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Relationship Between Effusion and Inflamatory Markers Including Platelet Count in Children with Parapneumonic Effusion

Parapnömonik Efüzyonu Olan Çocuk Hastalarda Trombosit Sayısı ve Diğer İnflamatuvar Belirteçlerle Efüzyon İlişkisi

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Abstract

Objective: Although mortality and morbidity due to community-acquired pneumonia (CAP) decrease in childhood, parapneumonic effusion (PE) and empyema still emerge as an important problem. There are many studies related to platelet count and mean platelet volüme (MPV) in CAP together with many inflammatory markers. In this study, the need for fibrinolytic therapy (FT) and its relationship with thrombocyte count and MPV in patients with CAP+PE was investigated.

Material and Methods: This retrospective study was conducted by including patients who were hospitalized and followed up with the diagnosis of CAP and PE between 2010 and 2017 in Clinic of Pediatric Infection, Gazi University Faculty of Medicine Hospital.

Results: Forty-one patients with the diagnosis of CAP+PE were included in the study. 46.3% of the patients were female and 53.7% were male. Median age was 72 months (2.5-192 months), median hospital stay was 14 days (2-26). Fibrinolytic therapy was applied to 19 of the patients (43.9%). Of the patients recieved who received FT, 13 (68.4%) received urokinase, five (26.3%) streptokinase, and one alteplase (5.2%). The hospitalization period of patients who received FT, was significantly longer (p= 0.001), and the leukocyte count and CRP levels on the day of hospitalization were significantly higher than those who did not (p= 0.009, p= 0.001). While there was no difference in CRP and leukocyte values on the day of discharge between the patients who received FT and those who did not; on the day of discharge, the platelet value was found to be significantly higher in patients who received FT compared to patients who did not (p= 0.02). In 77.8% of patients who received FT, the highest plate-

Öz

Giriş: Çocukluk çağında toplum kökenli pnömoniye (TKP) bağlı mortalite ve morbidite azalmakla beraber parapnömonik efüzyon (PE) ve ampiyem hala önemli bir problem olarak karşımıza çıkmaktadır. Toplum kökenli pnömonilerde birçok inflamatuvar belirteçle beraber trombosit sayısı ve ortalama trombosit hacmi ile ilgili bir çok çalışma mevcuttur. Bu çalışmada TKP'ye bağlı PE gelişen hastalarda fibrinolitik tedavi (FT) ihtiyacı ile trombosit sayısı ve MPV ile ilişkisi araştırılmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışma Gazi Üniversitesi Tıp Fakültesi Hastanesi, Çocuk Enfeksiyon Servisine 2010-2017 tarihleri arasında TKP ve PE tanısıyla yatırılarak izlenen hastalar dahil edilerek yapıldı.

Bulgular: Çalışmaya toplam TKP+PE tanılarıyla yatırılarak tedavi gören 41 hasta çalışmaya dahil edildi. Hastaların %46.3'ü kız, %53.7'si erkekti. Median yaş 72 aydı (2.5-192 ay), median yatış süresi 14 gündü (2-26). Hastaların 19 (%43.9)'una FT uygulanmıştı. Fibrinolitik tedavi uygulanan hastaların 13 (%68.4)'ü ürokinaz, 5 (%26.3)'i streptokinaz, 1 (%5.2)'i alteplaz almıştı. Fibrinolitik tedavi alan hastalarda FT almayanlara göre yatış süresi anlamlı olarak daha uzun (p= 0.001), yatış gününe ait lökosit sayısı ve CRP düzeyleri anlamlı olarak daha yüksekti (p= 0.009, p= 0.001). FT alan ve almayan hastalar arasında taburculuk günü CRP, lökosit değerleri açısından fark saptanmazken; taburculuk günü trombosit değeri fibrinolitik tedavi alan hastalarda almayan hastalara göre anlamlı olarak daha yüksek bulundu (p= 0.02). Fibrinolitik tedavi alan hastaların %77.8'inde en yüksek trombosit değeri yatışın 10. gününden sonra gelişmiş, fibrinolitik tedavi almayan hastaların %69.9'unda ise trombosit sayısının en

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let value was observed after 10th day of hospitalisation whereas 69.9% of the patients who did not receive FT reached the highest platelet count in the first 10 days (p= 0.006).

Conclusion: The significantly higher CRP and white blood cell values in pneumonia and parapneumonic effusion patients who received fibrinolytic therapy compared to those who did not receive FT may be attributed to the more severe inflammation in these patients. Besides the significant increase in discharge platelet values may indicate that thrombocytosis is a late acute phase reactant. However, it may be important that the platelet count reaches the highest level after the 10th day in patients receiving FT, in terms of the possibility that this treatment may contribute to thrombocytosis.

Keywords: Parapneumonic effusion, platelet count, fibrinolytic therapy

yüksek değere ilk 10 gün içinde ulaştığı görülmüştür (%34.8'i başvuru günü) ve bu fark istatistiksel olarak anlamlı bulunmuştur (p= 0.006).

Sonuç: Fibrinolitik tedavi alan pnömoni ve parapnömonik efüzyon hastalarında yatış CRP ve beyaz küre değerlerinin FT almayanlara kıyasla anlamlı olarak yüksek olması bu hastalarda akut dönemdeki inflamasyonun daha şiddetli olmasına bağlanabilir. Yine bu hastalarda taburculuk trombosit değerlerinin anlamlı yüksekliği, trombositozun geç akut faz reaktanı olmasının bir göstergesi olabilir. Bununla beraber fibrinotilik tedavi alanlarda trombosit sayısının 10. günden sonra, en yüksek seviyeye ulaşması, bu tedavinin de trombositoza katkı sağlayabilme olasılığı açısından önemli olabilir.

Anahtar Kelimeler: Parapnömonik efüzyon, trombosit sayısı, fibrinolitik tedavi

Introduction

Although mortality and morbidity related to community-acquired pneumonia (CAP) in the childhood period decreases, parapneumonic effusion (PE) and empyema remain to be important health problems (1-3). These complications lead to consequences such as prolonged treatment and hospitalization, FT, drainage, and surgical intervention (3,4).

Reactive thrombocytosis is a hematologic disorder rarely seen in the pediatric age group. It has been reported that reactive thrombocytosis is seen in 6-15% of hospitalized children (5). Infections, in particular, are the most common causes of reactive thrombocytosis (6). Reactive thrombocytosis is considered to develop along with other inflammation markers secondary to the increase in thrombopoietin, interleukin, and catecholamine levels (7). There are studies in the literature indicating that upper and lower respiratory tract infections are the most frequent causes of reactive thrombocytosis (8,9). Similarly, there are studies demonstrating a significant relation between empyema and thrombocytosis (9).

Mean platelet volume (MPV) is a marker that increases in inflammatory diseases with a similar mechanism found in platelets in inflammation. It has been shown that MPV increases in community-acquired pneumonia (10).

In this study, the relation between the need for fibrinolytic therapy (FT) in patients developing PE in relation to CAP and inflammatory markers, platelet count, and MPV was investigated.

Materials and Methods

This retrospective study was conducted including hospitalized patients followed with the diagnosis of CAP PE between 2010 and 2017 in Gazi University, Faculty of Medicine, Clinic of Pediatric Infectious Diseases. Diagnostic criteria found in the Pneumonia Guideline of American Centers for Disease Control and Prevention and the World Health Organization were used for the definition of pneumonia and hospitalization criteria (1,11). Patients with transudative parapneumonic effusion were excluded from the study. Light criteria were used to differentiate transudative and exudative pleural fluid (4). Fibrinolytic need related to parapneumonic effusion was determined according to the recommendations of Community-Acquired Pneumonia Guideline of the American Infectious Diseases Society (1). Moreover, patients with an underlying disease and those considered to have effusion related to other causes (congestive heart failure, chronic kidney failure, etc.) were also excluded from the study. Sex, age, vaccination status, length of hospital stay, white blood cell count, platelet count, mean platelet volume, and C-reactive protein (CRP) value at the time of admission and discharge, and the amount of effusion of 41 patients meeting the criteria were recorded. Patients' chest tube/pig-tail catheter need, and the type and timing of FT, if given, was recorded. The relation of laboratory values with FT need was also evaluated.

Complete blood count in our center is run automatically with Sysmex, 6-part analysis system (XN series), and for any differential anomaly, counting is performed by a pediatric hematologist. Thrombocytosis was accepted as a platelet count of over 450.000/mm^3. Mild, moderate and severe thrombocytosis were classified as 450.000 to 700.000/mm^3, 700.000 to 900.000/mm^3, and over 900.000, respectively (12,13). MPV normal value was accepted as 7-11 fl (13).

All socio-demographic, clinical, and microbiological data were analyzed on (SPSS for Windows 17.0, Inc., Chicago, IL, USA). The same statistical package was used for analysis. Descriptive statistics were used to calculate frequency and percentage distributions. Categorical variables were expressed as numbers and percentage, and numerical variables were expressed as mean ± standard deviation or median, minimum and maximum. Statistical significance was set at $p< 0.05$.

Chi-square test was used for the evaluation of inter-group differences in categorical variables. Student's t test or Mann-Whitney U test was used for the evaluation of inter-group differences in numerical variables according to the status of normal distribution.

This study was approved by a Local Ethics Committee in 2017 and was conducted in compliance to the Helsinki Declaration.

Results

A total of 41 patients hospitalized for CAP+PE were included into the study. Of the patients, 46.3% were girls and 53.7% were boys. Median age was 72 months (2.5-192 months), and median length of stay was 14 days (2-26). Of the patients, 24.4% were immunized with 7-valent pneumococcus vaccine, 48.8% with 13-valent pneumococcus vaccine, 24.4% were not vaccinated for pneumococcus or were not fully immunized with the vaccines of the immunization calendar. Of the patients, 2.4% were aged under one year.

FT was given to 19 (43.9%) of the patients. Of the patients receiving FT, 13 (68.4%) received urokinase, five (26.3%) streptokinase, and one (5.2%) alteplase. It was determined that receiving FT did not show any difference according to sex or age (p= 0.39). The amount of pleural fluid was over 1 cm in all patients receiving FT. Length of hospital stay was significantly longer in patients receiving FT compared to those not receiving FT (p= 0.001), and leucocyte count and CRP levels on the day of admission were significantly higher in patients receiving FT (p= 0.009, p= 0.001). However, there was no difference in terms of platelet count on the day of admission between patients receiving and not receiving FT (p= 0.74) (Table 1).

When tests conducted on the day of discharge were evaluated, while there was no difference in CRP and leucocyte values between the patients receiving and not receiving FT, platelet count on the day of discharge was found significantly higher in patients receiving FT (p= 0.02). When the whole patient group was considered, it was seen that 51.2% of the patients reached the highest platelet count after 10 days and 48.8% within 10 days. The highest platelet count developed after the 10th day of hospitalization in 77.8% of the patients receiving FT, and it was observed that the highest platelet count developed within 10 days of hospitalization in 69.9% of the patients not receiving FT (on the day of admission in 34.8%), and this difference was found to be statistically significant (p= 0.006). A relation was not found between thrombocytosis on discharge and the preferred FT (p= 0.82).

Discussion

This study investigated the relation between inflammatory markers, platelet count, and MPV and receiving FT in patients with pneumonia with effusion. Inflammation markers used most commonly in clinical practice are leucocyte count, erythrocyte sedimentation rate, CRP, and procalcitonin. Besides these, thrombocyte parameters such as platelet count, MPV and PDW are also used as acute phase reactants (10). Infectious diseases are the leading diseases in which acute phase reactants increase. As the severity of inflammation increases in these diseases, so does the acute phase reactant response. It is expected to have high inflammation severity and acute phase reactant response in parapneumonic effusion (10,14,15).

Thrombocytes play an important role in inflammation and repair of damaged tissues. They can destroy some bacteria and fungi by phagocytosis (16). While primary thrombocytosis is rarely seen in childhood, secondary thrombocytosis may develop secondary to many diseases. These diseases include infections, tissue damage, anemia, autoimmune diseases, and malignancies (17). Upper and lower respiratory tract infections have been shown to be the most common causes of reactive thrombocytosis in children (8). During respiratory tract infections, thrombocyte production increases due to elevated inflammatory cytokine level (12). In patients with CAP, it is considered that there is a relation between inflammatory cytokine levels and the severity of the disease. It is believed that thrombocytosis is indirectly related to poor prognosis as a result of increased systemic inflammatory response (15).

Wolach et al. have indicated that platelet count is higher in patients with CAP and empyema (9). In addition, some studies have put forth that thrombocytosis is a risk factor for negative outcomes like prolonged hospital stay and severe clinical course in these patients (12,18). Vlacha et al. have observed in their study that thrombocytosis occurred in 86% of PE patients (19). In our study, thrombocytosis was seen on the day of admission in 36.5% of the patients and on the day of discharge in 48.7% of the patients. The relation between platelet count on discharge and the need for FT was not detected; however, it was observed that platelet counts of the patients receiving FT were higher than those not receiving FT. Supportive of the literature, our study showed that thrombocytosis was observed more often in complicated pneumonia; however, this relation could not be shown at the time of admission, which is different from the studies mentioned in the literature.

A study in the literature shows that secondary thrombocytosis develops within the 2nd-3rd week of the diseases causing it (5). Vlacha et al. have established that the median time between the onset of symptoms and the highest platelet count is 11 days (2-21) (19). In our study, it was seen that platelet count in patients receiving FT reached its highest value at a later time compared to those not receiving FT, and this period of time was observed to be later than the 10th day. This finding, apart from the fact that inflammation is more severe in patients requiring FT, may support that FT contributes to thrombocytosis, and clinicians must keep in mind that this treatment might increase thrombocytosis. This finding should be supported by prospective studies with a great number of patients.

Just as platelet count, MPV also shows variability as response to thrombopoietic stress (10,12). It has been shown that this change is related to platelet function and activation

Table 1. Descriptive statistics, of the patients with parapneumonic effusion and the comparison of the groups receiving and not receiving FT

	Total	Not receiving FT	Receiving FT	p
Sex				
Boy	19 (%46.3)	11 (%50)	8 (%42.1)	0.39
Girl	22 (%53.7)	11 (%50)	11 (%57.9)	
Age (month) (median, min-max)	72 (2.5-192)	83 (2.5-180)	54 (12-192)	
Age range				
0-2 months	1 (%2.4)	1 (%4.5)	0	0.20
2-12 months	1 (%2.4)	0	1 (%5.3)	
12-48 months	13 (%31.7)	5 (%22.7)	8 (%42.1)	
48 months and over	26 (%63.4)	16 (%72.7)	10 (%52.6)	
Vaccination statsu				
Unvaccinated/lack vaccines	10 (%24.4)	5 (%22.7)	5 (%26.3)	0.18
7 valent complete dose	10 (%24.4)	8 (%36.4)	2 (%10.5)	
13 valent complete dose	20 (% 48.8)	8 (36.4)	12 (%63.2)	
Length of hospital stay (day) (median, min-max)	14 (2-26)	9.5 (3-26)	16 (2-26)	0.001
Hospitalization CRP (gr/L) (median, min-max)	130 (2-480)	68.9 (2.5-421)	173 (2-480)	0.009
Hospitalization white blood cell/mm^3 (median, min-max)	15900 (6460-33590)	10624 (6460-24100)	20600 (9200-33590)	0.001
Hospitalization platelet/mm^3 (median, min-max)	381100 (142000-1038000)	380550 (221000-1038000)	402400 (142000-1018000)	0.74
Hospitalization thrombocytosis				
Existing	15 (%36.5)	6 (%27.3)	9 (%47.4)	0.17
None	24 (%58.5)	14 (%63.6)	10 (%52.7)	
Hospitalization thrombocytosis				
Mild	9 (%60)	3 (%13.6)	6 (%66.7)	0.81
Moderate	4 (%26.6)	2 (%9.1)	2 (%22.2)	
Severe	2 (%13.3)	1 (%4.5)	1 (%11.1)	
Hospitalization MPV (median, min-max)	7.4 (5.92-9.8)	7.45 (5.92-9.46)	7.4 (6.09-9.8)	0.44
Pleural fluid amount (mm) (median, min-max)	15 (3-70)	8.5 (3-30)	30 (12-70)	0.000
Pleural fluid amount				
<1 cm	12 (%29.2)	12 (%54.5)		0.001
>1 cm	29 (%70.7)	10 (%45.5)	19 (%100)	
Discharge thrombocytosis				
Existing	20 (%48.7)	7 (%31.8)	13 (%68.4)	0.04
None	21(%51.2)	12 (%54.5)	6 (%31.6)	
Discharge platelet/mm^3 (median, min-max)	556900 (221900-881800)	438700 (221900-708000)	591450 (244000-881800)	0.026
Discharge thrombocytosis				
Mild	14 (%34.1)	5 (%22.7)	9 (%47.4)	0.69
Moderate	6 (%14.6)	2 (%9.1)	4 (%21.1)	
Severe	0 (%0)	0	0	
Platelet value maximum day				
0-3 days	12 (%29.3)	10 (%43.5)	2 (%11.1)	0.01
3-10 days	17 (%41.5)	10 (%43.5)	7 (%38.9)	
After 10 days	12 (%29.3)	3 (%13.0)	9 (%50.0)	
Discharge MPV/mm^3 (median, min-max)	6.7 (5.37-10.9)	6.75 (5.37-10.9)	6.7 (5.9-8.1)	0.84

(20). A higher MPV value is the indicator of platelet activation and thus intense inflammation (10,12).

There are many studies investigating the relation between mean platelet volume and inflammation. Some of these inflammatory diseases include cystic fibrosis, ulcerative colitis, familial Mediterranean fever, newborn respiratory distress syndrome, upper urinary system infections, and sepsis (21-26).

There are also various studies in the literature related to mean platelet volume and pneumonia severity. In a study by Öncel et al. MPV at the time of presentation in patients with severe community-acquired pneumonia requiring hospitalization was significantly higher than oupatients with community-acquired pneumonia and healthy controls (10). Distinctly from that study, Şahin et al. have found lower MPV at the time

of diagnosis in patients with pneumonia compared to those without (14). In our study, when the whole patient group was considered, median MPV value at the time of hospitalization was 7.4 (5.92-9.8) and at discharge, it was 6.7 (5.37-10.9); however, this difference was not found statistically significant. Nonetheless, hospitalization and discharge MPV values did not show any difference between patients receiving and not receiving FT. In the literature, the number of pediatric studies on this topic is low, and the studies include CAP studies, and as stated above, study results are contradictory. In addition, evaluation and commentary are given on only MPV value in those studies. All patients in our study had CAP+PE, which enabled an evaluation in a more homogenous group. In addition to these, our study might be superior to other studies since an evaluation was made on values determined on hospitalization and discharge days.

Limitations of our study include the nature of the study being retrospective, not having a control group, not determining the role of other factors, and having a low number of patients. Further prospective studies with higher number of patients are needed to better evaluate the relation between platelet count and FT and especially to better put forward the relation between MPV and parapneumonic effusion.

To conclude, the fact that hospitalization CRP and white blood cell count values of patients diagnosed with pneumonia and parapneumonic effusion receiving FT is significantly higher than those not receiving FT may be linked to the fact that inflammation during the acute phase of the disease is higher in these patients. Again, significant elevation in platelet value during discharge in these patients can be an indicator that thrombocytosis is a late acute phase reactant. The fact that platelet count reached its highest level after the 10th day in those receiving FT brings to mind that this treatment also contributes to thrombocytosis, but this outcome should be supported by prospective studies with a control group since our study was a retrospective one and did not include a control group and determine the role of other factors.

Ethics Committe Approval: The approval for this study was obtained from Gazi University Clinical Researches Ethics Committe (Decision No: 302, Date: 19.06.2017).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- AT; Design- HT; Supervision- AT; Resource- HT; Data Collection and/or Processing- TBD, CG; Analysis and/or Interpretation- TBD; Literature Search- BCCY, Writing- TBD; Critical Review- CG, HT, AT.

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