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Evaluation of Platelet Parameters and Acute Phase Reactants in Pediatric Patients Presenting with Fever

Ateş Şikayeti ile Başvuran Çocuk Hastalarda Trombosit Parametreleri ve Akut Faz Belirteçlerinin Değerlendirilmesi

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Abstract

Objective: Increased fever can suppress the reproduction of viral and bacterial agents and has also been shown to support body's acute phase reaction. Acute phase reactants, platelet count, mean platelet volume, platelet distribution width, and plateletcrit are all parameters that can change during bacterial and viral infections. In this study, we aimed to evaluate platelet parameters and acute phase reactants in patients presenting with fever in childhood.

Material and Methods: Febrile patients admitted to our outpatient clinic were enrolled in the study. The patients were divided into three groups depending on duration of fever; Group 1, < 24 hours; Group 2, 24-48 hours; and Group 3, > 48 hours. The subjects in the control group had no fever, but were all ill. Mean platelet volume, platelet distribution width, plateletcrit, platelet count, erythrocyte sedimentation rate, and C-reactive protein, albumin, and fibrinogen levels were measured for each patient.

Results: Two hundred seventy-two patients were included in the study. Platelet distribution width, plateletcrit, and platelet count were not statistically significantly different between the groups. However, mean platelet volume, erythrocyte sedimentation rate, and C-reactive protein, fibrinogen, and albumin levels were statistically significantly different.

Conclusion: Acute phase reactants and mean platelet volume were affected by the duration of fever.

Keywords: Acute phase reactants, childhood, fever, platelets, mean platelet volume

Öz

Giriş: Ateşin artmasının viral ve bakteriyel ajanların üremesini baskıladığı ve vücudun akut faz yanıtını desteklediği gösterilmiştir. Akut faz reaktanları, trombosit sayısı, ortalama trombosit hacmi, trombosit dağılım genişliği ve plateletkrit gibi tüm parametrelerin viral ve bakteriyel enfeksiyonları seyrinde değişebilmektedir. Bu çalışmada çocukluk çağında ateş şikayeti ile başvuran hastalarda platelet parametreleri ve akut faz belirteçlerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Polikliniğe ateş nedeniyle başvuran hastalar çalışmaya dahil edildi. Hastalar ateş sürelerine göre üç gruba ayrıldı; Grup 1 < 24 saat, Grup 2 24-48 saat ve Grup 3 > 48 saat. Kontrol grubu hastaları ateşi olmayan ancak hasta çocuklardan seçildi. Ortalama trombosit hacmi, trombosit dağılım genişliği, plateletkrit, trombosit sayısı, eritrosit sedimentasyonu ve fibrinojen her hasta için incelendi.

Bulgular: Çalışmaya 272 hasta dahil edildi. Gruplar arasında trombosit dağılım genişliği, plateletkrit ve trombosit sayısı açısından istatistiksel olarak anlamlı fark yoktu. Ancak, ortalama trombosit hacmi, eritrosit sedimentasyon hızı, C-reaktif protein, fibrinojen ve albumin açısından gruplar arasında istatistiksel olarak anlamlı fark vardı.

Sonuç: Akut faz belirteçleri ve ortalama trombosit hacmi ateş süresinden etkilenmektedir.

Anahtar Kelimeler: Akut faz belirteçleri, çocukluk çağı, ateş, platelet, ortalama trombosit hacmi

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Introduction

Fever is not an illness, but rather a clinical condition associated with numerous diseases in childhood. The causes of fever can be divided into four main groups: infectious, inflammatory, neoplastic, and miscellaneous (1). Infectious causes are the most common during childhood. Fever prevents bacterial and viral proliferation. It also affects neutrophil and lymphocyte counts, as well as acute phase reactions (1-3).

Platelets, which are central to both hemostasis and thrombosis, are one variety of blood cell. Recent studies have shown that platelets play an important role in the immune system (4,5). Platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) are all parameters routinely evaluated during complete blood count (CBC). Changes can occur in these platelet parameters during bacterial and viral infections, vascular inflammatory diseases, and malignant diseases, as well as in some specific patient groups (intensive care unit patients, newborn sepsis patients, etc.) (5-9).

This study evaluated changes in platelet parameters and acute phase reactants in pediatric patients presenting with fever.

Materials and Methods

This retrospective case-control study was performed at the pediatric outpatient clinic of the Adiyaman University School of Medicine, Turkey, between 1 April and 30 June, 2015. Febrile patients admitted to our outpatient clinic were enrolled as the patient group. Duration of fever was recorded for each patient, and these were then divided into three groups based on that duration: fever lasted less than 24 hours in Group 1, 24 to 48 hours in Group 2, and longer than 48 hours in Group 3. A control group (CG) was established from ill, but afebrile individuals. Fever was measured using a digital non-contact thermometer (Mesitas Ltd, Istanbul, Turkey) and was defined as a temperature of above 38°C. All subjects included in the patient group were febrile.

Patients with bone marrow disease, cancer (leukemia, solid tumors, etc.), immune thrombocytopenic purpura, immune deficiency diseases, inflammatory bowel disease or arthritis, receiving ongoing treatment with oral or inhaled corticosteroids, or using any antibiotic or drugs that might affect platelet parameters were excluded from the study. Healthy children attending the outpatient clinic for routine checkup were not included in the control group.

The medical files of the patient and control groups were investigated retrospectively. Age and gender, white blood cell (WBC) count, hemoglobin, MPV, PDW, PCT, platelet count, ESR, CRP, albumin, and fibrinogen levels were recorded for each group. Sixty-eight randomly selected children comprised the CG. Children in the CG were stratified by age and gender, and a specific number of control subjects were selected from each layer by simple random sampling. The members of the CG were proportional to those in the patient groups.

CBC was measured via the flow cytometric method using a Cell-Dyn Ruby Hematology System (Abbott Diagnostics, Illinois, USA). CRP was measured using the nephelometric method with an Image-800 System (Beckman Coulter, California, United States). Fibrinogen level was measured using the Clauss quantitative method with a Stago coagulometer (Diagnostica Stago, Siene, France). ESR was measured with an Alifax SIR20 device (SIRE Analytical Systems, Udine, Italy), while albumin levels were measured using an Abbot Architect C8000 apparatus (Abbot Laboratories, IL, USA).

SPSS version 13 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. The chi-square test was used for gender comparisons, while one-way analysis of variance (ANOVA) was used for the other parameters. Multivariate analysis of variance (post hoc test, Tukey HSD) was performed for $p< 0.05$ at analysis of variance. $p< 0.05$ was considered statistically significant.

Approval for the study was granted by the Local Biomedical Research Ethical Committee (approval no. 2015/02-6).

Results

Two hundred seventy-two patients were included in the study, 65 in Group 1, 70 in Group 2, 69 in Group 3, and 68 in CG. Data concerning age, gender, white blood cell (WBC) count, hemoglobin, MPV, PDW, PCT, platelet count, ESR, CRP, albumin,

Table 1. Groups' demographic data and laboratory results

	Age (months)	Gender (male/ female)	WBC (/mm³)	Hemoglobin (g/dL)	Platelet (10³/mm³)	MPV (fl)	PDW %	PCT %	CRP mg/dL	Fibrinogen (mg/dL)	ESR (mm/h)	Albumin (g/dL)
Group 1	41.82 ± 34.74	35/30	10374 ± 3504	12.34 ± 1.34	314 ± 85	7.71 ± 1.20	17.84 ± 2.30	0.24 ± 0.62	0.97 ± 1.02	340.48 ± 82.73	8.6 ± 8.1	4.23 ± 0.37
Group 2	50.02 ± 40.33	37/33	12637 ± 5156	12.13 ± 1.65	324 ± 104	7.20 ± 1.32	17.91 ± 1.90	0.23 ± 0.07	2.77 ± 2.49	387.02 ± 115.55	15.2 ± 18.6	4.19 ± 0.40
Group 3	54.12 ± 44.13	33/36	14608 ± 2197	12.65 ± 1.77	327 ± 110	7.87 ± 1.39	17.82 ± 2.02	0.24 ± 0.07	3.35 ± 2.77	390.54 ± 130.48	16.8 ± 12.3	4.31 ± 0.42
Control group	54.97 ± 44.97	36/32	9714 ± 3290	12.62 ± 1.33	352 ± 94	7.45 ± 1.34	18.24 ± 1.85	0.25 ± 0.06	0.42 ± 0.57	313.31 ± 98.74	5.5 ± 5.4	4.45 ± 0.37
p	0.328	0.895	0.070	0.214	0.148	**0.043***	0.581	0.116	**0.000***	**0.000***	**0.000***	**0.001***

* $p< 0.05$.
CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, WBC: White blood cell.

Table 2. Re-evaluated MPV, CRP, fibrinogen, albumin and ESR results (p< 0.05)

Comparison groups		MPV	Albumin	CRP	Fibrinogen	ESR
Group 1	**Group 2**	0.217	0.946	**0.000**	0.130	0.024
	Group 3	0.918	0.669	**0.000**	0.083	0.002
	Control group	0.702	**0.009**	0.385	0.510	0.470
Group 2	**Group 3**	**0.041**	0.316	0.367	0.998	0.892
	Control group	0.728	**0.001**	**0.000**	**0.001**	**0.000**
Group 3	**Control group**	0.254	0.177	**0.000**	**0.000**	**0.000**

MPV: Mean platelet volume, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.

Table 3. Diagnosis distribution

	Acute tonsillitis	Acute pharyngitis	Acute tonsillo-pharyngitis	Acute otitis media	Acute bronchitis	Acute bronchiolitis	Acute gastroenteritis	Urinary tract infection	Acute Sinusitis	Total (n)
Group 1 (n/%)	5 (7.7)	11 (16.9)	6 (9.2)	5 (7.7)	11 (16.9)	5 (7.7)	9 (13.8)	6 (9.2)	7 (10.8)	65
Group 2 (n/%)	6 (8.6)	14 (20)	7 (10)	7 (10)	12 (17.1)	6 (8.6)	5 (7.1)	6 (8.6)	7 (10)	70
Group 3 (n/%)	9 (13)	9 (13)	6 (8.7)	6 (8.7)	12 (17.4)	7 (10.1)	6 (8.7)	6 (8.7)	8 (11.6)	69
Control group (n/%)	10 (14.7)	14 (20.6)	4 (5.9)	5 (7.4)	12 (17.6)	4 (5.9)	8 (11.8)	7 (10.3)	4 (5.9)	68
Total (n/%)	**30 (11**)	**48 (17.6)**	**23 (8.5)**	**23 (8.5)**	**47 (17.3)**	**22 (8.1)**	**28 (10.3)**	**25 (9.2)**	**26 (9.5)**	**272**

and fibrinogen levels are shown in Table 1. Age, gender, WBC, hemoglobin, PDW, PCT, and platelet count were not statistically significantly different between the groups. However, MPV, CRP, fibrinogen level, albumin level, and ESR level were statistically significantly different. Three patients in this study had thrombocytopenia (two in Group 2 and one in Group 3), while thrombocytosis was observed in 23 (one in Group 1, five in Group 2, five in Group 3 and 12 in CG).

MPV, CRP, fibrinogen, albumin, and ESR levels were re-evaluated using the post hoc test, and the p-values are detailed in Table 2. MPV values were statistically significantly higher in Group 3 than in Group 2, although there was no statistically significant difference between the other groups. CRP values were not statistically significantly different between Group 1 and CG, but were higher in groups 2 and 3 than in CG. CRP values can therefore be seen to begin rising after the first day. Albumin levels were significantly lower in groups 1 and 2 than in Group 3 and CG. Similarly to the CRP levels, fibrinogen and ESR levels also began rising after the first day. Patients' diagnoses are presented in Table 3. These were recorded as a precise diagnosis for each patient based on the file system. No statistically significant difference was observed between the groups in terms of the distribution of diagnoses (p= 0.644).

Discussion

Fever is the most common clinical symptom in pediatric age group patients, and is observed in one-third of such patients admitted to hospital (1,10). Fever is a sign of underlying disease. Tachycardia, irritability, chills, and cutis marmorata may be seen in febrile patients. Several studies have shown that suppression of fever increases the reproduction of viral and bacterial agents and supports the body's acute phase reaction (1,11-14). Hyperthermia is defined as a body temperature higher than 40°C and can cause multiple organ dysfunction (encephalopathy, acute respiratory distress syndrome, intestinal ischemia, etc.) (15). However, no previous studies have investigated changes in platelet parameters in terms of duration of fever (of infectious origin) in the pediatric age group.

Platelets are one variety of blood cell. However, they have no nucleus, and some authors do not therefore regard them as cells (16,17). Nevertheless, platelets act like cells in many ways. Researchers agree on the role of platelets in hemostasis. Some tumor cells are also protected against the immune system by platelets (18). At the same time, platelets are also involved in the immune system response of host defenses (19). Platelet-leukocyte interactions have been shown in atherothrombosis, inflammatory lung disease, inflammatory bowel disease, and inflammatory skin disease (20). Platelets contain phospholipid vesicles, which are gemmate to the environment following viral or bacterial contact (5,16). Platelet parameters can therefore be affected by infectious diseases.

The normal platelet count range is 150.000-450.000 per microliter. Thrombocytopenia is defined as a platelet count below the normal range. In this study, thrombocytopenia was observed in only three patients. Several mechanisms have been described to explain the formation of thrombocytopenia. Two of these are decreased platelet production and enhanced platelet destruction (5,6). Thrombocytopenia is a predictor of mortality among patients admitted to the intensive care unit (7,21). The subjects enrolled in this study were all outpatient clinic patients. Their general condition was therefore good and they were not

septic. No instances of thrombocytopenia were observed in Group 1 or CG. We therefore think that there is no relation between thrombocytopenia and fever duration. Thrombocytosis is defined as a platelet count above the normal range. Platelet count elevation is an acute phase response. Infectious diseases (viral and bacterial) are the most common causes of thrombocytosis (22). Twelve patients in CG had thrombocytosis in this study. However, there was no statistically significant difference between the groups' platelet counts. Our study findings show that duration of fever does not affect platelet count (based on the incidence of both thrombocytopenia and thrombocytosis).

Mean platelet volume (MPV) shows platelets' average size and production rate (23). MPV values do not vary in terms of age or gender (24). Medical and non-medical conditions can affect MPV values, including infectious diseases such as rotavirus gastroenteritis, respiratory syncytial virus infection, hepatitis B and C virus infection, brucellosis, and pulmonary tuberculosis (23,25-29). Recent studies have also investigated MPV values in terms of specific diseases. In this study, patient diagnoses were homogeneous within the various groups. This made it possible to assess the effects of duration of on platelet parameters. MPV values were statistically significantly higher in Group 3 than in Group 2. This indicates that MPV values changed on the third day of fever, although these values were not statistically significantly different from those of the other groups. Assuming that MPV is an acute phase reactant, it should be evaluated on the third day of fever.

Platelet distribution width (PDW) indicates active platelet release (30). Many studies have shown that PDW values differ in various diseases (9,30,31). Zhang et al. (8) showed that low platelet counts, high MPV, and high PDW are associated with more severe illnesses in intensive care unit patients. Our results indicate no PDW changes in relation to fever duration. PCT describes circulating platelets in a unit volume of blood and is calculated using the formula PCT = Plt × MPV (32,33). Sahin et al. (32) demonstrated that a higher PCT value is correlated with acute phase reactants in tuberculosis patients. No change was observed in PCT depending on duration of fever in our study.

CRP, ESR, albumin, and fibrinogen are acute phase reactants. These levels peak at 6-36, 24-48, and 24-72 hours from onset of disease, respectively (34-36). Albumin is a negative acute phase reactant (35). According to our results, albumin levels in the first two days (i.e., Groups 1 and 2) were lower than those of Group 3 and CG, and were negatively affected by duration of fever. The levels of these acute phase reactants (CRP, ESR, albumin, and fibrinogen) in this study varied depending duration of fever, in agreement with the findings of previous studies.

The main limitation of this study was the lack of agent-based investigation. It was not therefore possible to determine the agent of each infectious disease.

Conclusion

Acute phase reactants were affected by the fever duration in common pediatric infectious diseases. In contrast, platelet parameters such as platelet count, PDW, and PCT were not affected. Only MPV was changed third day of fever. Further studies are now required to assess the effect of fever on platelet parameteres and acute phase reactants.

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