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MEAN PLATELET VOLUMES OF INFANTS WITH ACUTE BRONCHIOLITIS, IS THERE A CORRELATION BETWEEN THEM?

Akut Bronşiolit Tanılı İnfantlarda Ortalama Platelet Hacmi, İkisi Arasında Bir Korelasyon Var Mı?

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Abstract

Aim: Acute bronchiolitis is the most common lower respiratory tract infection of children younger than 2 years of age. There aren't any standardized diagnostic criteria and severity assessment classifications for acute bronchiolitis available in literature. Mean platelet volume (MPV) has shown to be effected in inflammatory conditions and to our knowledge there's only one recent study in children with acute bronchiolitis that demonstrated an association between MPV change and acute brınchiolitis.

Materials and Methods: In this retrospective study we enrolled 555 children diagnosed with Acute bronchiolitis and 516 healthy infants with a matching age and sex.

Results: MPV levels were found significantly higher in patient group (8,2 ± 0,8 fL) than the control group (7,9 ± 0,8 fL). In terms of hospitalization need, no significant difference was detected between the MPV values of the hospitalized group and the outpatients (8,3±0,8 fL; 8,2±0.7 fL, respectively).

Conclusions: In conclusion, our data show that MPV values are significantly elevated in acute bronchiolitis compared to healthy infants. However, MPV can't be used as a guidance in attack severity nor can it predict hospitalization and systemic steroid need.

Key words: MPV, bronchiolitis, platelet.

Öz

Amaç: Akut bronşiolit, 2 yaşından küçük çocuklarda en sık görülen alt solunum yolu enfeksiyonudur. Literatürde akut bronşiolit için standart tanı kriterleri ve şiddet değerlendirme sınıflamaları mevcut değildir. Ortalama platelet hacminin (MPV) lokal inflamasyondan etkilendiği gösterilmiştir ve akut bronşiolit ile MPV ilişkisini gösteren tek bir çalışma bulunmaktadır.

Materyal ve Metot: Bu çalışmada MPV ile akut bronşiyolit arasındaki ilişkiyi belirlemeyi amaçladık, ayrıca hastalığın şiddetini değerlendirmede yararlı bir belirteç olup olmadığını araştırdık. Bu retrospektif çalışmada akut bronşiolitis tanısı alan 555 çocuğa ve eşleştirilmiş yaş ve cinsiyete sahip 516 sağlıklı bebek çalışma grubuna dahil edilmiştir.

Bulgular: MPV düzeyleri hasta grubunda (8,2 ± 0,8 fL) kontrol grubuna (7,9 ± 0,8 fL) göre anlamlı olarak yüksek bulundu. Hastaneye yatış açısından hastaneye yatırılan grup ve poliklinik hastalarının MPV değerleri arasında anlamlı bir fark saptanmamıştır (sırası ile, 8,3 ± 0,8 fL; 8,2 ± 0,7 fL)

Sonuç: Sonuç olarak, verilerimiz, akut bronşiolit varlığında MPV değerlerinin sağlıklı bebeklere göre anlamlı derecede yükseldiğini göstermektedir. Bununla birlikte, MPV atak şiddetinde bir rehber olarak kullanılamaz ve hastaneye yatışı ve sistemik steroid ihtiyacını tahmin edemez.

Anahtar kelimeler: MPV, bronşiolit, platelet.

INTRODUCTION

Acute bronchiolitis is the most common lower respiratory tract infection of children younger than 2 years of age. It's characterized by bronchial inflammation causing the typical symptoms of wheezing, coughing, rapid breathing, abdominal withdrawal, and expiration prolongation.[1] Viruses are mostly responsible for the etiology. Among these viruses, RSV is the main cause for the acute bronchiolitis with more than 50% of the cases[1, 2]. Every year, 3-15% of the infants are hospitalized for the treatment of acute bronchiolitis and that pushes up the patient-care expenditures[3,4].

In the latest acute bronchiolitis guideline of the American Academy of Pediatrics[5], it's recommended that clinicians should diagnose acute bronchiolitis based on history and physical examination. According to the guideline, if the diagnosis of acute bronchiolitis is made by the clinical findings, no further investigation is needed, including radiological screenings and laboratory tests. The management decision is

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mainly made based on the severity of disease which can be hard to assess especially in young infants. Therefore, many different clinical scores are in use to determine the severity of respiratory distress and methods vary among the clinics. So, there's still a great need for the objective parameters that would quide clinicians through out the process of diagnose, treatment, and discharge[6].

Although their essential role in forming an effective hemostatic plug is the main focus in studies, recently platelets are getting more recognized for their significant roles in vascular remodeling, tissue renewal, host immunity and response to the infections[7,8]. Mean platelet volume (MPV) is an indicator to assess sizes of the platelets. There is an inverse relation with MPV and platelet count [9] which provides a stabile platelet mass (platelet count x MPV) in the blood circulation and that leads a stabile hemostatis[10]. Recent studies showed that MPV is associated with platelet activation and large platelets are known to be more active in function[11]. Although trombopoetin (Tpo) is the main regulator of megakariopoesis, many hormonal and immunological agents effect maturation and secretion of platelets from bone marrow, including granulocyte macrophage coloni situmulating factor (GM-CSF), IL-1, IL-3, IL-6, IL-11 and TNF-alpha[12]. IL-1beta, IL-6, and IL-8 are effective stimulators of acute phase response [13]. Therefore, while inflammatory cytokines activate platelets and cause an increase in their sizes, those active large platelets contribute to the inflammatory process by secretion of more inflammatory cytokines.

Results of the recent studies suggest that one of the platelet activation indice, MPV, can be used as an acute phase reactant in diseases[13]. In literature, there are many studies available investigating MPV and its relation between several diseases including; pneumonia[14], asthma[15], PFAPA[16], urinary tract infections[17], acute gastroenteritis[18], acute rheumatic fever (ARF)[19], neonatal sepsis[20], familial Mediterranean Fever (FMF) [21], acute renal failure, [22] and Kawasaki disease [23].

To our knowledge there's only one recent study in children with acute bronchiolitis that demonstrates a decrease in MPV[24]. The study group was small and the results of this study contradicts with our knowledge about platelet size changes in inflammation. Therefore more studies are needed to clarify the relation between MPV and acute bronchiolitis. In this present study we aim to determine the association between MPV and acute bronchiolitis, also identify whether it's a useful marker on assessing disease severity or not.

METHOD AND MATERIALS

Collection of the data:

In this retrospective study we enrolled 555 children diagnosed with acute bronchiolitis and 516 healthy infants with a matching age and sex, who were admitted to the Deparment of Pediatrics Outpatient Clinic at the Hospital of Namık Kemal University Faculty of Medicine in the years between 2014 and 2016, with an age interval of 2-24 months.

Exclution criteria:

Children who had a underlying chronical disease, immune deficiency and another infectious diseases were excluded from this study, including the diseases reported in the literature that were shown to effect MPV levels and other coexisting conditions which may effect MPV values. Some of those diseases are: respiratory conditions such as asthma and pneumonia; endocrinological diseases, hemotological disorders, rheumatic diseases, cardiac conditions,

immunodeficiencies, infections and other conditions including acute and chronic renal failure, malignancy, and protein energy malnutrition. Those with preterm birth (<36 weeks) were also not included in the study.

Only patients who had blood samples at their first visit were enrolled to this study. Patients who had corticosteroid treatment 1 month before the collection of blood samples were exluded from this study to avoid possible effects of corticosteroids on MPV levels.

Data classification:

In our institude we use an acute bronchiolitis clinical score based on patient's phsical examination, oxygen saturation and FiO2 need. The disease severity is classified as mild, moderate and severe (Table 1). In this study we used recorded clinical scores of the patients' on their first admittion our hospital.

Patients were divided into three groups as outpatients, patients admitted to the pediatrics clinic and patients admitted to the pediatrics intensive care unit (PICU). According to their ages patients were classified as 2 to 6 months of age, 7 to 12 months of age and 13 to 24 months of age and patients were also divided into two groups based on the length of their hospital stays as follows; 1 to 3 days and 4 to 15 days. Patients who received systemic corticosteroid treatments were also noted.

Table 1. Acute Bronchiolitis severity classification

	Mild	Moderate	Severe
Retractions	Mild	Moderate	Severe
Breath rate/minute	<50	50-70	>70
Pulse/minute	<140	140-160	>160
Apnea	None	None	Present
SaO2	>93%	86-92%	<85%
Cyanosis	None	None	Present
FiO2 needed for SaO2>93%	None	21-40%	>40%

Collection of the blood samples

In this study, complete blood count (CBC) and C-reactive protein (CRP) values were obtained from our instute's computerized patient database. Venous blood samples were taken at the blood sampling unit of our clinic at patients' first visit, before the treatment. Blood samples were collected in K2EDTA tubes and CBC analyses were performed by Pentra Dx Nexus (Japan) automated hematology analyzer. For this analyzer MPV reference range was 7.4-10.4 fL, platelet reference range was 130.000-400.000. CRP values were obtained from blood samples that were collected into standart tubes and analyzed by Hitachi Cobas 6000 automatic analyzer.

Necessary ethics committee approval was obtained from the local Ethics Committee.

Statistical analysis

Statistical analysis of the data was done with Statistical Package for Social Sciences for Windows 18.0 software (Ver. 18.0, SPSS, Chicago, IL). Descriptive statistical methods (Mean, Standard deviation, percentage) were used in the analysis of the data. The normality of our variables were checked by the Kolmogorov-Smirnov test and parametric tests were preferred because all of our variables were normally distributed. Student t test was used for comparison of parameters between two groups, and ANOVA test was used when there were three or more groups. Chi-square test was used for the comparison of qualitative data. In the statistical analysis findings of $p<0.05$ were considered significant, within the 95% confidence interval.

RESULTS

A total of 555 patients with acute bronchiolitis (214 girls and 341 boys) constituted the patient group whereas the control group was consisted

of 516 healthy children (212 girls and 305 boys) in this present study. There was no significant difference found between the mean ages of the patient group (8,9±6,0 months) and the control group (8,8±6,1), (p> 0,05). Also in terms of gender we found no significant difference between patient group (38,6% girls, 61,4% boys) and control group (41,1% girls and 58,9% boys), (p> 0,05). The patient group was classified as mild, moderare and severe according to the severity of the disease. There were 275 infants (41,8% girls, 58,2% boys) in the mild bronchiolitis attack group, 220 infants (33,6% girls, 66,4% boys) in the moderate bronchiolitis attack group and 60 infants (41,7% girls, 58,3% boys) in the severe bronchiolitis attack group. There was no significant association between attack severity and gender (p> 0.05). MPV levels were found significantly higher in patient group (8,2 ± 0,8 fL) than the control group (7,9 ± 0,8 fL), (p <0.01). To investigate the relation between MPV and hospitalization need, patients divided into three groups as outpatients, admitted to the clinic and admitted to PICU. In terms of hospitalization need no significant difference detected between the MPV values of hospitalized group and outpatients, 8,3±0,8 fL; 8,2±0.7 fL respectively (p> 0.05). Also PICU admitted group (8,3±0,8 fL) and non-PICU admitted group (8,2±0,8 fL) showed no statistically difference in their MPV values.

When patients divided into two groups according to their hospital stays, patients with a hospital stay of 1-3 days had a median MPV of 8,3±0,9 fL and patients with a hospital stay of 4-15 days had a median MPV of 8,2 ± 0,8 fL.MPV didn't differ significantly between two groups (p> 0,05).

Acute bronchiolitis group was divided into three groups based on the severity of the disease to investigate the association between MPV and attack severity. Mean MPV was 8,3±0,8 fL in the mild attack group, 8,2±0,8 fL in the moderate attack group, and 8,3±0,8 fL in the severe attack group (p> 0.05). There was no significant association found between attack severity and MPV levels.

To identify whether the need of systemic corticosteroid treatment has any impact on MPV values or not, patients catagorized according to having/not having systemic steroids in their medical treatment. MPV values of the infants who were treated with and without systemic corticosteroids were found as 8,2 ± 0,8 fL and 8,3±0,8 fL respectively. There were no significant differences between these two groups (p> 0.05).

White blood cell (WBC), platelet count and CRP rose significantly in patient group compared to healthy infants, CRP evelated significantly in hospitalized patients in comparison to outpatients, and in patients who stayed in hospital 4-15 days compared to patients stayed 1-3 days.

Among evaluated markers MPV and platelet count showed a significant difference between the age groups. MPV was higher in the age group of 7-12 months than 13-24 age group whereas platelet count was higher in the age group of 2-6 months than 13-24 age group.

Only CBC parameters showed a significant association with disease severity was % PNL and % lymphocytes. While %PNL was rose in severe attack group compared to mild and moderate attack groups, on the contrary %lymphosite was decreased in severe attack group compared to mild and moderate attack groups.

Table 2. Comparison of the demographic Characteristics with patient and control groups

Demographic	Control group	Patient	Mild attack

Characteristics	(n=516)	group (n=555)	group (n=275)
Sex (n/%)			
Girls	212 (41.1%)	214 (38.6%)	115 (41.8%)
Boys	304 (58.9%)	341 (61.4%)	160 (58.2%)
Median Age SD (months)	8.8 ± 6.1	8.9 ± 6.0	9.6 ± 6.2

SD, standard deviation

Table 3. Comparison of laboratory markers between patient and control groups

Laboratory Markers	Patient Group Mean ± SD	Control group Mean ± SD	P*
MPV (fL)	8.2 ± 0.8	7.9 ± 0.8	0.000
WBC (x 10^3/mm^3)	11.9 ± 4.8	9.1 ± 2.5	0.000
Platelet count (x 10^3/$mm^{3)}$	422.3 ± 136.9	381.6 ±108.2	0.000
CRP (mg/L)	7.1 ± 13.6	0.8 ± 0.8	0.000

MPV, mean platelet volume; WBC, white blood cell; CRP, C-reactive protein; SD, standard deviation

Table 4. Comparison of laboratory markers between acute bronchiolitis attack groups

Laboratory Markers	Mild attack Mean ± SD	Moderate attack Mean ± SD	Severe attack Mean ± SD	P
MPV (fL)	8.3 ± 0.8	8.2 ± 0.8	8.3 ± 0.8	0.682
WBC (x 10^3/mm^3)	12.0 ± 4.6	11.7 ± 4.9	12.5 ± 5.1	0.514
Platelet count (x 10^3/$mm^{3)}$	418.6 ± 141.5	422.0 ± 121.1	440.6 ±167.9	0.531
CRP (mg/L)	5.9 ± 13.4	8.1 ± 13.3	9.1±15.2	0.099
PMNL%	36.7 ± 23.2	36.5 ± 21.7	45.1 ±20.8	0.022[a]
Lymphocyte %	53.7 ± 14.8	54.0 ± 14.3	44.2 ±18.2	0.000[a]

MPV, mean platelet volume; WBC, white blood cell; CRP, C-reactive protein; PMNL, polymorphonuclear leukocytes, SD, standard deviation

a: Shows the significant difference of the severe attack group with both mild/moderate attack groups.

Table 5. Comparison of laboratory parameters with hospitalization, PICU admission and systemic steroid treatment

	n	WBC*	Trombosit*	MPV*	CRP*
Hospitalization	(116)	11,8±4,7	419,2±127,1	8,2±0,7	4,7±11,3
	(439)	12,0±4,8	423,1±139,5	8,3±0,8	7,8±14,1
p		0,667	0,783	0,512	0,015
PICU admission	(495)	11,9±4,7	420,1±132,7	8,2±0,8	6,9±13,4
	(60)	12,5±5,1	440,6±167,9	8,3±0,8	9,1±15,2
p		0,358	0,366	0,419	0,238
Systemic Steroid treatment	(241)	12,2±4,7	424,8±151,0	8,3±0,8	7,1±15,6
	(314)	11,8±4,9	420,4±125,2	8,2±0,8	7,1±11,9
p		0,378	0,711	0,444	0,970

***** Mean ± SD

DISCUSSION

In this present study, MPV values of children with acute bronchiolitis were found significantly higher than healthy infants. However there were no association between MPV and disease severity. Likewise, need for hospitalization, length of stay, systemic steroid treatment and PICU admittion showed no correlation with MPV levels.

In the literature, the majority of the studies in acute bronchiolitis evaluate and emphasize on the disease severity. As the traditional inflammatory markers fail to determine the severity of inflammation and lung injury, that led researchers to investigate more on new markers[25]. In the study of Garcia-Salido et al[3]. they found sRAGE (Soluble Form of Receptor for Advenced Glycation End Products) levels were significantly high in patients admitted to PICU because of severe acute bronchiolitis compared to the control group. Mehta et al[6]. demonstrated a significant lactate dehydrogenase (LDH) rise in nasopharyngeal secretion aspirations (NSA) of the children with acute bronchiolitis who were admitted to PICU compared to the children treated in emergency service. They suggested that NSA-LDH, apoptosis indicators NSA-Caspase 3 and 7, and NSA-LDH/NSA-Caspase 3/7 ratios are predictive markers for the severity of the acute bronchiolitis and can be useful to identify the infants who are in need of PICU admission. Although NSA-LDH and NSA Caspase 3/7 are useful parameters to determine the disease severity, none of the markers are routinely available in clinical settings. On the other hand complete blood count (CBC) is a common test, ordered in majority of the cases. Therefore, assessing MPV is more practical and can be done without extra cost.

Being responsible for the almost 50% of the acute bronchiolitis cases RSV and its cytokine responses are the most studied ones in the literature. Focusing only on RSV, leaves a great gap in cytokine profiles of other agents [26]. Despite the emerging studies, the immune response invoked by RSV is complex and not yet fully understood. In RSV bronchiolitis specific pro-inflammatory and anti-inflammatory response has shown in the literature. IL-6, IL-8, GM-CSF, IFN-gamma, TNF-alpa, IL-1beta, G-CSF and MIP-1beta levels are elevated in children with RSV bronchiolitis compared to RSV-negative bronchiolitis but greater inflammatory response doesn't have a major impact in terms of hospitalization need[27]. Possibly, that may provide an explanation for MPV and hospitalization need weren't found related in our present study. Although, the cytokine responses still not clear for every virus, it's known that many pro and anti-inflamatory cytokines elevate in acute bronchiolitis, this suggest MPV changes may occure during the disease as a reaction to inflammation.

In the literature there was only one study available investigating the relation of MPV and Acute bronchiolitis. In that study, Ergül et al[24]. enrolled 313 patients and 201 healthy infants under 2 years of age. They found that MPV values in all severity groups were significantly lower than control group. However MPV values didn't show any significant changes among the severity groups. On the contrary, in our present study we found that MPV values were significantly elevated in acute bronchiolitis compared to healthy infants. Rise in MPV values is an expected condition in acute inflammation since large and more reactive platelets are seen. The difference in our results can be explained by our larger study group, a total of 1071 children (555 patients, 516 healthy infants). Moreover our patient group wasn't only consist of hospitalized children as in Ergül et al.'s study. Similar with the previous study we found no relation with MPV and acute bronchiolitis severity.

In the study of Renshaw et al[28]. they investigated the relation between RSV infections of the respiratory tract and MPV. They enrolled 58 patients with positive rapid RSV antigen tests and 100 patients with positive viral culture. The results showed that MPV values were significantly decreased in children with RSV positive infection in comparison to the control group. They also reported that there were no association between other viruses and MPV. Thus, they suggested that changes in MPV is specific to RSV[28]. Although RSV is responsible for the 50% of the acute bronchiolitis cases, there're many other viruses in the etiology. Therefore, the results of their study don't reflect all of the acute bronchiolitis cases. Also, they enrolled adults in this study and their cohort group included not only acute bronchiolitis but also pneumonia and children with airway obstruction. Most strikingly, their results were similar with the study of Ergül et al[24], both demonstrated a decrease in MPV. That suggests, children with acute bronchiolitis enrolled in Ergül et al.'s study may had a viral etiology dominated by RSV. However, in our present study we provided data from a relatively large population and also included outpatients along with the hospitalized infants. Therefore, our results reflect all the acute bronchial cases caused by a wide range of viral agents seen in our region.

There are other studies in the literature that studies the relations between MPV and infections. In another respiratory infection research, it was reported that MPV decreases in children with community acquired pneumonia. They concluded that MPV can be helpful in diagnosis but its low spesivity and low negative

predictive value can cause false negative results[29]. Quite few studies in the literature were investigated MPV values in urinary tract infections. Lee et al[17]. demonstrated a significant rise in MPV levels in the children with acute pyelonephritis (APN) compared to children with lower urinary tract infections.

Studies in newborns reported a significant MPV rise in preterms with RDS compared to preterms who didn't develop RDS[30] and in newborns with neonatal sepsis compared to control group, also in proved neonatal sepsis compared to clinical sepsis[20].

Results of the studies in the literature are still contradictory. The majority of them provide evidence that MPV is effected in many diseases but even the studies done in the same diseases showed different results. That suggests platelets are effected by inflammatory mediators but the profile of cytokine and chemokines may play an important role in determining the size of the platelets. We agree with Cho et al[31]. duration of the inflammation is essential for the mediators to make their effects. Even in chronic diseases inflammatory conditions changes from early days to later stages. Also we suggest that for the infectious diseases the cause agent may effect the changes in MPV values by triggering different immunologic pathways.

In conclusion, our data show that MPV values significantly elevate in acute bronchiolitis compared to healthy infants. MPV is a CBC parameter which is available in every clinic without extra cost. Therefore, assessing MPV is practical and can be helpful for the clinicians in acute bronchiolitis diagnosis. However, MPV can't be used as a guidance in attack severity nor can predict hospitalization, PICU admition, and systemic steroid need. Further studies investigating the MPV value changes based on the causing virus may help us understand the mechanism of MPV variations and may show whether MPV can be used as a agent-specific predictive marker or not.

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