

Use of MPV and MPV/Plt ratio in the differentiation of migraine and tension-type headache

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*Department of Neurology, Kayseri Training and Education Hospital, Kayseri, Turkey***Abstract**

Purpose: Mean platelet volume (MPV) is an indicator of platelet (Plt) function and activation. The purpose of this study is to demonstrate whether MPV and MPV/Plt ratio, indicators of Plt activation, are increased in migraine patients, compared to tension-type headache (TTH) and healthy control groups, in our large-scale study, and whether these two primary headache types with unknown pathophysiology may be differentiated by using MPV and MPV/Plt ratio.

Materials and methods: Eighty patients diagnosed with migraine as per the 2004 diagnosis criteria of the International Headache Society (IHS), 80 patients with TTH who have applied to the Neurology Clinic of our hospital, and 80 healthy subjects who have applied to the Family Practice Clinic and Blood Bank were enrolled in this study. MPV and MPV/Plt ratio in both patients of similar age and gender who were diagnosed with migraine as well as in the TTH group and healthy control group were compared.

Findings: The MPV/Plt ratio was 0.046 ± 0.008 in migraine patients, 0.037 ± 0.009 in patients with TTH, and 0.036 ± 0.009 in the healthy control group. This difference was statistically significant ($p < 0.05$). The cutoff value of MPV/Plt ratio for differentiating migraine and TTH was 0.037. The sensitivity of this value was 92.5%, while specificity was 55%.

Conclusion: We have demonstrated that the most commonly confused primary headache types may be differentiated by using MPV and MPV/Plt ratio, and therefore, the disability caused by migraine and unsuitable, unnecessary, and long-term drug therapies may be avoided in patients.

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Keywords:

migraine, tension-type headache, mean platelet volume, platelet activation

Introduction

Since ancient times, one of the most common physical complaints of mankind are headaches [1]. Having various forms, headaches affect a large part of the population and lower the quality of life by causing discomfort, limits in professional life, and problems in daily relations [2, 3]. The International Headache Society (IHS) determined the diagnosis criteria by splitting headaches into two groups, namely, primary and secondary headaches. More than 90% of headaches are primary, and most of those consist of migraines and tension-type headaches (TTHs) [4, 5]. Although observed commonly, their pathophysiology is still not known completely [6].

Mean platelet volume (MPV) is a laboratory marker used commonly for measuring platelet (Plt) activation [7]. Large Plts have a more active and thrombogenic potential, compared to small ones, metabolically and enzymatically [8]. Some defects in the Plt functions of migraine patients have been studied. In studies, Plt activation and aggregation in migraine patients due to secondary changes that possibly arose during attacks are suggested to be associated with migraine. Moreover, it has been emphasized that Plt clots may induce cortical spreading depression with ischemia and inflammation as a result of blockage of small veins and may result in aura-like symptoms and pulsating headache [9, 10]. TTH is a disease that is most commonly confused with migraines since its diagnosis is difficult, and it has a prevalence varying between 5.1% and 78% [11]. Myofascial mechanisms occupy a significant space in the pathophysiology of TTH [12].

Migraine and TTH share common epidemiological and clinical characteristics in daily practice, and clinicians have trouble in the differentiation of these primary headache types [13]. Patients with episodic TTH generally have common migraine without aura. The diagnosis is important for primary headaches that cause a serious disability in society and have different treatments relative to each other. For this reason, accurate diagnosis and treatment are required for recurring headaches that negatively affect people and their families.

The purpose of our large-scale study is to determine whether episodic migraine patients and episodic TTH patients can be differentiated using increased MPV and MPV/Plt ratio, an indicator of Plt activation.

Materials and methods

The study was performed in accordance with the Declaration of Helsinki. Eighty patients with migraine-type headache, 80 patients with episodic TTH (who had applied to the Neurology Clinic of our hospital and diagnosed according to IHS criteria), and a control group consisting of 80 healthy subjects in a similar age and education level as these patients were included in this study. The control group was chosen from among the people who had applied to the Family Practice Clinic and Blood Bank, did not have any systemic disease, and did not smoke or drink alcohol. The permission of the local ethics committee was obtained for the study. Age, gender, occupation, starting age for headaches, frequency of attacks, attack period, and

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the medicines used were recorded for all patients. Aura or non-aura migraines were recorded for the migraine group.

Patients with a chronic disease (hypertension, diabetes, chronic liver/kidney/pulmonary disease, severe anemia, hematologic disease, and so on), chronic migraine and chronic TTH patients, patients receiving prophylactic treatment, patients with ischemic risk factors, patients with an acute or chronic infectious condition, patients using antibiotics, patients with intracranial space-occupying lesions, patients with malignancy, patients with a history of pregnancy, and patients who had received treatment in the past year for anemia or polycythemia were excluded from the study. None of the patients had a history of surgery in the past 6 months. Furthermore, patients who drank alcohol and smoked, received anticoagulant and anti-inflammatory treatment, used systemic corticosteroids, and had systemic inflammatory disease were excluded from the study.

The severity of pain was assessed with the visual analog scale (VAS). For using VAS, patients are asked to rate the severity of their headaches on a 10 cm scale varying from zero (no pain) to 10 (the worst pain imaginable).

Plt measurement

For the study, blood samples were taken from arm veins in tubes containing ethylenediamine tetraacetic acid (EDTA) and stored at room temperature. Samples were studied within 2 hours. The Plt number was observed using a Siemens automated blood counter.

Statistical method

Statistical analyses were performed with IBM SPSS for Windows, Version 22.0. Numeric variables are summarized as mean ± standard deviation. Categorical variables are shown as numbers and percentages. Differences between groups with regard to categorical changes were studied with the chi-square test. Normality of numeric variables was examined using the Kolmogorov-Smirnov test, and the homogeneity of the variances was examined with the Levene test. Differences between groups with regard to numeric variables were examined using a t-test in separate groups. More than two independent intergroup differences were examined with one-way analysis of variance for numeric variables. If differences were determined, two-way comparisons were performed with Tukey's

honest significant difference test. The relation between numeric variables is presented with Spearman's correlation coefficient. The intercept for MPV, Plt, and MPV/Plt ratio differentiating migraine and TTH groups was determined using receiver operating characteristic (ROC) curve analysis. The sensitivity and selectivity values for the best intercept are presented. Area under the ROC curve was calculated. The level of significance was taken as *P* < 0.05.

Findings

Eighty migraine patients, 80 TTH patients, and 80 healthy subjects are enrolled in the study. The average age of the migraine patients was 33.0 ± 7.9, and 57 were female (71.3%), while 23 were male (28.7%). There was no statistical difference with regard to age and gender between patients and healthy control groups (*P* < 0.05).

The average headache period for migraine patients was 4.4 ± 2.9 year, and the average starting age for headaches was 28.7 ± 6.4 years. Moreover, the average headache period for TTH patients was 5.3 ± 3.1 year. They experienced 6.1 ± 2.6 days of headache monthly on average, and this pain lasted for 20.6 ± 8.5 hours on average. The average VAS score for the migraine patients was 7.9 ± 0.9, and it was higher than that in TTH by a statistically significant level (*P* < 0.05).

The MPV was 10.84 ± 0.66 in migraine patients, 10.16 ± 0.59 in the TTH group, and 9.99 ± 0.69 in the healthy control group. When MPV, Plt number, and MPV/Plt ratio were compared between patient and healthy control groups, the migraine group was determined to be statistically different (*P* < 0.05). There was no statistical difference between TTH and control groups (Tab. I). The MPV/Plt ratio was 0.046 ± 0.008 in migraine patients, 0.037 ± 0.009 in patients with TTH, and 0.036 ± 0.009 in the healthy control group (Fig. 1). The cutoff value of MPV/Plt ratio for differentiating migraine and TTH was 0.037. The sensitivity of this value was 92.5%, while specificity was 55% (Tab. II).

While 65 of the migraine patients (81.25%) had migraine without aura, 15 (18.75%) patients had migraine with aura. When MPV and MPV/Plt ratio were compared among patients who suffered from migraine with or without aura, there was no statistically significant difference (*P* > 0.05). MPV and Plt number were correlated with the headache period, starting age for headache, headache frequency, and severity of pain in the migraine patient group, and there was no statistically significant correlation (Tab. III).

Table I. Mean platelet volume (MPV), platelet (Plt) number, and MPV/Plt ratio in migraine, tension-type headache (TTH), and healthy control groups

	Migraine (n = 80)	TTH (n = 80)	Healthy control (n = 80)	P
MPV	1084 ± 066	1016 ± 059	999 ± 069	< 0.001*
Plt number	2457 ± 513	2885 ± 671	2864 ± 534	< 0.001*
MPV/Plt ratio	0046 ± 0008	0037 ± 0009	0036 ± 0009	< 0.001*

Table II. Values differentiating migraine and tension-type headache groups

	Cutoff	Sensitivity	Specificity	AUC	P
MPV	>10.6	0.60	0.80	0.773	< 0.001*
Platelet (Plt) number	< 237	0.65	0.75	0.718	< 0.001*
MPV/Plt ratio	> 0.037	0.925	0.55	0.783	< 0.001*

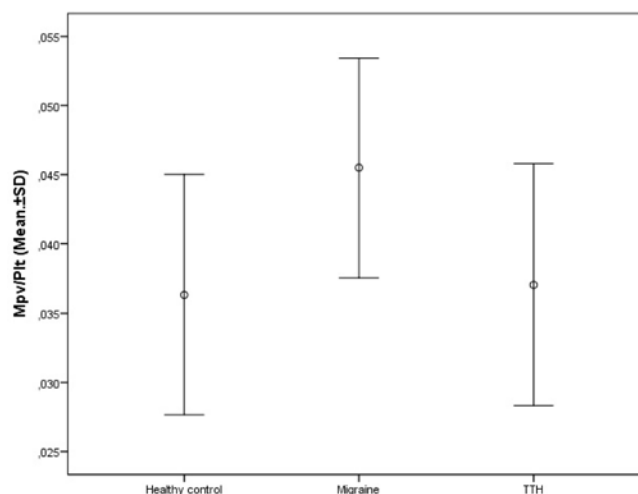


Fig. 1. Average mean platelet volume (MPV)/platelet (Plt) ratios for migraine, tension-type headache, and healthy control groups

Table III. Correlations in the migraine patient group

	Mean platelet volume (MPV)		Platelet (Plt) number		MPV/Plt ratio	
	Correlation coefficient	P	Correlation coefficient	P	Correlation coefficient	P
Headache period, year	0.078	0.490	0.146	0.196	-0.076	0.501
Starting age for headache, year	0.032	0.781	-0.164	0.147	0.137	0.225
Days of headache in a month, day	0.403	< 0.001	-0.089	0.431	0.205	0.068
Visual analog scale score, n	0.215	0.056	-0.021	0.852	0.077	0.498

Discussion

In this study, MPV and MPV/Plt ratio in migraine patients were compared with the MPV in TTH patients and normal population. According to the results obtained from the study, MPV in migraine patients was higher compared to the TTH patients and normal population, and this difference was statistically significant. The MPV/Plt ratio cutoff value for differentiating migraine and TTH was determined to be 0.037, and the sensitivity was 92.5% and specificity was 55% for this value.

Primary headaches comprise a health problem that causes the loss of capacity and performance. For this reason, accurate diagnosis and administration of suitable treatment is important. Since the diagnosis of migraine and other primary headaches depends only on the medical history obtained from the patient, clinicians have a hard time and, sometimes, they may apply the wrong treatment. TTH is the most common headache around the world; however, different prevalence values were determined in different studies. The IHS has determined the diagnosis criteria for patients suffering from TTH. However, TTH is the most common headache type that is confused with migraine without aura despite those criteria [14, 15]. Different biomarkers are used to differentiate TTH and migraine [16]. We suggest that MPV, a method that has not been used before, can be used in the differential diagnosis in order to differentiate the most commonly observed primary headache types. In our study, MPV and MPV/Plt ratio were higher in a statistically significant manner in the migraine group compared to the TTH group.

The deterioration in Plt functions has been suggested in previous studies in migraine pathophysiology [7, 17]. MPV is a sign of Plt

activation, which has an important role in the pathophysiology of the atherothrombotic process. There are numerous studies demonstrating the occurrence of increased MPV in migraine patients. Large Plts contain denser molecules than small Plts, and they have more Plt potential as they are enzymatic and metabolically more active. There are more prothrombotic components in large Plts, such as thromboxane A₂, collagen, and adenosine diphosphate (ADP). While MPV increases, Plt number tends to decrease. The reason may be increases in the production of Plts with increased aggregability from the bone marrow or increased Plt consumption [18, 19]. Zeller et al. reported increased Plt activation and leukocyte-Plt aggregation, determined by measuring P-selectin expression in the Plts of patients suffering from migraine without aura during the attack-free period compared to healthy controls [19]. In another study, Varol et al. determined that MPV is elevated in a nonspecific manner in 193 migraine patients compared to healthy controls [20]. However, Paradalier et al. found in their study that MPV and Plt number in migraine patients are not different from those in healthy controls [18]. In our study, we have determined that MPV is elevated to a statistically significant level in the migraine group and that the Plt number is decreased. The aspect of our study that distinguishes it from other studies and increases its value is that MPV and Plt levels have not been investigated for the differential diagnosis of migraine and TTHs before.

Many years ago, it was hypothesized that migraine is a primary Plt dysfunction [21]. It was determined that levels of Plt-activating factor, which has an important role in many inflammatory and thrombotic processes and is the mediator in phospholipid structure, increase during attacks [19]. In a study performed by Hanington et al., it was determined that spontaneous Plt aggregation and Plt adhesion are

higher in the Plts of migraine patients in the headache-free period compared to the same in the healthy control group, and therefore, they suggested that Plt behavior may have a role in recurring migraine attacks and in the start of attacks since it is different in migraine patients relative to that in healthy people [22]. We have determined in our study that MPV and MPV/Plt ratio increase in a statistically significant manner in migraine patients in the period between attacks. We have determined that this increase is independent of the starting age, period, and severity of the disease. Furthermore, this increase was of the same level in migraine patients with or without aura. We think that this also supports the hypothesis that there is a Plt dysfunction in the pathophysiology of migraine.

In the hypothesis suggested for the pathophysiology of TTH, it is indicated that there is pain modulation with nociceptive stimulations from pericranial myofascial tissues causing sensitization at the upper cervical spinal dorsal root trigeminal core level and secondarily the sensitization of the supraspinal structures such as the thalamus or somatosensorial cortex [23]. In the study of Bendtsen et al., performed on TTH patients, in vivo interstitial concentrations of inflammatory mediators and metabolites were determined to be normal [24]. In our study, we determined that MPV and MPV/Plt ratio have similar levels in the healthy population. We have used these ratios in the differential diagnosis of migraine-type headaches, which are often confused with one another.

The limitations of our study are that 1) MPV is a biomarker easily affected by the preanalytical process after sampling, 2) tubes containing EDTA in which the samples are stored may alter Plt type and increase MPV, 3) although the samples are studied within 2 hours after sampling, MPV may change proportionally with time. Consequently, MPV is an important sign of Plt activation, which has an important role in the pathophysiology of the atherothrombotic process. Although MPV correlation has been examined in migraine patients before, its relation in the differentiation of TTH has never been studied. We have demonstrated that most commonly confused primary headache types may be differentiated by using MPV and MPV/Plt ratio, and therefore, the disability caused by migraine and unsuitable, unnecessary, and long-term drug therapies may be prevented for patients. Our results support our diagnosis.

Declaration of conflicting interests

The author declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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