean \pm SS)	Control (n = 71) (mean \pm SS)	<i>p</i>
Leukocyte (K/mm ³)	11.2 ± 4.2	8.4 ± 2.3	0.004
Hemoglobin (g/dL)	10.0 ± 2.0	11.6 ± 1.0	0.001
Platelet (K/mm ³)	509.5 ± 193.4	311.9 ± 96.6	0.001
Mean platelet volume (fL)	8.6 ± 1.1	9.4 ± 1.1	0.002

group (8.6 ± 1.1 fL in patient group vs 9.4 ± 1.1 fL in control group, *p* value < 0.05) (Table 2). Although the mean MPV value at remission and relapse periods did not differ significantly, the mean platelet count was significantly lower at late period evaluation than levels on admission (*p* value = 0.005) (Table 3).

When the correlation analyzes were performed, the MPV values showed slightly negative correlation with platelet counts on admission ($r = -0.399$, *p* value = 0.043), but there was no significant correlation with either laboratory parameters, including ESR, CRP or clinical scores, PCDAI, and PUCAI. At early period evaluations, MPV values were negatively correlated with platelet counts ($r = -0.517$, *p* value = 0.01) and CRP levels ($r = -0.603$, *p* value = 0.004), while mean platelet count was positively correlated with CRP levels at late period evaluations ($r = 0.507$, *p* value = 0.014). There was no correlation between MPV levels, platelet counts, CRP levels, ESR, PCDAI, and PUCAI in remission period of the disease.

DISCUSSION

In childhood, where growth and development are fast, the prognosis and treatment of IBD is more important than adults. As a result, in order to prevent permanent damage in patients with IBD in childhood, whose incidence and prevalence are gradually increasing, risk factors should be well known, and disease follow-up should be done very well in this respect.

The results of the current study indicate that MPV is decreased in patients with IBD in children and adolescents compared to healthy controls at admission, but it cannot be used to diagnose remission or relapse periods in the disease course. Mean platelet volume values were similar at admission and follow-up in our patients. The contradictory relationship between MPV and CRP in our study supported the hypothesis that MPV was not closely related to IBD activity. In addition, we found a slightly significant relationship between platelet count and MPV.

In the literature, platelet count was first reported to be increased in IBD activation in 1968,⁷ and "reactive thrombocytosis" (defined as a platelet count $>450 \times 10^9/\text{L}$) was defined as a common feature during the active phase of IBD.⁸ The mechanism for this is still not well explained. Either a nonspecific response to inflammation (similar to other chronic inflammatory disorders)

Table 3: Evaluation of mean platelet volume and platelet count with clinical status

Variables	Before treatment (mean \pm SD)	Early response (mean \pm SD)	Long term response (mean \pm SD)	Relapse (mean \pm SD)
Platelet count (K/mm ³)	509.5 \pm 193.4 ^a	437.8 \pm 129.4	366.8 \pm 17.3 ^b	465 \pm 125.1
MPV (fL)	8.6 \pm 1.1	8.7 \pm 1.2	8.9 \pm 1.1	8.77 \pm 1.4

Correlation value between a–b ($p = 0.005$)

or a disturbance in thrombopoiesis (suggested by the increased plasma levels of thrombopoietin and interleukin 6) may cause reactive thrombocytosis. In 1996, subjects with active IBD were reported to have greater platelet density and lower MPVs, and it was suggested that this indicated augmented platelet granule content. The decrease in MPV in subjects with IBD may be related to a disturbance in thrombopoiesis and is often observed in the early stages of systemic inflammatory processes.⁹ Small platelets have lower functional capabilities than larger ones, and the low MPV observed in IBD may have a clinical importance. Bleeding diathesis is more frequent in patients with low MPV.¹⁰ This may explain the higher incidence of gastrointestinal bleeding in IBD patients with active disease. Our results support the literature showing that MPV is reduced in IBD, particularly in IBD patients compared to healthy controls. Decreased MPV may be helpful and suggestive for the diagnosis of IBD.

The importance of platelet abnormalities, by count or volume, may also be due to increased incidence of thromboembolic phenomena reported in IBD. The increased expression of surface activation markers (such as P-selectin, GP53 and β -thromboglobulin) and other factors including IL-3, IL-6, and thrombopoietin leads to increased activation of platelets and stimulation of thrombopoiesis.^{11,12} Webberley et al.¹³ demonstrated *in vitro* spontaneous platelet aggregation in IBD patients independent of disease severity. Moreover, platelet aggregates were found *in vivo* in IBD patients¹⁴ and were not found in patients with other inflammatory disorders. Thus, the increased incidence of thromboembolic phenomena may not simply represent a consequence of chronic inflammation. A number of studies suggest that MPV is a key predictor of thrombotic events in various disorders, including cardiovascular disease,¹⁵ cerebrovascular disease, venous thromboembolism, and other disorders.^{16,17} Microaggregates and microinfarction of mesenteric vessels play a potential role in platelets as an inflammatory cell in the pathogenesis of CD.^{14,18} Platelets were therefore proposed to be involved, at least partly, in the formation of microinfarction and the pathogenesis of CD.¹⁹

In recent years, it has been shown that thrombocytosis and associated low MPV level in inflammatory diseases (ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis) are more significant, especially in the active period of the disease, and therefore can be used as an indicator of activity. Kapsoritakis et al.⁴ reported significantly reduced MPV values in active IBD and a negative correlation of MPV levels with the known IBD activity markers and platelet activation products. In a study conducted by Bařar et al. in our country, MPV in patients with IBD was shown to be significantly lower in both active and inactive disease groups compared to the control group.⁵ Our results are consistent with previous studies of MPV values of healthy controls and IBD patients observed in our study.

Mean platelet volume values were similar in admission and follow-up in our IBD patients. Mean MPV value at remission and relapse periods did not differ significantly. In addition, in the study

by Jar-emo and Sandberg-Gertzen, an activity-dependent diversity of MPV, was reported.²⁰ The reason for this discrepancy is unclear; we assume that the number of enrolled patients in these studies was limited, and large sample studies are necessary to investigate the real diversity between active and inactive CD patients.

There are a few limitations of this study. First, this is a single-center and retrospective study, leading to a potential selection bias. Second, as only 26 IBD cases subjects were enrolled in our study, the sample size might be too small to detect the real diversity of MPV between remission and relapse IBD patients. The absence of any continuous correlation between MPV and CRP in our study supported the hypothesis that MPV values are not significantly related to IBD activity. When the literature was examined, the sensitivity of CRP was observed as 50–100% and its specificity as 65–100%.²¹ CRP is the most sensitive of all biomarkers of inflammation in adult population for detecting IBD.² The level of CRP in IBD patients is a valuable marker, but it is known that it is insufficient to show disease activity, degree of inflammation, and follow-up disease by itself. As a result of the studies published by Florin et al. in 2006, published by Vermeire et al. in 2004, and published by Mack et al. in 2007, the level of CRP was reported to be related to a specific level of inflammation rather than reflecting the degree of inflammation.^{22,23} It is clear that CRP cannot predict clinical activation in IBD alone. In contrast, Kapsoritakis et al.⁴ was first to report the negative correlation CRP and MPV. In our study, in accordance with the literature, apart from all stages, negative correlation was detected between MPV and CRP only in early period evaluation to treatment. According to our results, we suggest that, although nonspecific, physicians should take MPV levels into account when providing medical care for children with IBD.

CONCLUSION

Inflammatory bowel disease results in an increase in blood platelet count and a change in their activation and morphology because of chronic inflammatory process. We suggest that MPV measurement, which is an easy, cheap, and simple noninvasive biomarker in children with IBD, can be a guide in terms of disease follow-up in comparison to other modalities in IBD. We also suggest that it should not be considered a stand-alone test for this use because of the non-specificity with other diseases. Further studies are needed to establish the relation between platelet functions and IBD in pediatric population.

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