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Original article:

AN OVERVIEW OF PLATELET INDICES FOR EVALUATING PLATELET FUNCTION IN CHILDREN WITH SCORPION ENVENOMATION

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ABSTRACT

The aim of this study was to assess the correlation between platelet indices and scorpion envenomations (SE).

Medical records of 76 children who were hospitalised for scorpion stings in the paediatric intensive care unit (PICU) between February 2013 and November 2013, and 55 healthy children who were similar to the patient group in terms of age and sex, were analysed retrospectively. The leucocyte (WBC), thrombocyte (PLT), plateletcrit (PCT), platelet distribution width (PDW) and mean platelet volume (MPV) values of the 76 children with SE were recorded. These values were compared with the healthy control group.

Significantly higher WBC and PDW values were noted in patients with SE in comparison to the controls. Patients with SE had significantly lower mean MPV values compared to the healthy controls (9.03 ± 1.26 compared to 10.43 ± 1.44 fL, respectively; $p < 0.001$). Although the mean platelet count was slightly elevated in the SE group, no statistically significant difference existed between the two groups ($p = 0.097$). Furthermore, the mean PCT values in the SE group compared to the control group were slightly decreased, but this decrease was not statistically significant ($p = 0.141$). A significant inverse correlation existed between the MPV values and the WBC ($r = -0.450$, $p < 0.01$) and PLT counts ($r = -0.420$, $p < 0.01$). The PLT values were significantly correlated with the PCT values ($r = 0.687$, $p < 0.01$).

This study demonstrated that SE may lead to several alterations in platelet indices. Significantly lower values of MPV and higher values of PDW were detected in SE patients. However, the increase in the platelet counts and the decrease in the PCT values were not significant.

Keywords: children, platelet indices, scorpion envenomation

INTRODUCTION

Scorpion envenomation (SE) is a public health problem especially in tropical and subtropical countries. The majority of cases are admitted with pain localised to the site of the sting, and then follow a benign clinical course (Dittrich et al., 2002). However, severe envenoming may present cardiac and respiratory dysfunction leading to multisystem organ failure and death (Tarasiuk et al., 1998). Signs of severe envenoming are related to an excessive systemic host inflammatory response to stings (Petricevich, 2010). Mediators affecting inflammatory

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processes, including kinins, platelet activating factor (PAF), permeability increasing factor, nitric oxide and cytokines may be released after SE. The release of these biologically active substances may account for several of the inflammatory manifestations observed in SE (Amaral et al.,1993; De Matos et al.,1997; Petricevich, 2010).

Platelets, in addition to their function in haemostasis, play an important role in the inflammatory response (Trzeciak-Ryczek et al., 2013). Various inflammatory factors such as cytokines and coagulants are released by platelets (Bath and Butterworth, 1996). Platelet activation alters the morphology of these cells, which can be evaluated on the basis of mean platelet volume (MPV) and platelet distribution width (PDW) (Jackson and Carter, 1993). Plateletcrit (PCT) is another platelet parameter, which is a reliable measurement of platelet biomass, because it combines the MPV with the absolute platelet count (Akpinar et al., 2014). Platelet indices (PCT, PDW and MPV) are considered markers of platelet activation and are altered in different inflammatory diseases, such as inflammatory bowel disease (Öztürk et al., 2013), rheumatoid arthritis (Yazici et al., 2010), familial Mediterranean fever (Makay et al., 2009) and PFAPA syndrome (Tekin et al., 2014).

We hypothesised that scorpion envenomation, which is an inflammatory disease, may affect platelet indices. The purpose of this study was to assess the correlation between platelet indices and scorpion envenomation.

METHODS

Medical records of 76 children who were hospitalised for scorpion stings in the paediatric intensive care unit (PICU) between February 2013 and November 2013, and 55 healthy children who were similar to the patient group in terms of age and sex, were analysed retrospectively. Patients with chronic disorders, anaemia and other haematological diseases, hypercholesterolaemia, passive smoking, acute bacterial infection and autoimmune diseases, as well as scorpion-sting cases discharged from the emergency department without hospitalisation, were excluded from the study. Medical records of the patients were collected, and the demographic features, clinical and laboratory findings, and outcomes were recorded.

The diagnosis of SE was based on the history of a scorpion sting. Identification of scorpion type was based on the colour of the scorpion defined by the patient or bystander. *Androctonus crassicauda and Mesobuthus eupeus* are more commonly known as black and yellow scorpions, respectively (Ozkan et al., 2006). Patients were classified into three groups according to clinical severity as follows: class I for local manifestations, class II for systemic involvement and class III for cardiovascular, respiratory or neurological symptoms (such as cardiogenic shock, pulmonary oedema, altered consciousness and convulsive crisis) (Khattabi et al., 2011).

Blood samples from both groups were drawn by venepuncture. Since prednisolone can inhibit platelet adhesion, platelet aggregation and platelet interaction with monocytes, blood samples of scorpion-sting cases were drawn by venepuncture upon admission to the emergency department before steroid application (Liverani et al., 2012). All complete blood count (CBC) analyses were performed in the haematology laboratory of our hospital. Two millilitres of blood were collected from each subject and placed in a standardised tube containing ethylenediaminetetraacetic acid (EDTA). A CBC analysis was performed within one hour of collection of each blood sample using a Sysmex XT 2000i (Roche Diagnostics GmbH, Mannheim, Germany) automated analyser. White blood cell count (WBC), haemoglobin (Hb), platelet count (PLT), PCT, PDW and MPV values were recorded for each patient.

Statistical analysis

Patient data was assessed using SPSS (Statistical Package for Social Sciences Statistical Software) version 15.0 (SPSS, Inc., Chicago, IL). A Chi-square test was used to

evaluate the sex distribution between the groups. For the comparison of the age distribution and haematological parameters (WBC, Hb, PLT, MPV, PCT and PDW) of the patient and the control groups, independent two-sample T-tests were performed. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of significant variables. Relationships between variables in the patient group was assessed by using Pearson's correlation coefficient. Mean ± SD values of all variables were obtained, and $p < 0.05$ was considered to be significant. The study was approved by the ethics committee of Adiyaman University.

RESULTS

A total of 131 children with records of platelet indices were enrolled in the study, of whom 76 were patients with scorpion envenomation and 55 were assigned to the control group. The mean ages of the patient group and the control group were 7.12 ± 4.2 years and 6.14 ± 3.2 years, respectively (p = 0.179). 40 patients (52.6 %) in the SE group and 32 (58.2 %) in the control group were male ($X^2 = 0.397$; p = 0.529). There was no significant difference in terms of age and gender between the two groups.

The patients were mostly stung during the day (59.2 %). The average elapsed time between being stung and being admitted to the hospital was 100.2 ± 106.6 minutes (range: 20 to 490 minutes). In terms of the type of scorpion, 31 subjects (40.8 %) were stung by black scorpions and 25 (32.9 %) were stung by yellow scorpions. In 12 cases (15.8 %), the patient could not identify the colour of the scorpion. The most common sting sites were lower extremity (n = 52, 68.4 %), upper extremity (n = 16, 21.1 %) and body (n = 5, 6.6 %). Based on clinical severity, 32 (42.1 %), 42 (55.3 %) and 2 (2.6 %) of the patients were classified into classes I, II and III, respectively. While some patients exhibited localised symptoms, others demonstrated both local and systemic symptoms. The most common localised signs were pain (n = 69, 90.7 %), hyperaemia (n = 42, 55.2 %) and swelling (n = 20, 26.3 %), respectively. Cold extremities (47.3 %), pallor (13.1 %), hypotension (6.5 %), hypertension (6.5 %) and sweating (5.2 %) were observed as the most frequent systemic symptoms. The mean hospitalisation time was 2.2 ± 1.3 days (ranging from 6 hours to 6 days). All of the children were discharged after recovery except for one patient (1.3 %) who manifested evidence of severe envenomation and died as a result of cardiac and respiratory arrest. The clinical features of the patients are given in Table 1.

Significantly higher WBC and PDW values were noted in patients with SE than in the control group. Patients with SE had significantly lower mean MPV values than the healthy controls ($p < 0.001$). Although the mean platelet count was slightly elevated in the SE group, no statistically significant difference existed between the two groups ($p=0.097$). Furthermore, the mean PCT values in the SE group compared to the control group were slightly decreased, but this decrease was not statistically significant ($p = 0.141$). There was no significant difference between class I, II and III patients in terms of MPV, PDW and PCT (Table 2).

ROC curve analysis was performed to determine the optimal cutoff values of significant variables detected between the two groups (Figure 1). A 10.3 fl area under the curve (AUC = 0.761) optimal cutoff value of MPV, with a sensitivity of 84.3 % and a specificity of 56.4 %, was determined in children with SE. A 9.4 K/uL (AUC = 0.811) optimal cutoff value of WBC, with a sensitivity of 52.4 % and a specificity of 94.5 %, was determined in children with SE. A 9.9 fl (AUC = 0.60) optimal cutoff value of PDW, with a sensitivity of 67.7 % and a specificity of 52.7 %, was determined in children with SE (Table 3).

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Table 1: Clinical features of patients

Clinical features of patients	Number	Percent
Sex		
Female	36	47.3
Male	40	52.6
Scorpion identification		
Black	31	40.8
Yellow	25	32.9
Others	8	10.5
Unknown	12	15.8
Sting site		
Lower extremity	52	68.4
Upper extremity	16	21.1
Body	5	6.6
Head and neck	3	3.9
Envenomation severity		
Class I	32	42.1
Class II	42	55.3
Class III	2	2.6
Local sign		
Pain	69	90.7
Hyperemia	42	55.2
Swelling	20	26.3
Systemic sign		
Cold extremities	36	47.3
Pallor	10	13.1
Hypotension	5	6.5
Hypertension	5	6.5
Sweating	4	5.2
Dry mouth	4	5.2
Tachycardia	3	3.9
Womiting	3	3.9
Pulmonary edema	2	2.6
Myocarditis	2	2.6
Outcome		
Recovery	75	98.6
Death	1	1.3

The relationships between the variables in the patient group were considered by using Pearson's correlation coefficient (Table 4). A significant inverse correlation existed between the MPV values and WBC *($r = -0.450$, $p < 0.01$)*. Additionally, PLT counts were significantly correlated with PCT *($r = 0.687$, $p < 0.01$)* and were significantly inversely correlated with MPV *($r = -0.420$, $p < 0.01$)*.

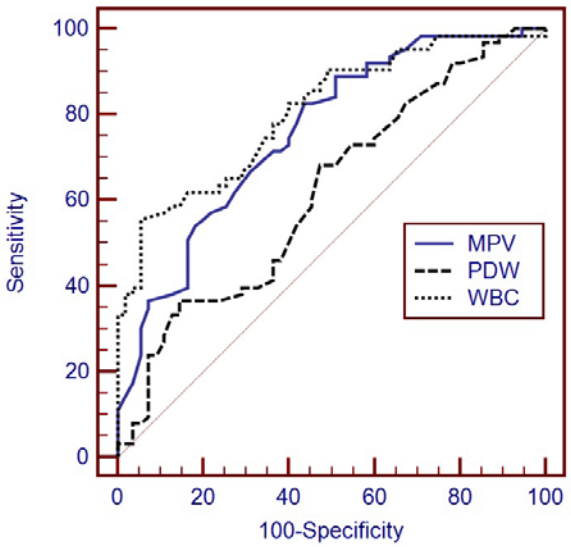

Figure 1: Results of ROC curve analysis

DISCUSSION

Pro-inflammatory and anti-inflammatory cytokines and mediators are released by the host in varying proportions according to the different species of scorpions after envenoming. The balance between pro-inflammatory and anti-inflammatory cytokines in envenomation determines the degree and extent of inflammation, which can lead to major clinical effects such as cardiac dysfunction, pulmonary oedema and shock (Petricevich, 2010). Platelets initiate and support inflammatory processes by secretion of numerous biologically active substances such as platelet activation factor, platelet-derived growth factor, platelet factor 4, IL-1 and beta-thromboglobulin in inflammatory conditions (Kaplan and Owen, 1981;Trzeciak-Ryczek et al., 2013). Considering that the clinical signs and symptoms observed in humans and experimental animals are related to an excessive systemic host inflammatory response to scorpion stings, some alterations in platelet counts and functions are expected in scorpion envenomations (Petricevich, 2010). Therefore, studies examining the interactions between platelet functions and scorpion envenomation have increased in recent years. Song et al. (2005) demonstrated that scorpion venom active polypeptide (SVAP) inhibited platelet aggregation induced by thrombin and ADP, both ex vivo and in vitro, and

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Table 2: Haematological features of the patient and control groups

Hematological features	Patients with SE	Controls	*p* Value
WBC ((K/uL)	10.51±2.54	7.09±1.89	<0.001
Hb (g/dL)	12.65±1.09	12.74±1.15	0.662
PLT (K/uL)	278.75±84.4	254.80±72.6	0.097
MPV (fL)	9.03±1.26	10.43±1.44	<0.001
PDW (fL)	10.80±1.86	10.07±1.57	0.023
PCT (%)	0.24±0.05	0.25±0.06	0.141

WBC: White blood cell count; Hb: Hemoglobin; PLT: Platelet count; MPV: Mean platelet volume; PDW: Platelet distribution width; PCT: Plateletcrit

Table 3: ROC analysis for various biomarkers in predicting scorpion envenomation compared to control group

	WBC (K/uL)	PDW (fL)	MPV (fL)
ROC area	0.81	0.61	0.76
Sensitivity	54.29	67.7	84.3
Specificity	94.55	52.70	56.4
Cut-off point	> 9.4	> 9.9	≤10.3
p Value	<0.001	<0.001	<0.001

MPV: Mean platelet volume; **PDW**: platelet distribution width;
WBC: White blood cell count; **ROC**: Receiver operating characteristic

Table 4: Correlation between the variables in the patient group

	WBC	PLT	MPV	PDW	PCT
WBC	1	0,251	-0,450**	-0,052	-0,047
PLT		1	-0,420**	-0,183	0,687**
MPV			1	0,178	0,074
PDW				1	-0,115
PCT					1

**: P<0.01; WBC: White blood cell count; PLT: Platelet count; MPV: Mean platelet volume; PDW: Platelet distribution width;PCT: Plateletcrit

promoted the PGI2/TXA2 ratio in rabbits and rats. However, Brazón et al. (2011) demonstrated that *Tityus discrepans* scorpion venom (TdV) stimulated integrin αIIbβ3-dependent aggregation of washed human and mouse platelets. Borges et al. (2000) reported that scorpion venom-induced neutrophilia is inhibited by a PAF receptor antagonist in rats. Furthermore, Coelho et al. (2007) showed that the influx of neutrophils in the lungs of mice injected with *Tityus serrulatus venom (TsV)* is dependent on activation of PAFR and on PAFR-dependent production of the chemokine KC and activation of CXCR2 on neutrophils. Almost all of these studies were performed using experimental animals or washed human platelets. However, there is no study examining the platelet counts and functions in SE patients. Since platelet indices are reported to be indirect markers of platelet functions in several diseases, in this study the platelet indices of the patient and control groups were compared in order to understand the effect of scorpion envenomation on platelet functions (Greisen-

egger et al., 2004; Öztürk et al., 2013; Chandrashekar et al.,2014).

Larger platelets are metabolically and enzymatically more active than smaller platelets (Thompson et al., 1983). MPV is an easily accessible haematological parameter that provides information about the mean platelet size. Therefore, MPV levels have been investigated in many inflammatory diseases. MPV levels were determined to be elevated in chronic urticaria (Chandrashekar et al., 2014), rheumatoid arthritis (Yazici et al., 2010), chronic hepatitis B (Turhan et al., 2010) and myocardial infarction (Balcik et al., 2013); conversely, low levels were noted in the acute exacerbation period of cystic fibrosis (Uysal et al., 2011), ulcerative colitis (UC) (Yüksel et al., 2009), and during attacks of familial Mediterranean fever (FMF) (Makay et al., 2009). In this study, the mean MPV values for the SE group were found to be significantly lower than for the control group ($p < 0.001$). It is reported that high-grade inflammatory diseases present with low levels of MPV, but low-grade inflammatory conditions present with high levels of MPV (Gasparyan et al., 2011). Therefore, we think that decreased MPV levels support the role of high-grade inflammation in SE patients.

PDW is a direct flow-cytometric measurement of platelet cell volume, as the platelet distribution width is measured at 20 % relative height of the total height of the curve, depicting their distribution. The activation of the platelets causes some morphological alterations: the activated platelets seem larger by becoming spherical in shape and forming pseudopodia. An increased PDW is an indication of the anisocytosis and activation of platelets (Vagdatli et al., 2010). An increased level of PDW has been measured in several diseases, including acute coronary syndrome and heart failure (Vatankulu et al., 2014), vascular micro-occlusion of sickle-cell disease (Amin et al., 2004), active tuberculosis (Tozkoparan et al., 2007), bacteraemia (Patrick and Lazarchick, 1990) and chronic urticaria (Chandrashekar et al., 2014). However, a decreased level of PDW has been measured in some studies (Öztürk et al., 2013; Arslan et al., 2013). In the present study, the mean PDW value in the SE group was measured to be significantly higher than in the control group.

Plateletcrit is another platelet index that is a reliable measurement of platelet biomass, because it combines the MPV with the absolute platelet count (Akpinar et al., 2014). Although PCT is the most neglected haematological parameter in clinical practice, PCT alterations are observed in some clinical conditions. Leal-Santos et al. (2013) showed low mean PCT values in patients with acute malaria. Öztürk et al. (2013) demonstrated that PCT percentage was lowest in the control group and highest in the active phase of UC and CD patients. Also, Akpinar et al. (2014) found a high PCT value in saphenous vein graft disease groups. In the present study, the mean PCT values in the SE patients were lower than in the control group; however, the difference was not significant. Similarly, the mean platelet counts were higher in the patient group but no significant difference was detected.

Previous studies have reported that leukocytosis is a significant laboratory finding of systemic scorpion envenomations (Petricevich, 2010; Borges et al., 2000; Amucheazi and Umeh, 2012). In this study, mean leukocyte counts were measured to be significantly higher than in the control group, consistent with the literature *($p < 0.001$).* We found a statistically significant inverse correlation between these values and MPV values. In our study, a 10.3 fl area under the curve (AUC = 0.761) optimal cutoff value of MPV, with a sensitivity of 84.3 % and a specificity of 56.4 %, was determined in children with SE.

There are several limitations in the present study. Firstly, it was a retrospective study and we could not access platelet aggregation and clotting time test results. Another limitation was that the relationship between platelet indices and clinical severity could not be demonstrated due to the small

number of patients with severe envenoming. Steroids were administered to all patients in the emergency department. An additional limitation of this study was that because prednisolone can inhibit platelet adhesion, platelet aggregation and platelet interaction with monocytes, we could not evaluate the relationship between SE and platelet indices for subsequent blood samples (Liverani et al., 2012).

CONCLUSIONS

In conclusion, our study demonstrated that SE may lead to several alterations in platelet indices. Significantly lower values of MPV and higher values of PDW were detected in SE patients. However, the increase in the platelet counts and the decrease in the PCT values were not significant. Our results support that platelets are activated in SE, and SE is a high-grade inflammatory disease. The relationship between platelet indices and clinical severity was not demonstrated due to a small number of patients with severe envenoming. Further trials including increased numbers of samples are needed to confirm the results.

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