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The Association Between Mean Platelet Volume, Platelet Distribution Width, Platelet Count and Varicocele

Ortalama Trombosit Hacmi, Trombosit Dağılım Genişliği ve Trombosit Sayısının Varikosel ile İlişkisi

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ABSTRACT Objective: The relationship between the increase in the mean platelet volume, which is the determinant of platelet activation, and vascular pathologies is known. Therefore, in order to elucidate varicocele etiopathogenesis, we aimed to examine whether there is an any connection among MPV and varicocele. **Material and Methods:** 348 patients who underwent unilateral varicocelectomy in our clinic between 2013 and 2019 were prospectively comprised in the study. Patient's age, MPV in complete blood count, platelet distribution width (PDW), platelet count (PC) and mean varicose vein diameters were recorded. These parameters were compared between patient groups (Group 1 is level 1 varicocele patients; Group 2 is level 2 varicocele patients and Group 3 is level 3 varicocele patients), which were divided according to the varicocele grades determined by scrotal Doppler USG and it was checked whether there was a difference between the groups. **Results:** Mean age of the patients was 27.6±7.1 years. While 44 of 348 patients had varicocele was right-sided, the remaining 304 patients had left-sided varicocele. Varicocele was Grade 3 in 71 (20.5%) patients, Grade 2 in 239 (68.7%) and Grade 1 in the remaining 38 (10.9%). The mean VVD (mm) value for all groups was 4.2±1.2. There was no significant difference between the groups in terms of age and TS (p=0.056 and p=0.071, respectively). There was a statistically significant difference between three groups in terms of PDW and MPV values (p=0.025 and p=0.018, respectively). Group 3 was significantly higher for both parameters than Group 1. According to the spearman correlation coefficient calculated by using VVD and PC, PDW, and MPV parameters, it was found that the VVD showed a significant positive correlation with PDW and MPV (r=0.190, p=0.002 and r=0.201, p=0.001 respectively). **Conclusion:** Based on the importance of the vascular component in the pathophysiology of varicocele, it should be emphasized that it supports the hypothesis that varicocele may be a component of systemic venous anomalies.

Keywords: Mean platelet volume; varicocele

ÖZET Amaç: Trombosit aktivasyonunun belirleyicisi olan ortalama trombosit hacmindeki (OTH) artışın vasküler patolojilerle olan ilişkisi bilinmektedir. Bu nedenle de varikoselin etiyopatogenezini aydınlatmak için OTH ve varikosel arasında bir ilişki olup olmadığını incelemeyi amaçladık. **Gereç ve Yöntemler:** 2013-2019 Ocak ayları arasında kliniğimizde tek taraflı varikoselektomi operasyonu yapılan 348 hasta prospektif olarak çalışmaya dâhil edildi. Hastaların yaşı, tam kan sayımındaki OTH, trombosit dağılım genişliği (TDG), trombosit sayısı (TS) ve ortalama varikoz ven çapları (VVÇ) kayıt edildi. Bu parametreler, skrotal Doppler ultrasonografi (USG) ile belirlenen varikosel derecelerine göre ayrılan hasta grupları (Grup 1, derece 1 varikosel; Grup 2, derece 2 varikoseli ve Grup 3, derece 3 varikosel) arasında karşılaştırıldı ve gruplar arasında bir fark olup olmadığına bakıldı. **Bulgular:** Ortalama hasta yaşı 27,6±7,1 yıl idi. 348 hastanın 44'ünde varikosel sağ taraflı iken kalan 304 hastada varikosel sol taraflı idi. Hastaların 71'inde (%20,5) varikosel derece 3 iken, 239'unda (%68,7) derece 2 ve kalan 38'inde (%10,9) derece 1 idi. Tüm gruplar için VVÇ (mm) ortalama değeri 4,2±1,2 idi. Gruplar arasında yaş ve TS açısından anlamlı bir fark yoktu (sırasıyla; p=0,056 ve p=0,071). Gruplar arasında TDG ve OTH değerleri açısından yapılan incelemede istatistiksel anlamlı farklılık saptandı (sırasıyla, p=0,025 ve p=0,018). Her iki parametre için de Grup 3, Grup 1'e göre anlamlı olarak yüksek izlendi. VVÇ ile TS, TDG ve OTH arasında yapılan spearman korelasyon katsayısına göre VVÇ'nin TDG ve OTH ile anlamlı düzeyde pozitif korelasyon gösterdiği saptandı (sırasıyla r=0,190, p=0,002 ve r=0,201, p=0,001). **Sonuç:** Varikoselin patofizyolojisinde vasküler bileşenin önemine dayanarak vurgulanmalıdır ki çıkan sonuç; varikoselin sistemik venöz anomalilerin bir bileşeni olabileceği hipotezini desteklemektedir.

Anahtar Kelimeler: Ortalama trombosit hacmi; varikosel

Varicocele appears to be the top ranked cause in infertile men. It is defined as enlargement and / or reflux in testicular venous vessels arising from different causes.[1] Varicocele is an andrological disorder that can delay the growth and development of the same-sided testicle, cause pain and discomfort, cause

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infertility and hypogonadism in men, and is frequently encountered in clinical practice. Varicocele diagnosis should be made by performing a physical examination and should be supported with scrotal Doppler ultrasound (USG).[2] Varicocele, which is an anatomical defect with pathophysiological results, is seen in 11.7% of adult men, while it is seen in 25.4% of patients whose semen analysis is impaired.[3] Inadequate venous valves that play a role in varicocele pathogenesis may cause insufficient blood flow, vasodilation and elongation. The varicocele thus reduces oxygenation of the testicular tissue through inadequate venous valves. Past-time studies in the literature show that varicocele also correlates with increased systemic intravascular viscosity.[4,5]

The most important task of platelets as a blood component is to contribute to hemostasis. It is well known that size of a platelet can influence its function.[6,7] Therefore, we can say that the mean platelet volume (MPV) can be used as a useful marker to guess platelet activation and changes in its function.[8-10] MPV, which is an index of platelet function, may show an increase in vascular pathologies such as acute coronary artery syndrome and stroke.[11-13]

There is a powerful relationship between increase in MPV and vascular pathologies. We also know that peripheral varicose veins may appear as a component of a systemic venous disease. These knowledges suggest that there may be a common mechanism for diseases related to vascular pathology. As a result, the question as to whether there can be a relationship between MPV and varicose veins arises in the minds. Therefore, in order to elucidate varicocele etiopathogenesis, we aimed to examine whether there is any connection between MPV and varicocele.

MATERIAL AND METHODS

A total of 348 patients who underwent unilateral varicocelectomy in our clinic between 2013 and January 2019 were prospectively examined and comprised in the study. A detailed history was gotten from all patients. All patients underwent careful and detailed physical examination. Routine biochemical tests were applied to the patients before surgery. All patients underwent scrotal Doppler USG. Patients with chronic diseases such as hypertension, diabetus mellitus, chronic heart disease, chronic lung ilnesses and systemic vascular ilnesses were casted out of study. Patients who had undergone scrotal, testicular or inguinal surgery, and patients with orchitis, epidimitis, undescended testicle, testicular mass or testicular atrophy were not included in the study. Kartal Dr. Lütfi Kırdar Training and Research Hospital Clinical Research Ethics Committee endorsed the study (date: 15/04/2020, number of IRB: 514/175/4) and current work was conducted according to the Declaration of Helsinki.

Varicocele grading of the patients according to the scrotal Doppler USG result was done as developed by Mihmanli.[14] Accordingly: First degree varicocele was defined as “very light dilation (vein diameter: 2-3 mm)”, second degree varicocele was defined as “moderate dilation (vein diameter: 3-5 mm)”, third degree varicocele was defined as “advanced dilation (vein diameter>5 mm)” or “reflux lasting longer than one second during valsalva regardless of vein diameter”.

Platelet count (PC), platelet distribution width (PDW) and MPV in patient’s complete blood count, age and mean varicose vein diameters (VVD) were recorded. These parameters were compared between patient groups (those with Group 1: level 1 varicocele, those with Group 2: level 2 varicocele, those with Group 3: level 3 varicocele), which were divided according to the varicocele grades determined by scrotal Doppler USG. It was also noted that the varicocele was right or left sided.

The data were analyzed using SPSS for Windows version 19.0. Whether the variables consort the normal distribution was investigated with the one-sample Kolmogorov-Smirnov test. The descriptive statistics of the data are presented as, if the variables are normally distributed, mean ± standard deviation; if not, the median with minimum-maximum. Whereas qualitative data were presented in numbers and percentages. When there were more than two independent groups, they were compared by ANOVA or Kruskal Wallis test, depending on the distributions of continuous data. When an important distinction was

TABLE 1: Comparison of the groups in terms of parameters examined.

	Group 1 (n=38)	**Group 2** (n=239)	**Group 3** (n=71)	
		Mean±SD / Median (Min-Max)		**p**[1]
Age (years)	29.4±6.7	27.9±6.8	25.8±5,6	**0,056**
PC (k/mm^3)	214 (46-266)	238 (82-374)	214 (82-398)	**0.071**
PDW (fl)	11.8 (10-17.6)	12.4 (9.7-19.9)	13.2 (10.1-22.2)	**0.025** (Group 1 vs Group 3) p[2]=0.014
MPV (fl)	10.1 (8.7-12.3)	10.2 (8.7-13.4)	10.5 (9.2-13.4)	**0.018** (Group 1 vs Group 3) p[2]=0.007

PC: Platelet count; PDW: Platelet distribution width; MPV: Mean platelet volume.
p[1] < 0.05 : Statistically significant difference
p[2] <0.05/3 : Statistically significant difference (Bonferroni correction)

observed, Mann-Whitney U test was used to understand among which two groups this significant difference was. Normally, p<0.05 was accepted as the boundary level for statistical significance. However, Bonferroni correction was made for the Mann-Whitney U test performed in the second stage and p<0.05/3=0.017 was accepted as the significant threshold value. Spearman's correlation coefficient was performed to measure the strength and direction of monotonic association between the variables.

RESULTS

The mean patient age was 27.6±7.1 years. While 44 of 348 patients had right-sided, the remaining 304 patients had left-sided varicocele. Varicocele grade was 3 in 71 (20.5%) patients, Grade 2 in 239 (68.7%) and Grade 1 in the remaining 38 (10.9%). The mean VVD (mm) value for all groups was 4.2±1.2.

There wasn't any important distinction among the groups according to age and mean PC (p=0.056 and p=0.071, respectively). There was a statistically significant distinction in PDW and MPV values among the groups (p=0.025 and p=0.018, respectively). Group 3 was significantly higher than Group 1 for both parameters. Comparisons of the parameters examined are summarized in Table 1. According to the Spearman correlation coefficient calculated by using VVD and PC, PDW, MPV parameters; it was found that VVD indicate a positive correlation with PDW and MPV (p=0.002 and p=0.001, respectively) (Table 2).

TABLE 2: The correlation between VVD and PC, PDW, MPV (Spearman).

	PC		PDW		MPV	
VVD	r	p	r	p	r	p
	0.032	0.609	0.190*	0.002	0.201*	0.001

VVD: Venous vein diameter; PC: Platelet count; PDW: Platelet distribution width; MPV: Mean platelet volume.
r : Correlation coefficient
* : The correlation is significant

DISCUSSION

It is a known fact that high pressure in the testicular venous system plays a key role in the formation of varicocele. This increased pressure leads to the expansion of the testicular venous system and subsequently venous damage. But, the extent to which platelets play a role in the formation of varicocele has not yet been fully clarified. Although varicocele pathogenesis also has not yet been fully clarified too, some vascular changes have been described microscopically by pathologists.[15] In addition, systemic vascular varices showed positive correlation with varicocele.[9,10] Changes in thrombocyte function that occur as a result of vascular damage may be related to varicocele. MPV shows functional differences in thrombocytes and platelet excitation due to changes in thrombocyte size.[8-10] Although the thrombocyte aggregation test is a test specifically used to detect thrombocyte dysfunctions, it has recently been found suitable to use thrombocyte indices such as MPV and PDW in various diseases, including varicocele.[16,17] However, the

correlation between varicocele formation and platelet indices has not yet been fully clarified, but it can be said that MPV may be useful in the diagnosis or monitoring of varicocele. Indeed, it is known that there is a correlation between the increase in thrombocyte activity and vascular disorders. We know that most of the mediators needed for coagulation, inflammation, thrombosis and atherosclerosis are secreted or expressed by thrombocytes.[18,19] In addition, PC and MPV are inversely related, and as a result, the total platelet mass remains approximately constant. It should also be noted that larger than normal platelets are metabolically and enzymatically more active and have prothrombotic potential.[20,21]

Physical examination, scrotal Doppler USG, and semen analysis are quite common and should be used when diagnosing varicocele and following surgical treatment. Since platelet indexes are evaluated from the routine full blood count, it can be said easily that they have the advantage of being easily studied and learned. Elevated MPV has been detected in many good natured ilnesses or carcinomas. In a meta-analysis published in 2016, MPV was found to be significantly higher in varicocele patients compared to healthy subjects (mean difference 0.834, 95% CI 0.195 to 1.473).[22] In this meta-analysis, there wasn't any distinction in PDW among varicocele patients and healthy subjects; but, in the subgroup analysis comparing low and high platelet numbers, PDW value was found to be significantly higher in the group with low PC. For MPV or PDW evaluation in varicocele, it was suggested to consider the platelet count of patients. In our study, both MPV and PDW were found to have a positive correlation with varicocele grade. In addition, it has been shown that MPV increases with increasing varicocele grade and decreases with surgery.[23,24] As a result, it can be said that MPV can be useful in diagnosing varicocele or monitoring patients with varicocele in our daily practice.

This study has concluded to support the view that supports the thesis that there may be a positive correlation between MPV and varicocele grade. Because elevated MPV levels are generally accepted as vascular risk factors, the fact that patients with third degree varicocele in our study had a significantly higher MPV compared to those with first degree varicocele reveals the important contribution of thrombocyte excitation in the vascular pathogenesis of varicocele.

The mechanism underlying elevated MPV in varicocele cases has not yet been fully clarified. There is new data in vascular and microvascular dysfunction that support co-activation of platelets with leukocytes and vascular endothelial cells.[25] Not only do platelet adhesion and activation explain the highly elevated rate of formation of thrombosis associated with acute and chronic inflammatory conditions, but also do reveal that in the inflammatory microvasculature, excitation of leukocytes with vascular endothelials is intensified, through contact-dependent and independent mechanisms.[23] In the light of these informations, it can be said that the formation of varicocele may be related to thrombocyte activation and / or vascular endothelial damage. However, it is clear that more studies are needed to clarify this situation.

The most important limitation of this study is that we did not include other determinants of thrombocyte excitation and clustering in our study. It is also obvious that the number of patients should be higher. If our number of patients was higher, we could find a positive correlation between MPV with an increased degree of varicocele between all groups, including patients with second degree varicocele, in our opinion. The fact that we did not examine the MPV values of the patients after the operation is another important deficiency of our study.

CONCLUSION

As a result, we have shown that patients with third degree varicocele have higly elevated MPV values when compared to those with first degree varicocele. It should be emphasized that the conclusion reached on the significance of the vascular component in the pathophysiology of varicocele supports the hypothesis that varicocele may be a part of systemic venous anomalies. However, it should also be highlighted that there is an increased need for controlled trials

with larger patient numbers which will provide more information on that issue.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özgür Yazıcı, Alper Kafkaslı, Utku Can;* ***Design:*** *Özgür Yazıcı;* ***Control/Supervision:*** *Özgür Yazıcı, Alper Kafkaslı;* ***Data Collection and/or Processing:*** *Alper Kafkaslı, Utku Can;* ***Analysis and/or Interpretation:*** *Özgür Yazıcı, Utku Can;* ***Literature Review:*** *Utku Can, Alper Kafkaslı;* ***Writing the Article:*** *Özgür Yazıcı, Alper Kafkaslı, Utku Can;* ***Critical Review:*** *Özgür Yazıcı, Alper Kafkaslı, Utku Can;* ***References and Fundings:*** *Özgür Yazıcı, Alper Kafkaslı, Utku Can;* ***Materials:*** *Özgür Yazıcı, Alper Kafkaslı, Utku Can.*

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