Original Paper

Mean Platelet Volume, Platelet Distribution Width, and Platelet Count in Varicocele: A Systematic Review and Meta-Analysis

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Key Words

Mean platelet volume • Meta-analysis • Platelet count • Platelet distribution width • Varicocele

Abstract

Background/Aims: The aim of this study was to elucidate the usefulness of platelet indices, mean platelet volume (MPV), platelet distribution width (PDW), and platelet count in diagnosis and monitoring of varicocele. **Methods:** The current study included 525 patients and 379 healthy subjects from five eligible studies. We performed meta-analysis of MPV, PDW, and platelet count and mean differences in these platelet indices between healthy subjects and varicocele patients. **Results:** The pooled MPVs were 8.168 fL (95% confidence interval [CI] 7.589 to 8.747) and 8.801 fL (95% CI 8.028 to 9.574) in healthy subjects and varicocele patients, respectively. The pooled mean difference in MPV between healthy subjects and varicocele patients was 0.834 fL in case-control studies (95% CI 0.195 to 1.473, $P = 0.011$). In both healthy subjects and varicocele patients, low platelet count subgroups showed higher MPV than high platelet count subgroups. The mean difference in MPV was higher in low platelet count subgroup. There was no significant difference in PDW between healthy subjects and varicocele patients. **Conclusion:** Taken together, our data showed that platelet count was significantly lower in varicocele patients than in healthy subjects. Varicocele patients showed significantly higher MPV and lower platelet count than healthy subjects. MPV levels of patients differed according to platelet counts.

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Introduction

The major function of platelets is to contribute to hemostasis as a component of blood. The size of platelets can impact their functions [1, 2]. Mean platelet volume (MPV) can be useful for predicting functional changes and activation of platelets [3-5]. Also, platelet distribution width (PDW) or platelet large cell ratio can be used as a platelet volume index. MPV, PDW, and other complete blood counts can be easily evaluated by routine hematological analyzers [4]. MPV is increased in various cardiovascular diseases, peripheral artery disease, and cerebrovascular disease [5-9]. In contrast, low MPV levels have been shown in some inflammatory diseases, including rheumatoid arthritis and ulcerative colitis [4, 10, 11].

Varicocele is present in about 15% of males and represents the primary cause of male infertility in 35% of cases [12, 13]. Moreover, varicocele is one of the surgically correctable causes of male infertility [14]. Varicocele is a mass of dilated tortuous veins of the pampiniform venous plexus of the spermatic cord. Incompetent valves of the left internal spermatic vein are involved in the pathogenesis of varicocele and can lead poor drainage and progressive dilatation and elongation. Thus, varicocele induces hypoxia of the testicular tissues by the destruction of the one way valves in the internal spermatic veins. In addition, previous studies have reported that systemic vascular viscosity was correlated with varicocele [15, 16]. Microscopic examination of varicocele shows vascular wall thickening, segmental obliteration, medial hypertrophy of longitudinal smooth muscle fibers, fragmentation of the internal elastic lamina, and occasional occlusive thrombi [17]. Vascular change and platelet indices might be useful for detection or screening of subclinical varicocele.

In the present meta-analysis, we investigated MPV, PDW, and platelet count in varicocele patients and healthy subjects in eligible studies. In addition, a systematic review and meta-analysis, including subgroup analysis based on platelet count, was performed to elucidate mean values and mean differences in MPV, PDW, and platelet count between varicocele patients and healthy subjects.

Materials and Methods

Published study search and selection criteria

Relevant articles were obtained by searching the PubMed and MEDLINE databases through February 29, 2016. The search was performed using the following key words: 'mean platelet volume, platelet distribution width, or platelet count' and 'varicocele'. The titles and abstracts of all returned articles were screened for exclusion. Review articles were also screened to identify additional eligible studies. The search results were then reviewed according to the following inclusion and exclusion criteria: (1) MPV, PDW, or platelet count investigated in human varicocele patients, (2) case reports or non-original articles were excluded, and (3) non-English language publications were excluded.

Data extraction

The following information was collected from the full texts of eligible studies and was verified: first author's name, publication year, study location, number of patients analyzed, mean value and standard deviation of MPV, platelet distribution width, and platelet count. We did not define a minimum number of patients for inclusion in our study. Any disagreements were resolved by consensus.

Statistical analysis

All data were analyzed using the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ, US). We investigated MPV, PDW, and platelet count in healthy subjects and varicocele patients. Meta-analysis was performed on mean values of MPV, PDW, and platelet count and mean differences in MPV, PDW, and platelet count between healthy subjects and pre-treated varicocele patients. A fixed effect meta-analysis estimates a single effect that is assumed to be common to every study, while a random effects meta-analysis estimates the mean of a distribution of effects. Although the present meta-analysis was performed using the fixed and random effect models, the values pooled using a random effect model were utilized for

interpretation. The heterogeneity between studies was assessed using Q and I^2 statistics and calculated P -values. A sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. Subgroup analysis based on platelet count was performed for mean values and mean differences in MPV and PDW. To identify any publication bias, Begg's funnel plot and Egger's test were performed. The results were considered statistically significant at $P < 0.05$.

Results

Selection and characteristics of studies

In the present study, 13 reports were identified in the database search. Of these, 8 reports were excluded due to lack of sufficient information. After applying the inclusion and exclusion criteria, 5 reports were finally selected for inclusion in the meta-analysis (Fig.1 and Table 1) [13, 14, 18-20]. The current study included 10 subsets of 5 eligible studies. Because Camoglio's report was subdivided into subgroups with and without testicular hypertrophy [20], 6 subsets included in patient group. In healthy subject group, 4 subsets were included from four eligible studies. The main characteristics of the eligible studies are shown in Table 1. In eligible studies, platelet count ranged from 219 to 243 ($\times 10^3/\mu\text{L}$) and from 223 to 258 ($\times 10^3/\mu\text{L}$) in varicocele patients and healthy subjects, respectively. PDW ranged from 13.90 fL to 17.41 fL in varicocele patients and healthy subjects, respectively.

Fig. 1. Flow chart of the study search and selection methods.

Table 1. Main characteristics of eligible studies

Study	Location	N	Patients				Healthy subjects			
			MPV (fL)	PDW (fL)	Platelet count ($\times 10^3/\mu\text{L}$)		MPV (fL)	PDW (fL)	Platelet count ($\times 10^3/\mu\text{L}$)	
Bozkurt 2012 [18]	Turkey	60	9.89 $\pm$ 1.58		219		7.97 $\pm$ 0.88		231	
Camoglio 2015 [20]	Italy									
without testicular hypertrophy		47	8.4 $\pm$ 0.9				7.6 $\pm$ 0.9			
with testicular hypertrophy		46	7.6 $\pm$ 0.8							
Coban 2015 [13]	Turkey	57	8.33 $\pm$ 0.99	8.10 $\pm$ 1.09	16.88	242				
Coban 2015 [19]	Turkey	264	8.52 $\pm$ 4.96		17.41	243	220	7.84 $\pm$ 1.03	17.85	258
Mahdavi-Zafarghandi 2014 [14]	Iran	51	10.10 $\pm$ 1.30		13.90	224	50	9.30 $\pm$ 1.10	12.60	223

MPV, Mean platelet volume; N, Number of patients or healthy subjects; PDW, Platelet distribution width

Table 2. Meta-analysis for mean platelet volume, platelet count and platelet distribution width. CI, Confidence interval

	Number of subsets	Number of patients	Fixed effect [95% CI]	Heterogeneity test [P-value]	Random effect [95% CI]	Egger's Test
Mean platelet volume (fL)						
Healthy subjects	4	379	7.981 [7.881, 8.081]	< 0.001	8.168 [7.589, 8.747]	0.418
Varicocele	6	525	8.806 [8.383, 8.629]	< 0.001	8.801 [8.028, 9.574]	0.193
Platelet distribution width (fL)						
Healthy subjects	2	270	17.65 [17.52, 17.78]	1.000	15.24 [10.09, 20.38]	-
Varicocele	3	372	17.08 [16.89, 17.27]	0.001	16.09 [14.28, 17.90]	0.359
Platelet count ($\times 10^3/\mu\text{L}$)						
Healthy subjects	3	327	247.4 [240.8, 254.1]	< 0.001	238.1 [213.6, 262.5]	0.703
Varicocele	4	432	233.7 [229.4, 238.0]	< 0.001	231.9 [218.0, 245.7]	0.662

Table 3. Subgroup analysis based on platelet count for mean platelet volume between healthy subjects and varicocele patients. CI, Confidence interval; PLT, Platelet

	Number of studies	Number of patients	Fixed effect [95% CI]	Heterogeneity test [P-value]	Random effect [95% CI]	Egger's Test
Mean platelet volume						
Healthy subjects	3	327	8.057 [7.984, 8.166]	< 0.001	8.359 [7.603, 9.116]	0.352
Low PLT count ($< 233 \times 10^3/\mu\text{L}$)	2	107	8.448 [8.265, 8.631]	< 0.001	8.631 [7.328, 9.934]	-
High PLT count ($\geq 233 \times 10^3/\mu\text{L}$)	1	220	7.840 [7.704, 7.976]	1.000	7.840 [7.704, 7.976]	-
Varicocele patients	4	432	9.085 [8.908, 9.262]	< 0.001	9.215 [8.227, 10.203]	0.627
Low PLT count ($< 233 \times 10^3/\mu\text{L}$)	2	111	10.007 [9.741, 10.273]	0.442	10.007 [9.741, 10.273]	-
High PLT count ($\geq 233 \times 10^3/\mu\text{L}$)	2	321	8.360 [8.123, 8.596]	0.567	8.360 [8.123, 8.596]	-

Mean values of MPV, PDW, and platelet count

To evaluate the mean values of platelet indices in varicocele patients, we performed meta-analysis of MPV, PDW, and platelet count in healthy subjects and varicocele patients. The pooled MPV was higher in varicocele patients than in healthy subjects (8.801 fL, 95% CI 8.028 to 9.574 vs. 8.168 fL, 95% CI 7.589 to 8.747, Table 2). In sensitivity analysis, eligible studies had no effect on the pooled MPVs in healthy subjects (range: 7.812 to 8.359) or varicocele patients (range: 8.536 to 9.048). There was no significant publication bias according to Egger's test ($P = 0.418$ and $P = 0.193$, respectively) and Begg's funnel plots of healthy subjects and varicocele patients. The pooled PDW was 15.24 fL (95% CI 10.09 to 20.38) and 16.09 fL (95% CI 14.28 to 17.90) in healthy subjects and varicocele patients, respectively. In addition, the pooled platelet counts of healthy subjects and varicocele patients were $238.1 \times 10^3/\mu\text{L}$ (95% CI 213.6 to 262.5) and $231.9 \times 10^3/\mu\text{L}$ (95% CI 218.0 to 245.7), respectively.

Subgroup analysis

To elucidate the impact of platelet count on MPV, subgroup analysis was performed based on platelet count. For subgroup analysis, the criterion dividing groups into high and low platelet count subgroups was determined as the median value of platelet counts of

Table 4. Mean difference of mean platelet volume, platelet count and platelet distribution width between healthy subjects and varicocele patients. CI, Confidence interval; PLT, Platelet

	Mean difference between varicocele patients and healthy subjects			
	Fixed effect [95% CI]	Heterogeneity test [P-value]	Random effect [95% CI]	Egger's Test
Mean platelet volume (fL)	0.725 [0.536, 0.914]	< 0.001	0.834 [0.195, 1.473]	0.467
Low PLT count ($< 233 \times 10^3/\mu\text{L}$)	1.364 [1.033, 1.695]	0.001	1.360 [0.263, 2.458]	-
High PLT count ($\geq 233 \times 10^3/\mu\text{L}$)	0.680 [0.013, 1.347]	1.000	0.680 [0.013, 1.347]	-
Platelet distribution width (fL)	-0.32 [-0.57, -0.07]	0.001	0.37 [-1.33, 2.07]	-
Low PLT count ($< 233 \times 10^3/\mu\text{L}$)	1.30 [0.34, 2.26]	1.000	1.30 [0.34, 2.26]	-
High PLT count ($\geq 233 \times 10^3/\mu\text{L}$)	-0.44 [-0.70, -0.18]	1.000	-0.44 [-0.70, -0.18]	-
Platelet count ($\times 10^3/\mu\text{L}$)	-11.99 [-20.14, -3.84]	0.375	-11.99 [-20.14, -3.84]	0.479

patients ($233 \times 10^3/\mu\text{L}$). In both healthy subjects and varicocele patients, the pooled MPVs were higher in low platelet count subgroups than in high platelet count subgroups. The pooled MPV of healthy subjects was 8.631 fL (95% CI 7.328 to 9.934) and 7.840 fL (95% CI 7.704 to 7.946) in low and high platelet count subgroups, respectively. In varicocele patients, the pooled MPV was 10.007 fL (95% CI 9.741 to 10.273) and 8.360 fL (95% CI 8.123 to 8.596) in low and high platelet count subgroups, respectively (Table 3).

Mean differences in MPV, PDW, and platelet count

Next, we performed meta-analysis of mean differences in MPV, PDW, and platelet count between varicocele patients and healthy subjects. The pooled mean difference in MPV was 0.834 (95% CI 0.195 to 1.473, $P = 0.011$) in the random effect models (Table 4). The mean difference in MPV was higher in low platelet count subgroups than in high platelet count subgroups (1.360, 95% CI 0.263 to 2.458, $P = 0.015$ vs. 0.680, 95% CI 0.013 to 1.347, $P = 0.046$, respectively). The pooled mean differences in PDW and platelet count were 0.37 (95% CI -1.33 to 2.07, $P = 0.673$) and -11.99 (95% CI -20.14 to -3.84, $P = 0.004$), respectively.

Discussion

It is known that increased pressure in the pampiniform venous plexus and venous drainage are involved in the pathogenesis of varicocele. These occurrences lead to dilatation of the veins of the pampiniform plexus and to subsequent vascular damages. However, the role of platelets in the pathogenesis of varicocele is not fully understood. The current study is the first meta-analysis of published studies on the roles of MPV in varicocele and shows four major findings. First, there was a significant difference in MPV between varicocele patients and healthy subjects. Second, platelet count was significantly lower in varicocele patients than in healthy subjects. Third, there was no significant difference in PDW between varicocele patients and healthy subjects. Fourth, varicocele patients with low platelet count showed higher MPV level than patients with high platelet count.

Although the pathogenesis of varicocele has not been fully elucidated, various vascular changes, including vascular wall thickening, segmental obliteration, fragmentation of the internal elastic lamina, and occasional occlusive thrombi, have been microscopically identified [17]. In addition, a systemic vascular varicosity has been positively correlated

with varicocele [15, 16]. Changes in platelet function, induced by vascular damage, could be associated with varicocele. MPV reflects functional changes and activation of platelets according to average platelet size [3-5]. Although platelet aggregation could be a specific test for platelet function [21, 22], the diagnostic roles of platelet indices, such as MPV and PDW, have been recently introduced in various disease including varicocele. Nevertheless, the correlations between pathogenesis of varicocele and platelet indices have not yet been fully elucidated, and MPV could be useful for diagnosis or monitoring of varicocele.

Varicoceles are most frequently diagnosed before 30 years of age and occur in 15-20% of all males. Although varicocele is basically diagnosed through physical examination and/or color Doppler ultrasonography, little is known regarding the pre-operative and post-operative monitoring hematologic modalities for diagnosis and monitoring of varicocele patients, including subclinical status. Platelet indices have the common advantage that they can be routinely evaluated using hematological analyzers. Among these indices, high MPV has been identified in various benign diseases and malignant tumors. In the present meta-analysis, MPV of varicocele patients was significantly higher than that in healthy subjects (mean difference 0.834, 95% CI 0.195 to 1.473). In addition, MPV has been shown to be increased by varicocele grading [18] and decreased by surgery [13]. Consequently, MPV might be a candidate for diagnosis or monitoring of varicocele in daily practice. In our data, the ranges of MPV in varicocele patients and healthy subjects were 7.60 to 10.10 fL and 7.60 to 9.30 fL, respectively. Because these values overlapped and the included studies were evaluated in limited geographic areas, the interpretation of MPV level in varicocele patients is limited. The possible causes for overlapped MPV values might be associated with study location, race, age, patient condition, and so on. Thus, meta-analysis of the mean differences in MPV between varicocele patients and healthy subjects is required. In addition, subgroup analysis based on various factors, including patient age, could be helpful for understanding the MPV levels of varicocele patients.

Little is known as to whether platelet count affects MPV and PDW in varicocele patients. Patients with varicocele showed significantly lower platelet count and higher MPV than healthy subjects. Interestingly, varicocele patients with high platelet count showed lower MPV level than healthy subjects with high platelet count (Table 3). However, the mean differences in MPV between varicocele patients and healthy subjects were 1.360 (95% CI 0.263 to 2.458, $P = 0.015$) and 0.680 (95% CI 0.013 to 1.347, $P = 0.046$) in low and high platelet count subgroups, respectively. Our data showed that MPV in varicocele patients was significantly higher than that in healthy subjects, regardless of platelet count. Calculating of MPV/platelet count ratio would be useful for interpretation of the impact on MPV. However, the current study could not perform the test for MPV/platelet count ratio due to insufficient information. There was no difference in PDW between varicocele patients and healthy subjects; however, subgroups with low platelet count showed significantly higher PDW than high platelet count subgroups. For application of MPV or PDW in varicocele, platelet count of patients should be considered, and more detailed information is needed.

There are a number of limitations in the current study. First, Coban et al. have reported that MPV was significantly decreased after surgery [13]. The present study could not analyze the correlation between post-operative and pre-operative patients and healthy subjects due to insufficient information in the original studies. Second, in subgroup analysis based on platelet count, MPV was higher in low platelet count subgroups than in high platelet count subgroups. However, we could not explain the correlation between platelet count and MPV in the current study. Third, as described above, high MPV level is identified in various diseases, including vascular disorders. Although MPV increases in varicocele and positively correlates with varicocele grade, there may be a limitation to its application in screening of varicocele in the general population. Fourth, Demirin et al. have reported an MPV value of 8.9 ± 1.4 fL (95% CI 7.2 to 11.7) in 326 healthy subjects [23]. In our meta-analysis, the pooled MPV of male samples was 8.359 fL (95% CI 7.603 to 9.116). In our unpublished data, the pooled MPV of overall healthy subjects and female samples was 8.428 fL (95% CI 8.118 to 8.738) and 8.674 (95% CI 8.076 to 9.273), respectively. In addition, the normal range of MPV in

males should first be elucidated in order to evaluate the usefulness of MPV as a monitoring or diagnostic parameter.

In conclusion, our results showed that MPV was significantly higher in varicocele patients than in healthy subjects. Moreover, low platelet count was associated with high MPV level. Further cumulative studies of varicocele will be required before application of MPV in diagnosis or monitoring.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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