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ORIGINAL ARTICLE **ARAŞTIRMA YAZISI**

ACETYLSALYCYLIC ACID RESISTANCE AND RISK FACTORS IN ACUTE ISCHEMIC STROKE PATIENTS

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ABSTRACT

OBJECTIVE: The aim of the study was to investigate prevalence of acetylsalicylic acid (ASA) resistance in acute ischemic stroke patients by using Platelet Function Analyzer (PFA) 100 test and to determine the effect of risk factors that may be responsible for ASA resistance.
METHODS: Fifty acute ischemic stroke patients (mean age: 66.32±12.983 years, 34 male) were given 300 mg/day aspirin for at least 10 days and all risk factors were investigated for a correlation to ASA resistance by using PFA 100 test. These factors were; age, gender, hemoglobin (Hgb), hematocrit (Htc), platelet (plt) total cholesterol, von Willebrand Factor (vWF) levels, hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), smoking and previous cerebrovascular disease (CVD). In PFA-100 system, a collagen/epinephrine (C/EPI) closure time in the range of 85-157 sec. and a collagen/ADP closure time of 65-125 sec. were considered normal. Maximal test duration was 300 s. C/EPI closure time is sensitive for ASA resistance. Subjects with duration shorter than 300 s. were accepted as ASA-resistant or non-responder.
RESULTS: ASA resistance was apparent in 32% of the study group. vWF levels were higher in ASA resistant patients group. All risk factors were compared in ASA sensitive and resistant group. vWF levels and mean age were higher in ischemic stroke ASA non responder group, but not statistically significant.
CONCLUSION: In 50 acute ischemic patient aspirin resistance rate was 32%, this means aspirin was pharmacologically non effective in those. Clinical outcome for aspirin non responders may be revealed through the follow up at least six months.
Key Words: Cerebrovascular ischemic stroke, PFA 100 test, ASA resistance, risk factors.

AKUT İSKEMİK İNME HASTALARINDA ASETİL SALİSİLİK ASİT DİRENCI VE RİSK FAKTÖRLERİ

ÖZET

AMAÇ: Bu çalışmanın amacı, akut iskemik inme hastalarında PFA 100 testini kullanarak, ASA direnç prevelansını araştırmak ve ASA direncine neden olabilecek faktörlerin etkilerini saptamaktır.
GEREÇ ve YÖNTEM: En az 10 gün 300mg/gün ASA kullanan elli iskemik inme hastası (ort.yaş: 66.32±12.983, 34 erkek) çalışma grubu PFA 100 test kullanılarak ASA direnci için karşılaştırıldı ve ilişkili tüm risk faktörleri araştırıldı. Bu faktörler; yaş, cinsiyet, hemoglobin (Hgb), hemotokrit (Htc), trombosit, total kolesterol, von Willebrand Factor (vWF) düzeyleri, hipertansiyon (HT), diabetes mellitus (DM), koroner arter hastalığı (CAD), sigara içimi ve geçirilmiş serebrovasküler hastalık (CVD) dır. PFA 100 sisteminde kollajen/epinefrin (C/EPI) kapanma zamanı 85-157 sn. ve kollajen/ADP kapanma zamanı 65-125sn. aralıklarında normal olarak değerlendirilmiştir. Maksimal test süresi 300 sn. dir. C/EPI kapanma zamanı ASA direnci için duyarlıdır. 300 sn.'den kısa süreli olgular ASA dirençli veya cevapsız olarak kabul edildi.
BULGULAR: ASA direnci çalışma grubunda %32 olarak saptandı. vWF düzeyleri, ASA dirençli çalışma grubunda yüksekti. Tüm risk faktörleri ASA dirençli ve duyarlı grupta karşılaştırıldı. vWF düzeyleri ve ortalama yaş ASA dirençli iskemik inmelerde daha yüksekti, ancak istatistiksel olarak anlamlı değildi.
SONUÇ: 50 akut iskemik inme geçiren hastada aspirin direnci 32% idi, bu bulgu aspirinin bu kişilerde farmakolojik olarak etkisiz olduğu anlamına gelir. Aspirin cevapsızlarda klinik sonuç en az altı ay takip ile ortaya çıkabilir.
Anahtar Sözcükler: Serebrovasküler iskemik İnme, PFA-100 test, Aspirin direnci, risk faktörleri.

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INTRODUCTION

Acetylsalicylic acid (ASA) is the most investigated and preferable agent in secondary prevention of ischemic stroke (IS) (1,2) . ASA inhibits convertion of arachidonic acid to tromboxan A2 through acetylation of cyclooxygenase (COX)1 enzyme. Tromboxan A2 is the major metabolite of prostaglandin synthesis and vasoconstrictor agent inducing platelet aggregation(2,3). ASA decreases relative risk of major vascular events and vascular death by 20-25% following IS and acute coronary syndrome (4,5,6). Low dose ASA (80-160 mg) is recommended for primary prevention in DM, carotid stenosis, peripheral arterial disease and end-stage kidney disease, while high dose ASA (160-300 mg) is recommended for secondary prevention (4,7). Recently some studies indicated that, ASA does not have the same effectiveness in all patients, although adequate doses are taken, recurrent arterial thrombosis occurs (8,9,10,11). This clinical finding is called ''ASA resistance or non-responders'' (8,9,12). Meta-analyzes have shown 28% ASA resistance in IS patients (9,12).

In literature, some clinical, biological and genetic factors that may be responsible for ASA resistance were researched (5,10,13,14,15,16,17,18,19,20,21,22,29). Possible mechanisms were summarized in Table 1. A few laboratory tests were used to investigate ASA resistance (8,12). In our study, PFA 100 test measuring platelet function by in vitro capillary system was used. This test is fast, easy and 95% sensitive method that measures platelet adhesion and aggregation. We investigated ASA resistance prevalence and factors that might induce ASA resistance by PFA 100 test in acute ischemic stroke patients.

MATERIAL AND METHODS

Our study is prospective, randomize, not including control group. We used covariate adaptive randomization technique for patient randomization. We investigated ASA resistance theory and possible mechanisms. Also risk factors which may induce ASA resistance and interaction between them were researched.

Study population: We enrolled 50 subjects over 45 years of age with a history of acute ischemic stroke using referrals to emergency services between December 2006 and May 2007. Brain computed tomography (CT) scans were obtained, and patients with hemorrhagic infarcts were excluded. All patients were given a non-enteric coated ASA 300 mg/day for at least 10 days. Patients were asked about any medications taken in the previous 10 days before enrollment in the study and for comorbid diseases stated in the literature to be linked to ASA resistance. Hemoglobin (hgb), platelet (plt) numbers, and total cholesterol levels were recorded. Subjects with platelet number <100.000 /dl or >500.000 /dl, or a hgb < 9 mg/dl were excluded, since these values could affect ASA resistance by causing a prolongation in the PFA-100 laboratory test. Subjects using non-steroidal anti-inflammatory drugs (NSAID) and/or other antithrombotic agents that have the potential to influence test results in the final 10 days before the study commenced were excluded. In addition, subjects with gastrointestinal bleeding, active duodenal or gastric ulcers, familial bleeding diathesis, malignancy, systemic vasculitis, aspirin allergy and also subjects with a major surgical operation within the last month, chronic renal failure, and liver disease were excluded.

Obtaining Blood Samples: Following a 12-hour fasting period, 5-ml blood was drawn for hemogram, total biochemistry and another 5 ml blood for PFA-100 test to measure C/EPI and C/ADP closure time into vacuum tubes containing sodium citrate; the samples were studied in 2-2,5 hours period. vWF levels were measured by the tests vWF antigens and ristocetin cofactor activity (vWF:RCo) in hemotology laboratory.

Assessment with PFA-100 system: Investigations were performed by PFA 100 test device (Germany, Dade Behring). This test is based on stimulation of primary hemostasis by flowing blood through capillary system coated with collagen membrane that is covered by epinephrine or adenosine diphosphate (ADP) (8,17,23). During blood flowing, platelets adhere and aggregate to the surface of the membrane. Platelet tampon formation occurs and blood flow interrupts, this elapsed time is called 'closure time' (8,17,23,24). In this system, a C/EPI closure time in the range of 85-157 s and a C/ADP closure time of 65-125s were considered normal. Maximal test duration was determined as 300 s. C/EPI closure time is detected as > 300 s in individuals regularly taking 300 mg ASA for at least 10 days. Subjects with

Table 1. Aspirin resistance possible mechanisms.

Clinical Factors	Patient inadaptability of drug intake and inadequete drug doses Chronic aspirin intake and reduced bioavailability Diabetes mellitus and insulin resistance Hypertension Different formulations of aspirin (e.g.enteric coated) Obesity Hyperlipidemia Smoking
Biological Factors	Platelet activation by non COX-1 pathway Increased activity of COX-1 and COX-2 enzymes Low platelet number Increase of platelet turnover and reactivity Insufficient suppresion of tromboxan A2 COX 2 enzyme mediated synthesis of tromboxane in monocyte and macrophage The presence of alternative pathways of platelet activation Catecholamine, collagen, fibrin and ADP-induced platelet aggregation Oxidative stress Erythrocyte-induced aggregation High vWF levels Low hemotocrit
Genetic Factors	Single nucleotid polymorphism a) COX 1 polymorphism and/or mutation b) Platelets' glycoprotein IIb/IIIa complex of III a subunits' polymorphism
Drugs	ACE inhibitors, nitrates Proton pump inhibitors and statins NSAID

*NSAID: Non- steroidal anti- inflammatory drug, †COX: cyclooxygenase.

duration shorter than 300 s were accepted ASA-resistant or non-responder. ASA prolongs only C/EPI closure time, and does not affect C/ADP closure time.

Statistical analyses: Statistical analysis was performed using SPSS 20.00 software package at the Department of Biostatistics. Results were expressed as mean ± standard deviation. Categorical variables were compared using Chi-square and Fisher's exact test and parametric data were compared using independent t test. A p value of <0.05 was considered statistically significant for all tests.

RESULTS

The mean age of study group was 66.32±12.983 and 34 male. All risk factors were analyzed in Table 2. (Age, gender, hemoglobin, hematocrit, platelet number, vWF, total cholesterol, smoking, hyperlipidemia, diabetes Mellitus, hypertension, coronary artery disease, previous cerebrovascular disease, angiotensin converting enzyme (ACE) inhibitor, statins). 32% of patients had previous CVD history, 30% had CAD, 70% had HT, 18% had DM, 52% hyperlipidemia, 22% were smoking .vWF min. and max. levels were 39 and 420 respectively, mean value was 200.96 IU/dl). Only one patient was taking statin and 18 patients were taking an ACE inhibitor. None of the patients were taking nitrates or proton pump inhibitors (Table 3). In 50 ischemic stroke patients, 16 (%32) of them were aspirin resistant. Mean age and vWF levels were higher in ASA resistant group, but not statistically significant. Hemoglobin, hemotocrit, platelet and total cholestrol levels were appoximately same in two groups. 9 of 11 smokers, 19 of 24 hyperlipidemic patients, 9 of 8 diabetic patients, 23 of 35 hypertensive patients were aspirin non responders. The number of patients were higher in aspirin resistant group, so this finding confirms that these risk factors have impact on ASA resistant. Because of limited case number, we could not determine statistically significant results.

Table 2. The characteristics of the study group.

	n	min	max	mean	s.d.
Age	50	35	94	66.32	±12.983
Hemoglobin (gr/dl)	50	11.10	15.90	13.548	±1.299
Hematocrit (%)	50	32.10	46.90	39.512	±3.866
Platelet (plt/mm^3)	50	120000	705000	255020	±95154.759
Von Willebrand factor	50	39	420	200.96	±80.376
Total cholestrol (mg/dl)	50	122	310	196,32	±43.262
		YES **n (%)**		NO **n (%)**	
Smoking		11(22)		39(78)	
Hyperlipidemia		24(52)		26(48)	
Diabetes Mellitus		9(18)		41(82)	
Hypertension		35(70)		15(30)	
CAD		15(30)		35(70)	
Previous CVD		16(32)		34(68)	
ACE inhibitor		18(36)		32(64)	
Statins		1(2)		49(78)	
Male		34(68)		16(32)	

*n(%) or mean ±standard deviation(sd) values were stated in the table.

Table 3. The comparison of Aspirin sensitive and resistant groups.

	Aspirin sensitive (responder) (n=34)		Aspirin resistant (non responder) (n=16)		p value
Age	64.56 ±12.81		70,06±12,94		.164*
Hemoglobin (gr/dl)	13.72±1.23		13.18±1.41		.166*
Hematocrit	40.08±3.77253235,29		38.3±3.90		.130*
Platelet (plt/mm^3)	±105384,74		258812,50±71569,29		.849*
Von Willebrand factor	189.18±80.72		226.0±76.07		.132*
Total cholestrol (mg/dl)	201.24±41.27		185.88±46.87		.246*
	N	**%**	**N**	**%**	
Male	22	64.7	12	75.0	.467†
Smoking	9	26.5	2	12.5	.466‡
Hyperlipidemia	19	55.9	5	31.3	.104†
Diabetes mellitus	8	23.5	1	6.3	.240‡
Hypertension	23	67.6	12	75.0	.746‡
CAD	10	29.4	5	31.3	1.0‡
Previous CVD	9	26.5	7	43.8	.222†
ACE inhibitor	12	35.3	6	37.5	.880†

*Independent Samples t Test, †Chi square, ‡Fisher's exact test.

DISCUSSION

Recurrent major vascular events despite aspirin intake have been increasingly subject to clinical debate and research. Laszlo K. Sztriha et al. and A.D.Michelson et al mentioned possible mechanisms of aspirin resistance as defined in Table 1 (16,31). In literature there are several studies about aspirin resistance and its mechanisms. Harrison P. and Homoncik M. et al. showed an inverse correlation, even in healthy population, between the closure time and platelet numbers, hemotocrit and vWF levels (19). Some studies reported that low platelet numbers and hemotocrit may prolong C/EPI time and induce pseudo-resistance (18,29). Abacı A.et al. detected a lower suppression of thromboxane by ASA in diabetics. This condition has been explained by an activated status of platelets leading to more thromboxane synthesis in diabetics compared to

non-diabetics. In addition, it has been suggested that hyperglycemia decreases effectiveness of antiplatelet therapy by increasing reactive oxygen radicals (20,21). Smoking has been suggested to result in platelet thrombosis uncontrollable by ASA (13). Hypercholesterolemia has been implicated in decreased effectiveness of ASA on thrombocytes (21). High mean total and low density lipoprotein cholesterol levels have also been related to weak ASA response. Luzak B. et al determined tahat the ASA-induced acetylation of platelet proteins significantly increased in the course of atorvastatin therapy and was associated with reduced platelet cholesterol (34). ASA may exert antiplatelet properties beyond the cyclooxygenase pathway. The mechanism of such an association between hypercholesterolemia and ASA resistance is unclear, but may be related to the diminished platelet membrane fluidity and inability of ASA to downregulate such 'strong' protected platelets (35). Furthermore, some studies have reported that ACE inhibitors and ASA decrease the effect of one another, when used together (13). On the other hand, ratio of ASA resistance also depends on the dose; studies have found a rate of ASA resistance of 56% in those taking <81mg/day low dose compared to 28% in those taking >325 mg/day high dose (9). We reduced ASA resistance risk by using the dose 300 mg/day. Aspirin resistance was assessed by PFA-100 test. Its main difference from conventional tests measuring bleeding time is that, in addition to demonstrating whether platelet functions are normal or abnormal, it also shows the difference between primary platelet dysfunction and drug-induced platelet dysfunction (18,32,33). Various studies confirmed that this test also demonstrates clinical aspirin resistance in recurrent vascular events (8,9,10,11,12). As indicated, we should have followed up these patients for recurrent stroke or other vascular events to determine the accurate clinical ASA resistance at least 6 months .

In the present study the mean age and vWF levels of ASA non responders were higher than responders group. T. Chakroun et al. indicated that higher vWF levels in plasma suggest endothelial injury, vascular risk and those may lead to ASA resistance and may facilitate in vivo adhesion of platelets to subendothelial structures and aggregation (5,22). Furthermore, high levels may increase the C-EPI closure time, thus masking effect of ASA (20,25). Dominick JH.et al. obtained that mean vWF levels are higher in early and late-phase stroke patients compared to controls. However, Giorgio B. Boncoraglio et al. (2009) suggested that acute events and COX-independent mechanisms (including higher vWF levels) cause non-responsiveness in PFA-100 test whereas non-acute conditions such as ischemic stroke, transient ischemic attacks, and vascular cognitive failure do not cause non-responsiveness (8). Many different factors may increase vWF levels and activity. Among these; blood groups, genetic variability, acute phase response, proteolysis of vWF by metalloproteinase and A disintegrin (ADAMTS13), together with Thrombo Spontin (26). Inflammation may play a role in determining levels of vWF, but it will not be the only important regulatory mechanism, because vWF levels are independent of the inflammation that is also associated with the relative risk of IS (27). Bongers T.N. et al. assesed 124 patients with first stroke in regard of vWF levels and reported that the increase observed in acute stroke was not affected by other factors, similar to acute phase reaction (23). Recently, Schwammenthal et al. found supporting evidence for a correlation between stroke grade and ASA resistance. Moreover, Röden–jüllig et al. reported an ASA effectiveness varying with stroke grade and showed a higher ASA efficacy in mild strokes.

Nevertheless, these mechanisms may be cooperating at the acute stage of stroke (9). Stroke patients were not graded by NIHSS (National Institute of Health Stroke Scale) or mRS (modified Rankin Scale) in our study. Impaired responsiveness to ASA in acute brain ischemia is associated with worse neurological deficits at stroke onset, early clinical deterioration and poorer functional outcome (28). So, there must be further studies to evaluate its effect on ASA resistance. Another antiagregant agent may be chosen in ASA-resistant patients. We preferred clopidogrel in our study. However, it has been shown that ASA resistant patients had a decreased response to clopidogrel, as well (9). Commonly preferred antiplatelet agents such as ASA, dipyridamole, and the platelet P2Y12 receptor inhibitor clopidogrel show only limited efficacy and substantially increase the risk of fatal bleeding. These limitations emphasize the need for a better understanding of the pathophysiological mechanisms of thrombus formation in acute IS to successfully improve treatment (27).

Limitation of our study is investigating ASA resistance in only acute ischemic stroke patients after at least 10 day ASA intake. However, the

resistance may also occur 3-6 months later. We should have recall the patients using 300mg/day ASA at least 3 months later to determine the accurate resistance ratio, to compare vWF levels in subacute and acute phase, and also in this study stroke severity should be mentioned for each subject.

We indicated that ASA resistance is higher than expected in acute IS patients, studies with longer follow-up duration and larger groups are needed to clarify the mechanisms of ASA resistance. Consequently, in our opinion ASA resistance should be investigated routinely in all recurrent IS patients using aspirin by PFA-100 test and furthermore vWF levels, other known risk factors and inflammation ought to be evaluated in those.

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