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Original Article *Özgün Araştırma*

ACETYLSALICYLIC ACID RESISTANCE IN PATIENTS WITH ACUTE CORONARY SYNDROME AND ITS RELATIONSHIP BETWEEN MEAN PLATELET VOLUME

Akut Koroner Sendrom Hastalarında Asetilsalisilik Asit Direnci ve Ortalama Platelet Hacmi ile İlişkisi

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ABSTRACT

Objective: Insufficient biochemical response to Acetylsalicylic Acid (ASA) is defined as 'ASA resistance'. Its prevalence is unknown. The frequency of death and cardiovascular events rises as the mean platelet volume (MPV) increases in patients with acute coronary syndrome (ACS). Patients with high MPV are more resistant to antiplatelet agents. Our study aimed to evaluate the temporal variability of ASA resistance and platelet reactivity in ACS patients and to demonstrate its relationship with MPV.

Material and Methods: Our study is single-center prospective, cross-sectional study. Patients over 18 years of age who were hospitalized due to ACS and underwent percutaneous coronary intervention were included. ASA resistance and MPV measurements were taken at admission and first month. The prevalence and alteration of ASA resistance and its relationship with MPV were analyzed.

Results: 115 patients were included in the study. 7 patients (6.08%) were ASA-resistant at first admission and increased to 22 (19.13%) at the 1st month follow-up (p=0.003). A significant numerical increase in ASA resistance was observed in the first month of controls (p<0.01). The prevalence of ASA resistance was calculated as 22.6%. MPV was found to be high in 16 patients (13.9%) at the time of admission, while it was found to be high in 15 patients (13.04%) at the 1-month follow-up (p=0.98). MPV values were found to be similar in patients with and without ASA resistance.

Conclusion: ASA resistance is more common than thought. Therefore, evaluating platelet functions in predicting the clinical outcomes of patients is important in determining the effectiveness of the antiplatelet agent used.

Keywords: *Acute coronary syndrome, acetylsalicylic acid, mean platelet volume*

ÖZ

Amaç: Asetilsalisilik asite **(**ASA) yetersiz biyokimyasal yanıt 'ASA direnci' olarak tanımlanır. Yaygınlığı bilinmemektedir. Akut koroner sendrom (AKS) hastalarında ortalama trombosit hacmi (OTH) arttıkça mortalite ve kardiyovasküler olayların sıklığı artar. Yüksek OTH'li hastalar antiplatelet ajanlara daha dirençlidir. Çalışmamız AKS hastalarında ASA direnci ve trombosit reaktivitesinin zamansal değişkenliğini değerlendirmeyi ve OTH ile ilişkisini göstermeyi amaçlamıştır.

Gereç ve Yöntemler: Çalışmamız tek merkezli prospektif, kesitsel bir çalışmadır. AKS nedeniyle hastaneye yatırılan ve perkütan koroner girişim uygulanan 18 yaş üstü hastalar çalışmaya dahil edildi. ASA direnci ve OTH ölçümleri başvuruda ve birinci ayda alındı. ASA direncinin yaygınlığı ve değişimi, OTH ile ilişkisi analiz edildi.

Bulgular: Çalışmaya 115 hasta dâhil edildi. İlk başvuruda 7 hasta (%6,08) ASA dirençliydi ve 1. ay kontrolünde bu sayı 22'ye (%19,13) yükseldi (p=0,003). 1. ay kontrollerinde ASA direncindeki sayısal artış anlamlı bulundu (p<0,01). ASA direnci prevalansı %22,6 olarak hesaplandı. Başvuru anında MPV 16 hastada (%13,9) yüksek bulunurken, 1. ay kontrolünde 15 hastada (%13,04) yüksek bulundu (p=0,98). ASA direnci olan ve olmayan hastalarda MPV değerlerinin benzer olduğu görüldü.

Sonuç: ASA direnci düşünüldüğünden daha yaygındır. Bu nedenle, trombosit işlevlerini değerlendirmek hastaların klinik sonuçlarını tahmin etmede, kullanılan antiplatelet ajanın etkinliğini belirlemede önemlidir.

Anahtar Kelimeler: *Akut koroner sendrom, asetilsalisilik asit, ortalama platelet hacmi*

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INTRODUCTION

Despite significant advances in the diagnosis and treatment of acute coronary syndromes (ACS), it remains a leading cause of death worldwide.[1] Platelets play an important role in the pathogenesis of atherosclerosis. Therefore, antiplatelet therapies (AT) are of key importance in the treatment of atherosclerotic diseases such as coronary artery disease (CAD), peripheral artery disease (PAD), and ischemic cerebrovascular diseases (CVD).[2] Dual AT used after ACS and/or percutaneous coronary intervention (PCI) is the mainstay of treatment.[3] Dual AT consists of acetylsalicylic acid (ASA) and platelet P2Y12 receptor blockers. ASA prevents platelet aggregation by inhibiting Thromboxane-A2 synthesis through cyclooxygenase-1 (COX-1) enzyme blockade. ASA reduces serious events in patients with CAD.[4] However, a significant number of patients experience recurrent ischemic events under ASA. This can be explained by reasons such as the patient's compliance with treatment and platelet activation through multiple pathways. Additionally, studies have proven that variable platelet inhibition occurs under ASA treatment.[3,5,6] Insufficient biochemical response to ASA is defined as 'ASA resistance'. Its prevalence is unknown due to differences in definitions regarding this issue, the use of different doses of medication and the use of different diagnostic tests.[7]

The frequency of death and cardiovascular events rises as the mean platelet volume (MPV) increases in patients with acute coronary syndrome (ACS).[8] However, increased platelet reactivity in ACS is associated with increased MPV.[9-11] There are studies showing that patients with high MPV are more resistant to antiplatelet agents.[12]

Our study aimed to evaluate the temporal variability of ASA resistance and platelet reactivity and its effect on short-term prognosis in ACS patients and to demonstrate its relationship with MPV.

MATERIALS AND METHODS

Our study is a single-center prospective, cross-sectional and before-after comparative study. Patients over 18 years of age who were hospitalized due to ACS and underwent PCI were included in the study. The exclusion criteria were as follows: patients with contraindications for ASA use, those discharged or who passed away before 24 hours, individuals who regularly use anticoagulants or anti-inflammatory drugs, those with active malignancy, patients with bleeding or known bleeding disorders, individuals receiving fibrinolytic therapy, and patients with poor treatment compliance. Patients were given 100 mg ASA maintenance treatment after 300 mg ASA loading. Blood samples were taken from the patients within 24 hours after the loading dose. ASA resistance was evaluated with the Multiplate impedance aggregometer device. 0.2 mM/lt ADP was used as an inducer. In the aggregometer device, the impedance increase caused by the aggregation of platelets against time in the electrodes was converted to AU units and this value was indirectly reflected in the graphs as AUC. Patients with AUC ≥500 were considered ASA resistant.

The MPVs of the patients were recorded and 1 standard deviation above the mean MPV values was accepted as the cut-off value. Patients above this value were considered to have high MPV.

The primary composite endpoint was determined as recurrent ACS, heart failure, shock, stroke and death. Secondary endpoints were determined as major and minor bleeding. Major bleedings were defined as intracranial, intraocular, intra-abdominal (retroperitoneal or intraperitoneal, bleeding requiring invasive intervention), bleeding that caused a decrease in hemoglobin of more than 2 units and required more than 3 units of blood transfusion. Minor bleeding was defined as bleeding other than these bleedings. Patients were followed for clinical composite endpoints over a 1-month period. At the 1st month follow-up, a blood sample was taken again and re-evaluated for ASA resistance and MPV. The 1st month samples were compared with the samples taken at the first admission. The study was carried out with the permission of the local ethics committee (Akdeniz University Clinical Research Ethics Committee, Date: 2013, Decision No:2013.04.0103.013). We obtained an informed consent form from all patients for the procedure. All procedures were conducted in accordance with ethical guidelines and principles of the Declaration of Helsinki.

Statistical analysis

Data were analyzed using Predictive Analytics SoftWare (PASW) 18 (SPSS/IBM, Chicago, IL, USA). Descriptive statistics such as frequency distribution, mean, and standard deviation were used to describe the sample. The assumption of compliance with normal distribution was examined with the Shapiro Wilk test. The difference between the means of two independent groups was analyzed by "Student t test" or "paired t test" when parametric test assumptions were met. When the assumptions were not met, they were analyzed with the "Mann-Whitney U" or "Wilcoxon Sign Rank test" test. Categorical data were examined with the "chi-square significance test" or "Fisher's Exact test". A 95% significance level was used to determine differences in the analyses. The p value of <0.05 was considered statistically significant. The consistency of the measurements taken at the time of admission and at the first month was evaluated by Bland Altmann analysis.

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RESULTS

115 patients were included in the study. The mean age of the patients was 57.38±10.11. The basic characteristics of the patients, ACS types and type of antithrombotic drugs they used at the time of admission are shown in Table 1.

Table 1: Baseline characteristics of patients

Parameter	N (%)
Gender (Male)	96 (%83.4)
DM	40 (%34.8)
HT	51 (%44.3)
Smoking	54 (%47)
Presence of CAD	24 (%20.9)
Presence of CVD	2 (%1.7)
Presence of PAD	1 (%0.9)
Type of ACS:	
-USAP	18 (%15.7)
-NSETMI	33 (%28.7)
-STEMI	64 (%55.6)
ASA use	31 (%26.9)
Clopidogrel use	11 (%9.5)

ACS: Acute coronary syndrome, ASA: Acetyl-salicylic acid, CAD: Coronary artery disease, CVD: Cerebrovascular disease, DM: Diabetes mellitus, HT: Hypertension, NSTMI: Non-ST elevation myocardial infarction, PAD: Peripheral arterial disease, STEMI: ST elevation myocardial infarction, USAP: Unstable angina pectoris

Seven patients (6.08%) were ASA-resistant at first admission and increased to 22 (19.13%) at the 1st month follow-up (p=0.003). It was determined that ASA resistance disappeared in 4 of the 7 patients who were initially ASA resistant at the 1st month follow-up, and 3 of them continued to remain ASA resistant. While 19 (16.52%) patients did not have ASA resistance on admission, they became ASA resistant in the first month. The numerical increase in the AU values of ASA resistance in the 1st month control was found to be statistically significant (p<0.01) (Figure 1). Ultimately, a total of 26 patients were evaluated as ASA resistant and the prevalence of ASA resistance was calculated as 22.6%.

The mean MPV values at the time of admission were 8.50±0.77 fl (6.9-10.2 fl) and 8.49±0.78 fl (6.8-10.5 fl) at the 1st month follow-up. Based on the 9.27 fl limit value for MPV, it was found to be high in 16 patients (13.9%) at the time of admission, while it was found to be high in 15 patients (13.04%) at the 1-month follow-up (p=0.98). The values of 12 (75%) of 16 patients with high baseline MPV values normalized at the 1st month control, and the values of 4 (25%) remained high. An increase in MPV values was detected in the 1st month follow-up of 11 (9.5%) patients whose MPV values were normal at baseline (Figure 2).

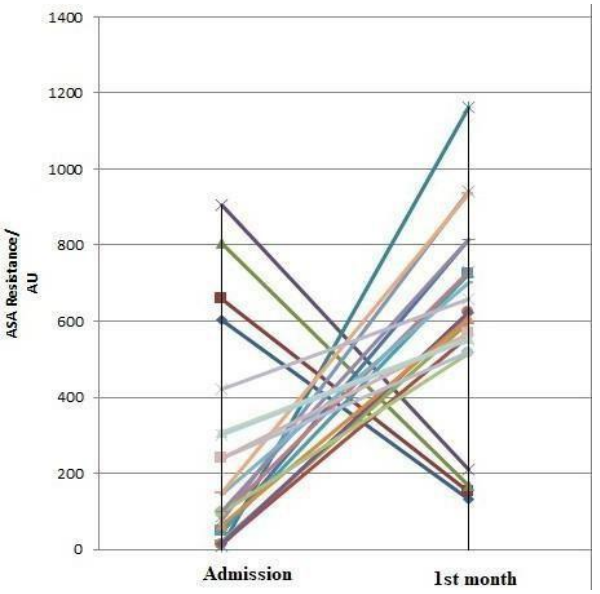

Figure 1: Display of ASA resistance on admission and 1st month: ASA resistance disappeared in 4 of 7 patients with ASA resistance at admission, and ASA resistance developed in the 1st month in 16 patients who did not have ASA resistance at baseline.

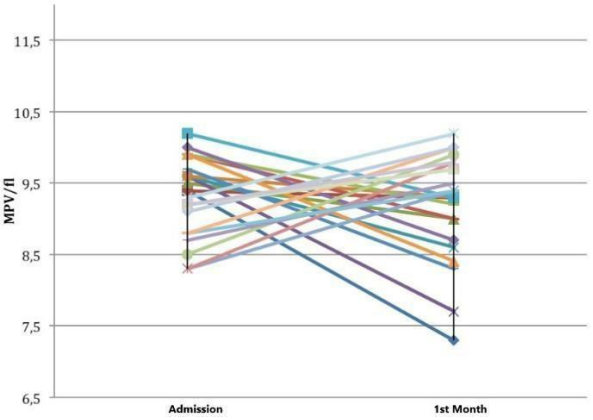

Figure 2: Display of MPV values on admission and 1st month: In 12 of the 16 patients with high MPV values at admission, MPV normalized in the first month, and in 11 patients whose initial values were normal, it increased in the first month.

MPV values at the time of admission and after the first month were found to be similar in patients with and without ASA resistance (Table 2).

Table 2: Mean MPV values in patients with and without aspirin resistance

	AR+	AR-	p value
MPV on admission (fl)	8.54	8.5	0.907
MPV at 1 st month (fl)	8.65	8.45	0.408

AR: Acetyl salicylic acid resistance, MPV: Mean platelet volume

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A 94.8% agreement was observed between the MPV measurements at admission and the 1st month control, and a 90.5% agreement in the AU values of ASA resistance (Figure 3).

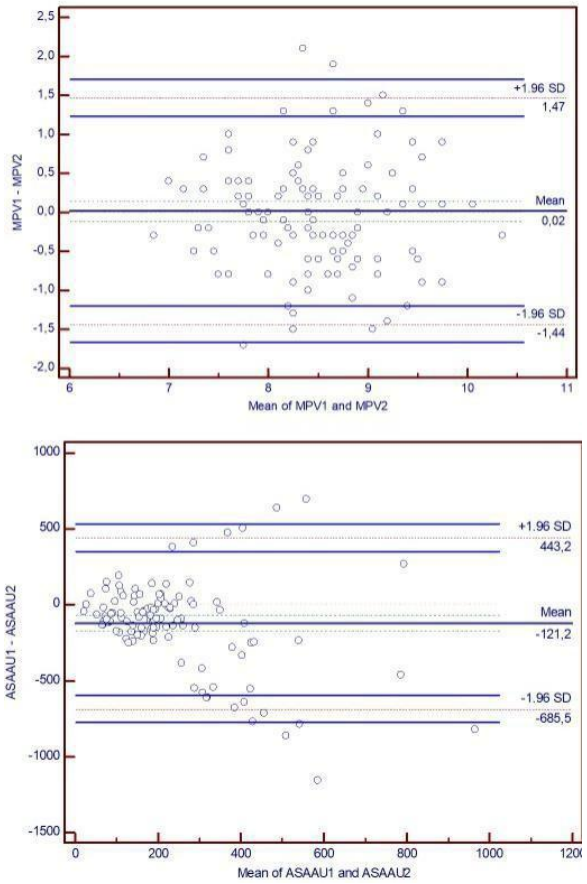

Figure3: Consistency analysis of acetyl salicylic acid resistance and mean platelet volume (MPV) values at admission and 1st month: ASAAU1 stands for: numerical value of ASA resistance in admission, ASAAU2 stands for: Numerical value of ASA resistance in the 1st month, MPV1 stands for; MPV value on admission, MPV2 stands for; MPV value in the 1st month, SD: Standard deviation

Except for smoking no difference was found in patients with and without ASA resistance according to classical cardiovascular risk factors and ACS type. Aspirin resistance was detected in 6 (11.1%) of 54 smokers and a relationship was found between smoking and aspirin resistance ($p<0.01$).

No major or minor bleeding developed in any of the patients included in the study. A total of 4 clinical events occurred, and statistical analysis was not performed because the frequency of events was low.

- ASA resistance was not detected in any of these 4 patients at the time of admission.
- 1 patient was hospitalized due to heart failure
- 1 patient had a stroke after CAG
- Stent restenosis was detected in 1 patient.
- Aneurysm formation was observed in the stent area in 1 patient.

DISCUSSION

ASA resistance is generally defined as the inability to produce the expected biological response (biological/pharmacodynamic resistance) or the inability to prevent atherothrombotic events (clinical resistance). The mechanism of resistance is not yet fully understood. However, the possible mechanism is a combination of clinical, biological and genetic features that affect platelet functions. As a result of evaluating ASA resistance with different platelet function tests, the prevalence of resistance is observed at 20-30%, with some studies determining resistance as high as 60%.[14] In our study, the prevalence of ASA resistance was found to be 22.6%. However, it was observed that ASA resistance increased within 1 month. The relationship between ASA resistance and MPV, classical cardiovascular risk factors, and type of ACS at presentation has not been demonstrated. It has been observed that ASA resistance is higher in smokers.

ASA resistance has been associated with inadequate serum levels of ASA, metabolic and pharmacological alterations in ASA's mechanism of action, drug interactions, and genetic mutations in the enzymes targeted by ASA.[11]

The relationship between MPV and clinical adverse events has been questioned in many studies. In a meta-analysis by Chu et al., high MPV values were found to be associated with the risk of myocardial infarction (MI), increased risk of mortality after MI, and increased risk of restenosis after angioplasty.[8] In the study of Binita Shah et al., it was found that mortality remained significantly higher in patients with increasing compared with non-increasing (decreasing or no observed change) in MPV.[12] In a study conducted by Aksu et al., the relationship between MPV and ASA resistance was investigated in patients with non-ST segment elevation MI. The combination of ASA resistance and high MPV value has been defined as an independent risk factor for death and MI.[15] In our study, no relationship was found between high MPV values, ASA resistance and clinical events. This may be due to the short follow-up period and the relatively small number of patients. In the literature, it is seen that there is no relationship between ASA resistance and diabetes in studies comparing various diabetic and non-diabetic patient groups.[15,17] Studies have shown that ASA resistance increases with smoking in both patients with stroke and CAD.[18,19] This is attributed to the fact that smoking causes platelet activation.

The limitations of our study are the small number of patients, the short follow-up period, and the inability to perform genetic tests for ASA resistance. In addition, another limitation is that there are no clear cutoff values for ASA resistance and MPV values in predicting adverse clinical events. Due to the short follow-up

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period, the number of clinical adverse events was low and we did not include them in the analysis. Therefore, we could not evaluate the effect of ASA resistance on clinical outcomes.

ASA resistance is more common than thought. Therefore, evaluating platelet functions in predicting the clinical outcomes of cardiovascular patients is important in determining the effectiveness of the antiplatelet agent used. Studies in this area are increasing. This shows that the routine use of existing platelet function tests will increase and they will be recommended with stronger evidence in the guidelines.

Conflict of Interest: The authors have no conflicts of interest to declare.

Researchers' Contribution Rate Statement: Concept/Design: MU, İB; Analysis/Interpretation: MU, İB, SÖ; Data Collection: MU; Writer: MU, AYK, FAD; Critical Review: AYK, FAD; Approver: AYK, FAD, İB

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