Ischemic priapism: Can eosinophil count and platelet functions be positive predictive factors in etiopathogenesis

Mehmet Giray Sönmez, MD[1]; Cengiz Kara, MD[2]; Adnan Karaibrahimoğlu, PhD[3]; Leyla Öztürk Sönmez, MD[4]; Yunus Emre Göğer, MD[1]; Mehmet Balasar, MD[1]; Hakki Hakan Taşkapu, MD[1]; Mehmet Mesut Pişkin, MD[1]; Ahmet Öztürk, MD[1]; Mehmet Kilinç, MD[1]

[1]Department of Urology, Meram Medical Faculty, Necmettin Erbakan University, Konya; [2]Department of Urology, Medical Park Ankara Hospital, Ankara; [3]Biostatistics Unit, Department of Medical Education and Informatics, Meram Medical Faculty, Necmettin Erbakan University, Konya; [4]Department of Physiology, Selcuklu Medical School, Selcuk University, Konya; Turkey

Cite as: *Can Urol Assoc J* 2017;11(7):E297-301. http://dx.doi.org/10.5489/cuaj.4263
Published online July 11, 2017

Abstract

Introduction: We evaluated the relation between ischemic priapism (IP) and blood count parameters in IP patients. We especially wanted to examine the contribution of eosinophil count (EC), platelet count (PC), and mean platelet volume (MPV) values, which are suspected predictive parameters for vascular endothelium damage and venoocclusive pathogenesis and etiopathogenesis, particularly in IP.

Methods: A total of 40 IP patients fulfilled the study criteria. Forty healthy volunteers in a similar age group were included as the control group. Complete blood count values were compared between the two groups. Intergroup comparisons were performed using the Mann-Whitney U test, and the chi-square test was used to assess the relationship between categorical variables in the patient groups. The area under the curve was calculated by receiver operating characteristic (ROC) regression analyses. Epidemiological diagnosis percentages were calculated by finding cutoff values.

Results: The IP group's high MPV, PC, and EC values compared to those of the control group were detected to be statistically significant ($p<0.001$, $p=0,03$, $p=0.001$, respectively). No statistically significant difference was observed between the two groups for other blood count parameters. Statistically significant values for IP were measured as MPV: positive predictive value: 84%; EC: positive predictive value: 71.4%; and PC: positive predictive value: 61.4%.

Conclusions: High MPV, PC, and EC values are significant positive predictive factors in IP etiopathogenesis. No proof was detected for other blood count parameters playing an active role in IP etiopathogenesis.

Introduction

Priapism is a painful erection condition of the penis or clitoris lasting more than four hours without sexual desire. Glans and corpus spongiosum do not participate in this period.[1]

Although its incidence is rare (0.3–1/100 000), it is more common in males than in females. It is often observed in males aged 20–50.[2,3]

Although the possible causes of priapism differ according to priapism types, it is observed that it is mostly related to idiopathic and iatrogenic causes. Alcohol, medicine, drug use (21%), perineal trauma (12%), and or sickle cell nephropathy (5%) are other possible etiological causes.[3]

Three types of priapism exist: ischemic (venoocclusive, low-flow), non-ischemic (arterial, high-flow), and stuttering (recurrent). The causes and treatment methods of each priapism type are different. Blood gas analysis of the initial corporal aspirate is performed after admission to differentiate the type of priapism. Hypoxia, hypercapnia, and acidosis are usually seen in cavernosal blood gas analyses of ischemic priapism (IP); in non-ischemic priapism, blood gas analysis demonstrates normal arterial oxygen pressure without acidosis and hypoxia.[4]

In IP, no or very low arterial flow is observed in the corpus cavernosum. In non-ischemic priapism, cavernosal arterial flow can be normal, high, or irregular, and arteriosinuzoidal fistule or pseudoneurism may be observed. Shuttering priapism is demonstrated by recurrent and intermittent erections.[1-4]

Due to the frequent use of phospodiesterase enzyme 5 (PDE5) inhibitors in erectile dysfunction (ED) treatment and the use of penile Doppler ultrasonography (PDU) for ED diagnosis, priapism cases have increased recently.

Platelet count (PC) and mean platelet volume (MPV) are significant indicators of platelet function and activation. Thromboembolic event incidence and endothelial damage risk increase with platelet activation. Thus, recently, the connection between vasculogenic diseases and MPV and PC has become more important. The relation between vascular-sourced disorder and platelet activation has been examined in various studies,[5,6] with some claiming that a relationship does in fact exist between eosinophilia and vascular dysfunction. It is known that eosinophils plays an important role in

endothelial dysfunction, vasoconstriction, inflammation, and thrombosis. Eosinophils stimulates thrombocyte activation and aggregation, and make thrombosis formation easier by preventing thrombomodulin.[7-9] Thus, eosinophil count (EC) and PC demonstrating platelet activation and MPV may play a positive role in damages that occur in vascular endothelium and the venoocclusive mechanisms that may cause IP.

We evaluated the relationship between IP and blood count parameters in IP patients. We especially wanted to examine the contribution of EC, PC, and MPV values, which are suspected predictive parameters for vascular endothelium damage and venoocclusive pathogenesis and etiopathogenesis, particularly in IP. To the best of our knowledge, no studies have yet demonstrated the relationship between EC and IP and only one study examined the relationship between platelet activity and priapism,[10] although predictive value and cutoff values were not stated in this study. Ours is the first study examining the relationship between IP and EC-platelet activation and providing predictive and cutoff values.

Methods

A total of 40 IP patients fulfilled the study criteria among the patients referred to Necmettin Erbakan University Meram Medical Faculty Hospital and Medical Park Ankara Hospital between October 2006 and July 2016. Forty healthy volunteers in a similar age group were included as the control group. The values of a total of 80 patients in the study and control groups were examined. Complete blood count values were compared between the two groups. A condition of erection lasting more than four hours without orgasm and ejaculation was defined as priapism. After a detailed history and physical examination, cavernosal blood gas examinations and confirmatory penile Doppler ultrasound were performed.

The laboratory values of the patients (blood sugar, kidney and liver function tests, and complete blood count) were examined. Before intervention in priapism took place, blood samples were taken from the anticubital vein in the first hour after the patient's referral. The blood samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid.

Inclusion criteria

Included in the study were patients who were older than 18 years old; had blood gas values for IP in corporeal aspiration and blood gas analysis (pO_2 <30 mmHg, pCO_2 >60 mmHg, pH <7.25); had low blood flow levels in the cavernosal arteries in PDU or had no blood flow demonstrated; and had their first priapism attack.

Exclusion criteria

Excluded from the study were patients who were younger than 18 years old, as well as those with blood gas values for non-IP in corporeal aspiration and blood gas analysis, normal blood flow levels in the cavernosal arteries in PDU, recurring and previous priapism attacks, histories of pelvic surgery and pelvic trauma, recently diagnosed coronary artery disease (CAD), peripheral vascular disease or hematological disorder, active infectious disease, malignancy, immunological disease or renal or hepatic failure, and those using antiplatelet and anticoagulant medicine.

Statistical analysis

Statistical analysis was performed with SPSS 15.0 for Windows version 15.0 (SPSS Inc., Chicago, IL, U.S.). A power analysis was conducted with definitive measurements acquired by preliminary examination. Intergroup comparisons were performed using the Mann-Whitney U test, and the chi-square test was used to assess the relationship between categorical variables in the patient groups. The area under the curve was calculated by receiver operating characteristic (ROC) regression analyses. Epidemiological diagnosis percentages were calculated by finding the cutoff values. $p<0.05$ was used as a threshold for statistical significance. Data were presented as mean ± standard deviation (SD).

Results

First, power analysis was conducted with the acquired definitive measurements to determine the size of the ideal sampling for the study. The effect size in the power analysis conducted according to MPV definitive measurements was calculated as d=0.75. The sample size was calculated as 33 for both groups when the error level was determined to be 5% and the power value 95%. The study was completed with this sampling because 40 patients were reached during the study period. The sample size was detected to be nearly 35 cases for each group when power analysis was conducted according to the EC and PC definitive measurements. It was understood that the number of cases in the priapism group determined for our study was enough for all three measurements. Thus, a total of 80 patients were included in the study. Patients were separated into the two groups: IP patients and healthy control group, with both containing 40 individuals. All IP patients had their first priapism attacks and had blood gas values for IP in the corporeal aspiration and blood gas analysis (pO_2 <30 mmHg, pCO_2 >60 mmHg, pH <7.25). It was demonstrated that the blood flow level in the cavernosal arteries was low in PDU or that there was no blood flow. In the IP group, it was detected that eight patients used the PDE 5 enzyme inhibitor in the 24 hours before priapism develop-

ment and that intracavernosal 60 mg papaverin was applied for PDU in 28 patients. Four patients were regarded as idiopathic because no causes were found. The average priapism duration was 16.2 hours (range 6–98). Corporeal aspiration and/or phenylephrine irrigation was conducted at the beginning of treatment in all priapism patients. Detumescence was provided in 33 patients with aspiration and irrigation. A spongiocavernosal (distal) shunt was applied in seven patients who were unresponsive to aspiration and irrigation. Three patients irresponsive to this approach were treated with a saphenocavernous (proximal) shunt.

In the IP group and the control group, the mean age was detected to be 46.7 ± 12.3 years (range 23–61) and 48.25 ± 7.8 years (range 29–63), respectively (p=0.916). Other measurements were, respectively: MPV 9.11 ± 1.02 fL and 8.28 ± 0.78 fL (p<0.001); PC 292.037 ± 76.08 x 10^3/µL and 258.947 ± 62.94 x 10^3/µL (p=0.03); and EC 0.286 ± 0.12 x 10^3/µL and 0.191 ± 0.88 x 10^3/µL (p=0.001). The IP group's high MPV, PC, and EC values compared to those of the control group were detected to be statistically significant (p<0.001, p=0.03, and p=0.001, respectively).

Regarding blood count, the IP group and the control group measures, respectively, were as follows: White blood cells (WBC) 8.16 ± 2.68 x 10^3/µL and 7.72 ± 2.12 x 10^3/µL (p=0.637); red blood cells (RBC) 4.79 ± 0.73 x 10^6/µL and 4.87 ± 0.61 x 10^6/µL (p=0.589); hemoglobin (Hgb) 13.49 ± 1.44 (g/dL) and 14 ± 1.34 g/dL (p=0.083); platelet distribution width (PDW) 17.06 ± 8.58% and 15.1 ± 1.63% (p=0.119); and reticulocyte distribution width (RDW) 14.25 ± 1.43% and 13.95 ± 1.34% (p=0.292).

No statistically significant difference was observed among the two groups when age, WBC, RBC, Hgb, PDW, and RDW values were considered (p=0.916, p=0.637, p=0.589, p=0.083, p=0.119, and p=0.292, respectively). Patient findings and complete blood count values are shown in Table 1.

In the evaluation made with ROC regression analysis (Fig. 1), statistically significant values for IP were measured as: MPV: sensitivity: 52.5%, specificity: 90%, positive predictive value: 84%, cutoff value: 9.11 fL; EC: sensitivity: 62.5%, specificity: 75%, positive predictive value: 71.4%, cutoff value: 0.225 x 10^3/µL); and PC: sensitivity: 62.5%, specificity: 65%, positive predictive value: 61.4%, cutoff value: 286.500 x 10^3/µL). The findings for sensitivity, specificity, positive predictive values, and cutoff values of the parameters that were statistically significant for IP are shown in Table 2.

Table 1. Patient findings and complete blood count values

	Ischemic priapism group	Control group	p
Number	40 (50%)	40 (50%)	
Mean age	46.7 ± 12.3 (23–61)	48.25 ± 7.8 (29–63)	0.916
MPV (fL)	9.11 ± 1.02	8.28 ± 0.78	<0.001*
PC (10^3/µL)	292.037 ± 76.08	258.947 ± 62.94	0.03*
EC (10^3/µL)	0.286 ± 0.12	0.191 ± 0.88	0.001*
WBC (10^3/µL)	8.16 ± 2.68	7.72 ± 2.12	0.637
RBC (10^6/µL)	4.79 ± 0.73	4.87 ± 0.61	0.589
Hgb (g/dL)	13.49 ± 1.44	14 ± 1.34	0.083
PDW (%)	17.06 ± 8.58	15.1 ±1.63	0.119
RDW (%)	14.25 ± 1.43	13.95 ± 1.34	0.292

Values are presented as mean ± standard deviation. *Statistically significant. EC: eosinophil count; Hgb: hemoglobin; IIEF: International Index of Erectile Function; MPV: mean platelet volume; PC: platelet count; PDW: platelet distribution width; RBC: red blood cells; RDW: reticulocyte distribution width; WBC: white blood cells.

Discussion

IP is the most common type of priapism, accounting for 95% of all priapism cases. It is characterized by painful erection accompanied by significant permanent hardening in the corpus cavernosum with venous blood exit disorder.[4]

Hypoxia, hypercapnia, and acidosis occur similarly to penile compartment syndrome, and this condition may result in tissue damage. In IP, the ultrastructural changes in the cavernosal flat muscle are observed 12 hours later and focal necrosis 24 hours later, and finally, necrosis and the transformation of wide necrosis and fibroblast-like cells are observed 48 hours later. Thus, emergency examination and management are required, and delayed treatment may cause total ED.[1,2,4] Understanding the role of vascular endothelium cells in IP pathophysiology is important. Vascular endothelium cells release different contraction and relaxation factors against mechanic forces and neurohumoral mediators, and they regulate the basal vascular tonus and reactivity of the penis. As much as nitric oxide (NO) and adenosis impact the vascular endothelium, serving as vascular relaxation factors in the penis, they are also the source of RhoA/Rho-kinase, which are contraction factors. It was demonstrated that failure in the vascular endothelium plays a role

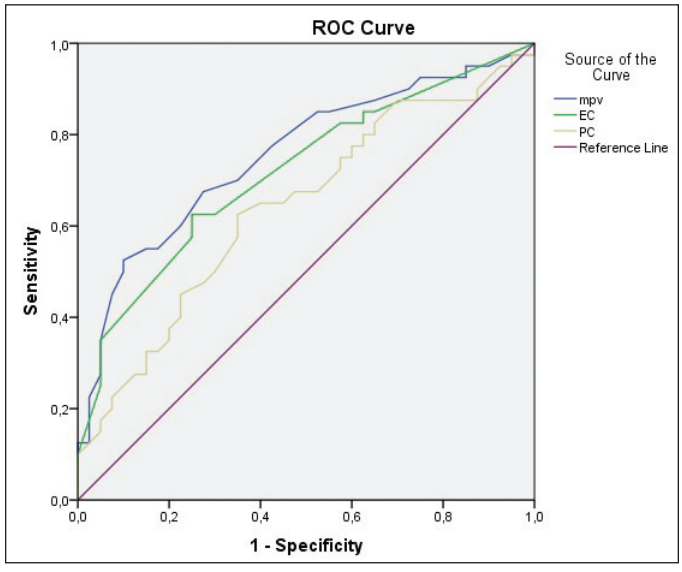

Fig. 1. Receiver operating characteristic (ROC) curve showing statistically significant values for ischemic priapism (IP). EC: eosinophil count; MPV: mean platelet volume; PC: platelet count.

Table 2. Findings for sensitivity, specificity, and positive predictive values of the parameters statistically significant for ischemic priapism

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Cutoff value	p
MPV	52.5	90	84.0	9.11 (fL)	<0.001
EC	62.5	75	71.4	0.225 (10^3/μL)	0.001
PC	62.5	65	61.4	286.500 (10^3/μL)	0.03

All p values are statistically significant. EC: eosinophil count; MPV: mean platelet volume; PC: platelet count.

in pathophysiology, causing abnormality in NO/adenosine signalization, RhoA/Rho kinase signalization, and the NO/cyclic guanosine monophosphate (cGMP) cycle. In addition to the pathologies in the vascular endothelium, veno-occlusive mechanisms are also blamed for IP.[11-13]

Platelets play an important role in the atherosclerosis formation phase. PC and MPV platelet activity are significant demonstrators of platelet activity and platelet function, reflecting platelet production speed and platelet stimulation. MPV is a potential indicator of thrombocyte reactivity. Large thrombocytes have a more active and more prothrombotic potential in metabolic and enzymatic aspects. Increased MPV is related to indicators demonstrating thrombocyte activity, such as increased thrombocyte gathering, tromboxan synthesis, and the increased expression of adhesion molecules. Some studies have shown that increased MPV triggers and increases atherosclerotic processes, such as acute coronary syndrome, myocardial infarction, and thrombosis. It is known to be connected to the atherosclerosis process in penile arterial deficiency.[5-8] As seen in many studies, platelets play an active role in vascular pathologies. Eosinophils activate the coagulation system and thrombocytes. This situation may cause vasospasm in the arteries. It was reported that eosinophil granule proteins may affect the cardiovascular system negatively by causing vascular injury and inflammatory cell infiltration. The studies conducted demonstrated that eosinophils are related to stent thrombosis, stent restenosis, and acute coronary syndrome.[7,14] Some studies reported that EC is related to vasospastic angina pectoris and large thrombus formation.[15] A connection may exist between EC and vasculogenic events due to the strong vasoconstrictor, procoagulant, and local inflammatory effects of eosinophils. We included EC, PC, and MPV counts as suspected predictive factors demonstrating platelet activation in our study.

In other studies conducted, a positive relationship was detected between varicocele, vasculogenic ED, acute mesentery ischemia, bullous pemphigoid and similar diseases, and platelet activation and eosinophil count.[7,8,16-20]

The basis of our study was the suspicion that platelet activation and EC are predictive factors for damaged veno-occlusive mechanism and endothelial damage, which has a role in ischemic pathophysiology.

In the study by Ufuk et al, the relationship between IP and platelet activation was examined; the link between IP and high MPV and PC were found to be significant; however, EC was not included in the parameters examined in this study and no statistical studies were conducted with predictive and cutoff values.[10] Similarly to the study by Ufuk et al, our study showed that PC and MPV demonstrating platelet activation in the IP group were statistically significantly high. The significance of our study was the addition of EC as a suspected predictive factor for the parameters compared. Predictive and cutoff values were calculated statistically. In the IP group, EC, MPV, and PC were detected to be statistically significantly high compared to the control group (p=0.001, p<0.001, and p=0.03, respectively). It was detected that EC, MPV, and PC had strong positive predictive effects on IP etiopathogenesis (71.4%, 84%, and 61.4%, respectively).

Cutoff values for the parameters measured to be statistically significant for IP were MPV: 9.11 fL; PC: 286.500 x 10^3/μL; and EC: 0.225 x 10^3/μL. According to this study, the probability of IP development may be higher in patients with higher values than these cutoff values among the patients who use the PDE5 enzyme inhibitor and have PDU with intracavernosal injection. Thirty-six of 40 IP patients in our patient group (90%) were using PDU and the PDE5 enzyme inhibitor. Thus, although the examination and treatment were done for patients referring with ED especially, attention should be paid to MPV, PC, and EC levels for priapism development risk.

Even though no cardiovascular diseases are known, system evaluation should be recommended in this patient group when MPV, PC, and EC values are high and accompanied by IP. Because high MPV, PC, and EC values carry vascular dysfunction risk, these patients should be examined carefully for possible asymptomatic cardiovascular system disease.

Conclusion

High MPV, PC, and EC values are significant positive predictive factors in IP etiopathogenesis. No proof was detected for other blood count parameters playing an active role. Attention should be paid to IP development risk when planning PDU and giving PDE5 enzyme inhibitors to patients with high MPV, PC, and EC values. Because possible systemic vascular dysfunction can occur in IP patients accompanied by high MPV, PC, and EC values, we suggest cardiovascular system evaluation in these patients. Studies containing higher numbers of patients and different priapism types would be beneficial.

Competing interests: The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

References

1. Salonia A, Eardley I, Giuliano F, et al. European Association of Urology guidelines on priapism. *Eur Urol* 2014;65:480-9. https://doi.org/10.1016/j.eururo.2013.11.008
2. Shigehara K, Namiki M. Clinical management of priapism: A review. *World J Mens Health* 2016;34:1-8. https://doi.org/10.5534/wjmh.2016.34.1.1
3. Song PH, Moon KH. Priapism: Current updates in clinical management. *Korean J Urol* 2013;54:816-23. https://doi.org/10.4111/kju.2013.54.12.816
4. Broderick GA, Kadioglu A, Bivalacqua TJ, et al. Priapism: Pathogenesis, epidemiology, and management. *J Sex Med* 2010;7:476-500. https://doi.org/10.1111/j.1743-6109.2009.01625.x
5. Pizzulli L, Yang A, Martin JF, et al. Changes in platelet size and count in unstable angina compared to stable angina or non-cardiac chest pain. *Eur Heart J* 1998;19:80-4. https://doi.org/10.1053/euhj.1997.0747
6. Kamath S, Blann AD, Lip GY. Platelet activation: Assessment and quantification. *Eur Heart J* 2001;22:1561-71. https://doi.org/10.1053/euhj.2000.2515
7. Otunctemur A, Bozkurt M, Besiroglu H, et al. Erectile dysfunction is positively correlated with mean platelet volume and platelet count, but not with eosinophil count in peripheral blood. *Urol J* 2015;12:2347-52.
8. Ciftci H, Yeni E, Demir M, et al. Can the mean platelet volume be a risk factor for vasculogenic erectile dysfunction? *World J Mens Health* 2013;31:215-9. https://doi.org/10.5534/wjmh.2013.31.3.215
9. Wang J, Mahmud SA, Thompson JA, et al. The principal eosinophil peroxidase product. HOSCN. Is a uniquely potent phagocyte oxidant inducer of endothelial cell tissue factor activity: A potential mechanism for thrombosis in eosinophilic inflammatory states? *Blood* 2006;107:558-65. https://doi.org/10.1182/blood-2005-05-2152
10. Ufuk Y, Hasan Y, Murat U, et al. Does platelet activity play a role in the pathogenesis of idiopathic ischemic priapism? *Int Braz J Urol* 2016;42:118-22. https://doi.org/10.1590/S1677-5538.IBJU.2015.0126
11. Mi T, Abbasi S, Zhang H, et al. Excess adenosine in murine penile erectile tissues contributes to priapism via A2B adenosine receptor signaling. *J Clin Invest* 2008;118:1491-501. https://doi.org/10.1172/JCI33467
12. Bivalacqua TJ, Musicki B, Hsu LL, et al. Establishment of a transgenic sickle cell mouse model to study the pathophysiology of priapism. *J Sex Med* 2009;6:2494-504. https://doi.org/10.1111/j.1743-6109.2009.01359.x
13. Champion HC, Bivalacqua TF, Takimoto E, et al. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. *Proc Natl Acad Sci USA* 2005;102:1661-6. https://doi.org/10.1073/pnas.0407183102
14. Umemoto S, Suzuki N, Fujii K, et al. Eosinophil counts and plasma fibrinogen in patients with vasospastic angina pectoris. *Am J Cardiol* 2000;85:715-9. https://doi.org/10.1016/S0002-9149(99)00846-2
15. Sakai T, Inoue S, Matsuyama TA, et al. Eosinophils may be involved in thrombus growth in acute coronary syndrome. *Int Heart J* 2009;50:267-77. https://doi.org/10.1536/ihj.50.267
16. Mahdavi-Zafarghandi R, Shakiba B, et al. Platelet volume indices in patients with varicocele. *Clin Exp Reprod Med* 2014; 41:92-5. https://doi.org/10.5653/cerm.2014.41.2.92
17. Bozkurt Y, Soylemez H, Sancaktutar AA, et al. Relationship between mean platelet volume and varicocele: A preliminary study. *Urology* 2012;79:1048-51. https://doi.org/10.1016/j.urology.2012.01.019
18. Bilgic İC, Gelecek S, Ozmen MM, et al. The association of elevated mean platelet volume with the outcome of acute mesenteric ischemia. *Blood Coagul Fibrinolysis* 2015;26:727-30.
19. Rifaioglu EN, Sen BB, Ekiz Ö, et al. Mean platelet volume and eosinophilia relationship in patients with bullous pemphigoid. *Platelets* 2014;25:264-7. https://doi.org/10.3109/09537104.2013.784735
20. Demir M, Şentürk M, Kuzeytemiz M. The relationship between eosinophil and cardiac syndrome X. *Clin Appl Thromb Hemost* 2015;21:325-8. https://doi.org/10.1177/1076029613502256

Correspondence: Dr. Mehmet Giray Sönmez, Department of Urology, Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey; drgiraysonmez@gmail.com