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RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

ASSESSMENT OF ACETYLSALICYLIC ACID AND CLOPIDOGREL RESISTANCE RESULTS OF THE PATIENTS WITH SIGNIFICANT STENOSIS ON CAROTID COLOR DOPPLER ULTRASONOGRAPHY

Fatma YILMAZ CAN, Beyza Nur ÇETİN

University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Clinic of Neurology, Ankara, TURKEY

ABSTRACT

INTRODUCTION: Acetylsalicylic acid resistance and clopidogrel resistance occur when platelet reactivity is higher than the reference range despite receiving antiaggregant therapy. The continuation of thrombotic events despite the use of antithrombotic drugs has led to the concept of antithrombotic resistance. This study aimed to determine the frequency of acetylsalicylic acid-clopidogrel resistance and risk factors associated with resistance in the patients with significant stenosis or occlusion on carotid color Doppler ultrasonography.
METHODS: The files of the patients who were hospitalized in our hospital's neurology clinic between 2019-2021 due to the diagnosis of ischemic stroke and transischemic attack were scanned. A total of 60 patients with significant (≥50%) stenosis on carotid color Doppler ultrasonography. and who had acetylsalicylic acid-clopidogrel resistance test were included in the study. Age, gender, obesity, diabete, hypertension, stenosis level, drug use period, HbA1c, creatinine, low-density lipoprotein, haemoglobin value, platelet count, smoking and alcohol, and their relationships with resistance were examined.
RESULTS: 28,3% of 60 patients were included in the study were female and 71,7% of them were male. The mean age was found to be 68 Diabetes was determined in 65% of the patients, hypertension was determined in 71,7% of them, elevated low-density lipoprotein was determined in 63,3% and elevated HbA1c was determined in 75%. Acetylsalicylic acid resistance was found in 11 patients (18,3%), and clopidogrel resistance was identified in 12 patients (20%). Acetylsalicylic acid resistance was significantly higher in the patients with older age (≥67) and with low haemoglobin value (≤12,4) (p=0,042 and p=0,014, respectively). Clopidogrel resistance was significantly higher in females (p=0,027).
DISCUSSION AND CONCLUSION: Firstly, the main goal should be reducing the risk of stroke with appropriate preventive treatment for risk factors. Patients over the age of 67 and female patients need to be more careful about resistance. We would like to emphasize that low haemoglobin levels should be treated.
Keywords: Carotid artery disease, acetylsalicylic acid resistance, clopidogrel resistance.

Address for Correspondence: Fatma Yılmaz Can M.D. Dışkapı Yıldırım Beyazıt Training and Research Hospital, Neurology Clinic, Ankara, Türkiye.
Phone: +90312 596 28 14 **E-mail:** fatmayilmazcan33@hotmail.com
Received: 22.03.2022 **Accepted:** 06.04.2022
ORCID IDs: Fatma Yılmaz Can 0000-0003-0995-4911, Beyza Nur Çetin 0000-0002-8230-0597.
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KAROTİS RENKLİ DOPPLER ULTRASONOGRAFİDE ANLAMLI DARLIĞI OLAN HASTALARIN ASETİLSALİSİLİK ASİT VE KLOPİDOGREL DİRENÇ SONUÇLARININ DEĞERLENDİRİLMESİ

ÖZ

GİRİŞ ve AMAÇ: Asetilsalisilik asit-klopidogrel direnci, antiagregan tedavi almasına rağmen trombosit reaktivitesinin referans aralığından daha yüksek olmasıdır. Antitrombotik ilaçların kullanımına rağmen trombotik olayların devam etmesi antitrombotik direnç kavramına yol açmıştır. Yeteri kadar antitrombotik etki sağlayamama daha yüksek iskemik olayla ilişkilendirilmiştir. Bu çalışma, karotis renkli Doppler ultrasonografide anlamlı stenoz yada oklüzyonu olan hastalarda asetilsalisilik asit-klopidogrel direnç sıklığını ve dirençle ilişkili risk faktörlerini belirlemeyi amaçlamaktadır.

YÖNTEM ve GEREÇLER: Hastanemiz nöroloji kliniğinde 2019-2021 tarihleri arasında iskemik inme, transiskemik atak tanılarıyla hospitalize edilen hastaların dosyaları tarandı. Karotis renkli Doppler ultrasonografide anlamlı (≥%50) darlığı olan ve asetilsalisilik asit-klopidogrel direnç testi yapılan 60 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, risk faktörü olabilecek hastalıkları, laboratuar sonuçları, kullandıkları ilaçlar, asetilsalisilik asit-klopidogrel direnç test sonuçları değerlendirildi, direnç sıklığı belirlendi. Yaş, cinsiyet, obesite, diyabet, hipertansiyon, stenoz derecesi, ilaç kullanım süresi, HbA1c, kreatinin, düşük dansiteli lipoprotein, hemoglobin değeri, platelet sayısı, sigara ve alkol kullanımı ile direnç arasında ilişki olup olmadığı araştırıldı.

BULGULAR: Çalışmaya dahil edilen 60 hastanın %28,3'ü kadın, %71,7'si erkekti. Yaş ortalamaları 68'di. Hastaların % 65'inde diyabet, %71,7'sinde hipertansiyon, %63,3'ünde düşük dansiteli lipoprotein, %75'inde HbA1c yüksekliği bulundu. 11 hastada (%18,3) asetilsalisilik asit, 12 hastada (%20) klopidogrel direnci saptandı. Asetilsalisilik asit direnci; yüksek yaş grubu (≥67) ve düşük hemoglobin değeri olan (≤12,4) hastalarda anlamlı olarak fazlaydı (sırayla p=0,042 ve p=0,014). Klopidogrel direnci ise kadın cinsiyette anlamlı olarak fazlaydı (p=0,027).

TARTIŞMA ve SONUÇ: Hastalarının büyük çoğunluğunda iskemik inme için ikili yada üçlü risk faktörü varlığı görüldü. Öncelikle risk faktörlerine yönelik uygun koruyucu tedaviyle, inme geçirme riskinin düşürülmesi esas hedef olmalıdır. İkinci olarak dirençle ilişkili olduğu saptanan; 67 yaş üzeri hastalar ve kadın hastalarda direnç konusunda daha titiz davranılması gerektiğini; hemoglobin düşüklüğü gibi tedavi edilebilir risk faktörlerinin tedavi edilmesi gerektiğini vurgulamak isteriz.

Anahtar Sözcükler: Karotis arter hastalığı, asetilsalisilik asit direnci, klopidogrel direnci.

INTRODUCTION

Acetylsalicylic acid (ASA) is an antiaggregant that is widely used for preventing thrombotic events. Its main mechanism of action is to irreversibly inhibit cyclooxygenase 1 (COX-1) enzyme activity, reducing thromboxane A_2 (TxA_2) activation (1). Thienopyridines, including clopidogrel, inhibit platelet aggregation via adenosine diphosphate (ADP). ADP binds to the platelet receptors purinergic $P2Y_1$ and $P2Y_{12}$. The $P2Y_1$ receptor is involved in the shape change and transient aggregation of platelets, while the $P2Y_{12}$ receptor is involved in permanent aggregation. Hence, the $P2Y_{12}$ receptor is also the target molecule of thienopyridines (2). For daily clinical practice, only the $P2Y_{12}$ receptor has become a target for clopidogrel (3). In healthy subjects, a single dose of 100 mg ASA reduces TxA_2 formation by 80%. This inhibition disappears in more than 50% of platelets 5-6 days after using a single dose of ASA. Because, 10% of platelets are renewed every day (4). Sincethey are acaryote, inhibited enzymatic activity cannot be restored and they become inactive for the remainder of their life cycle (5).

Even though antiplatelet therapy is expected to prevent platelet aggregation, some patients may not display the desired effect. The explanation for this was first introduced in the 1980s, named resistance to antiplatelet therapy or aspirin resistance (6). The concept of ASA and clopidogrel resistance is used to describe patients with platelet reactivity higher than the reference range and therefore at higher risk of ischemic events despite receiving antiplatelet therapy (7,8). One study on symptomatic carotid stenosis patients found a significantly higher frequency of ASA resistance among patients with microembolic signals, suggesting an association between ASA resistance and an increased risk of ischemic stroke (9). Antiplatelet therapy reduces the annual risk of stroke by 9% for all patients with carotid artery disease and prevents 20% of secondary strokes in patients with recent cerebral ischemia; hence, it has been adopted as the main treatmentmethod (10,11). According to research on resistance, the prevalence of ASA resistance was statistically higher among patients with recurrent cerebral ischemia while receiving ASA compared to those

without ischemia (12). Data from similar research has encouraged further investigation into individualized treatment plans and reviews about resistance to reduce the risk of stroke for all patients (9).

A structured treatment plan based on the strategy of "Test and treat" can significantly reduce the risk of inadequate antiplatelet therapy and minimize unnecessary dual antiplatelet use and associated side effects (13).

In the present study, we aimed to determine the frequency of ASA and clopidogrel resistance and the factors on developing resistance in patients with ischemic stroke or transient ischemic attack (TIA), significant carotid stenosis on carotid Doppler ultrasonography (USG), using dual antiplatelets.

METHODS

We retrospectively scanned the files of patients hospitalized in the neurology clinic of our hospital with the diagnosis of cerebral stroke and TIA between 2019-2021. We reviewed the files of patients who had an ischemic stroke or TIA and significant (≥50%) carotid stenosis or occlusion on carotid Doppler USG for etiological purposes. We also recorded the demographic and clinical characteristics of these patients and examined their radiological and laboratory results. Accordingly, we included 60 patients with significant (≥50%) stenosis on carotid Doppler USG, who were using ASA and clopidogrel, and were undergoing resistance testing. Patients had no significant stenosis or occlusion on carotid Doppler USG, who used drugs irregularly, who used antithrombotic drugs other than ASA or clopidogrel, who had known hematological, myeloproliferative, or oncological diseases, and who were on dialysis were excluded. According to the Doppler USG results, the right and left common carotidarteries and right and left internal carotid arteries were evaluated by considering their flow velocities and stenosis levels. All patients were using equal doses of dual antithrombotic agents (ASA 100 mg and clopidogrel 75 mg).According to the laboratory test results and information from the physician working at the laboratory; all patients were informed about using the antiaggregant for at least seven days before the resistance test. Also, blood samples were taken into a tube with 3.2% citrate and the test was performed at the third hour. The resistance test was performed with the optical aggregometry method using a Chrono-Log Corporation Model 700 instrument. The resistance test results were compared according to age, sex, obesity (body mass index=BMI), type 2 diabetes mellitus (Type 2 DM), hypertension (HT), creatinine (Cr), HbA1c, hemoglobin (Hb), low-density lipoprotein (LDL) levels, platelet (Plt) count, drug use time, smoking, and alcohol use.

The research was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 13.12.2021, No: 126/10). This was a retrospective chart review, so signed consent was not obtained.

Statistical Analysis: Wetransferred the data to the IBM SPSS 26.0 software for preparation for analysis. After the analysis, descriptive statistics were presented as number, percentage, minimum and maximum values, mean, standard deviation, median, and interquartile range. Because some groupshad less than 30 patients, we used the Mann-Whitney U test to evaluate the differences between two independent groups. We also used the Chi-squared test to determine the correlations between categorical variables. The level of statistical significance was accepted as $p<0.05$.

RESULTS

Of the 60 patients in our sample, 17 (28.3%) were female and 43 (71.7%) were male. Their mean age was 68 (45-87) and mean BMI was 27.1 (20.8-38.5). Type 2 DM was detected in 39 patients (65%), HT in 43 (71.7%), LDL elevation in 38 (63.3%), and HbA1c elevation in 45 (75%). 29 patients (48.3%) were smokers and 12 (20%) used alcohol. The mean time of ASA use was 33 months (0.5-120) and the mean time of clopidogrel use was 12 months (0.25-60) (Table 1). 11 (18.3%) patients had ASA resistance (Table 2). The mean age was 72 years for patients with ASA resistance and 67 for those without ASA resistance, with a statistically significant difference ($p=0.042$). The mean Hb level was 12.4for patients with ASA resistance and 14.09 for those without resistance. There was a significant correlation between low Hb levels and anti-platelet resistance ($p=0.014$). The frequency of Type 2 DM was

Table 1. Descriptive characteristics

		Number	Percentage	Median	Interquartile Range
Sex	Male	43	71,7		
	Female	17	28,3		
Age				69	12,75
Weight				75	10,75
Height (meters)				1,65	0,09
BMI				26,82	3,25
LDL				112,95	54,00
LDL (0-100 mg/dL) †	Normal	22	36,7		
	High	38	63,3		
HbA1C				6,50	2,65
HbA1C (3.5-6 mmol /mol Hb) †	Normal	15	25,0		
	High	45	75,0		
Platelet				227500,00	93750
Platelet (150.000-372.026) †	Low	2	3,3		
	Normal	55	91,7		
	High	3	5,0		
Hemoglobin				13,75	2,47
Hb (13.2-17.3 g/dL) †	Low	22	36,7		
	Normal	36	60,0		
	High	2	3,3		
Diabetes	Yes	39	65,0		
HT	Yes	43	71,7		
Smoking	Yes	29	48,3		
Alcohol Use	Yes	12	20,0		
ASA Resistance	Negative	49	81,7		
	Resistant	11	18,3		
Degree of Stenosis	>70% and occluded	35	58,3		
	50-69%	25	41,7		
Clopidogrel Resistance	Negative	48	80,0		
	Resistant	12	20,0		
ASA Use Time (Months)				19,00	56,00
ASA Use Time	12 months or less	28	46,7		
	>12 months	32	53,3		
Clopidogrel Use Time(Months)				5,00	11,50
Clopidogrel Use Time	12 months or less	45	75,0		
	>12 months	15	25,0		
Creatinine				0,85	0,35
Cr(0.7-1.2 mg/dL) †	Normal	52	86,7		
	High	8	13,3		

†: Reference range

Table 2. ASA resistance (difference analyses).

	ASA Resistance	n	Mean	Standard Deviation	p*
Age	Negative	49	67	9,00	**0,042**
	Resistant	11	72	4,10	
BMI	Negative	49	27,28	2,97	0,573
	Resistant	11	26,56	2,22	
LDL	Negative	49	117,05	44,68	0,811
	Resistant	11	115,60	28,08	
HBa1C	Negative	49	7,48	2,17	0,566
	Resistant	11	7,31	2,21	
PLT	Negative	49	238836,73	65249,95	0,139
	Resistant	11	261545,45	59500,19	
Hb	Negative	49	14,09	1,80	**0,014**
	Resistant	11	12,40	2,08	
ASA Use Time (Months)	Negative	49	34,90	33,11	0,130
	Resistant	11	23,81	40,03	

*Mann Whitney U Test

numerically higher among patients with ASA resistance, although without a significant difference according to the chi-squared test. The Mann-Whitney U test revealed that the time of ASA use was shorter among patients with resistance, although without statistical significance. Finally, ASA resistance was not significantly correlated with LDL level, platelet count, obesity, HT, smoking, alcohol use, or sex. Twelve (20%) patients had clopidogrel resistance (Table 3). According to the chi-squared test, clopidogrel resistance was significantly correlatedwith the female sex (p=0.027). However, clopidogrel resistance was notcorrelatedwith Type 2 DM, HT, LDL, HbA1c, Hb levels, platelet count, time of clopidogrel use, alcohol use, smoking, or obesity.

Table 3. Clopidogrel resistance (difference analyses).

	Clopidogrel Resistance	n	Median	Standard Deviation	p*
Age	Negative	48	68	8,32	0,598
	Resistant	12	66	9,66	
BMI	Negative	48	26,78	2,43	0,144
	Resistant	12	28,62	3,92	
LDL	Negative	48	120,72	43,52	0,186
	Resistant	12	101,04	31,58	
HBa1C	Negative	48	7,30	1,99	0,443
	Resistant	12	8,08	2,75	
PLT	Negative	48	242604,17	69098,98	0,579
	Resistant	12	244583,33	42587,78	
Hb	Negative	48	13,98	1,94	0,129
	Resistant	12	12,97	1,83	
Clopidogrel Use Time (Months)	Negative	48	10,66	14,42	0,294
	Resistant	12	15,83	20,26	

*Mann Whitney U Test

DISCUSSION AND CONCLUSION

Extracranial carotid artery atherosclerotic diseasemay present with a wide spectrum of signs, ranging from mild carotid intima-media thickness to high-risk, sensitive carotid plaque and carotid stenosis. Although most cases are asymptomatic, some of these findings are strongly associated with an increased risk of stroke, cognitive impairment, and even death in the future (14). A systematic review and meta-analysis on patients with high-grade carotid artery stenosis (≥70%) found a significant positive correlation between abnormal oxygen extraction on positron emission tomography (PET) and future ipsilateral stroke (15). Symptomatic carotid stenosis is considered when other etiologic causes are excluded and >50% stenosis is found in the internal carotid system (16). A plaque with stenosiscan limit cerebral blood flow, resulting in hemodynamic changes, hypoperfusion, and potentially hypoxia and infarction (14).

Today, the most common agents in antiplatelet therapy are ASA and clopidogrel. The main benefit of antiplatelet therapy is preventing thrombus formation and subsequent thromboembolism on fragile atherosclerotic plaques (17). The failure of antiplatelet therapy to achieve the desired effect in ischemic events is associated with resistance (8). Nearly 30% of patients who receive platelet inhibitor therapy to prevent arterial thromboembolism are resistant to therapy (18). Among stroke patients who receive ASA for secondary protection, 40% of those who had ASA resistance and 4.4% with response to ASA experienced a serious vascular event within 2 years (19). Having ASA or clopidogrel resistance leads to a significantly higher risk of cardiovascular complications and stent thrombosis (20). These data clearly demonstrate the significance of developing resistance to platelet inhibitor agents that are used to prevent stroke. Studies on this subject report quite different rates of antiplatelet resistance among stroke and TIA patients, ranging from 3 to 85% for ASA and 28 to 44% for clopidogrel (21). According to one study on resistance before carotid endarterectomy, 21% of patients receiving ASA and 42% of patients receiving clopidogrel had resistance to platelet inhibitor therapy, with an overall resistance frequency of 26.3% (18). Other studies investigated ASA resistance and increased risk of stroke among patients with a history of carotid endarterectomy or symptomatic carotid disease

using a platelet function analyzer (PFA) and found that theprevalence of ASA resistance ranged from 16 to 21% (22,9). Researchers have used various tests to investigate ASA resistance among TIA and ischemic stroke patients. ASA resistance was present in 17%according to Aspirin VerifyNow tests, 22% according to the PFA-100 test, and 5% according to optical aggregometry tests (23,24). In another research, VerifyNow tests revealed an ASA resistance frequency of 14% and a clopidogrel resistance frequency of 38.8% (25). The prevalence of antiplatelet resistance appears to varyover a wide spectrum,which can be explained by the different methods used (23,24) or the different ASA doses used by the patients (26).

In the present study, we performed optical aggregometry tests on patients with significant stenosis on carotid Doppler USG after ischemic stroke and TIA and who used equal doses of ASA or clopidogrel. We observed an ASA resistance in 18.3% of the patients and clopidogrel resistance in 20%. Our ASA resistance results are in parallel with the literature, but the clopidogrel resistance results are not.

According to the literature, diabetes mellitus, acute coronary syndrome, positive troponin level (27), renal failure, decreased left ventricular function (13), female sex, and smoking are associated with ASA resistance (28). The risk factors for clopidogrel resistance include blood sugar level, diabetes, elevated systolic and diastolic blood pressure (29,30), elevated HbA1c, elevated platelet count, elevated C-reactive protein, and patient age (>65) (28).

In the current study, we found that ASA resistancewas significantlycorrelated with low Hb level and advanced age (>67), similar to the literature. Also, Type 2 DM was more common among patients with ASA resistance, although with no significant difference. We observedno correlation between ASA resistanceand LDL, Cr, and HbA1c levels, platelet count, HT, obesity, time of ASA use, smoking, alcohol use, or sex.

We detected a significant correlation between clopidogrel resistance and the female sex. However, clopidogrel resistance was not correlated with HT, obesity, Type2 DM, LDL, Cr, and HbA1c levels, platelet count, time of clopidogrel use, alcohol use, or smoking.

The concomitant use of nonsteroidal anti-inflammatory drugs, particularly ibuprofen, blocks the site of coupling in COX-1, hindering the clinical benefit of ASA (31). Proton pump inhibitors may reduce the absorption of the active form of ASA (32). Nifedipine, verapamil, and diltiazem have also been reported to have inhibitory effects against platelet (33). However, we excluded patients using these drugs, because their number was not sufficient.

Studies have demonstrated that a higher maintenance dose increases platelet inhibition in patients who respond poorly to both ASA and clopidogrel; increasing the dose may be an option for treatingthe resistance (34-36). Similarly, research reports that ASA resistance is more common among patients who receive low-dose ASA (81 mg daily) and enteric-coated preparations (37). Another study prospectively examined the effect of ASA on platelet function and found that the frequency of ASA resistance was not dependent on the ASA dose (38). In the current study, all patients were using equal doses of ASA and clopidogrel, which reduced the variability of our findings. Besides, all our patients were using enteric-coated ASA tablets.

Since large randomized studies have shown additional clinical benefit for the combined use of clopidogrel and ASA, they have been increasingly used together (39). ASA and clopidogrel act on platelet activation and aggregation through different mechanisms, but they share the endpoint of reducing platelet-associated thrombus formation (40). Hence, this combined therapy has an extra beneficial effect (39). In the present study, all our patients were using dual antiaggregant therapy.

While applying all these principles is crucial, the indicator of failure is not necessarily antiplatelet resistance by laboratory parameters. Widely used for preventing vascular events, antiplatelet agentsdo not inhibit all pathways of platelet activation and aggregation (41). Aside from clinical factors, genetic factors also affect ASA and clopidogrel resistance. The CYP 2C19 polymorphism, which is involved in the metabolism of clopidogrel and has genetic variability that affects the Cytochrome P450 system, is the most important genetic variant that contributes to a poor response to clopidogrel (42,43). The clearest cause of ASA resistance is polymorphisms of the COX-1 gene (44).

It should be noted that cerebral stroke is caused by different etiological factors and that it is only effective in a limited group of patients,

regardlessof the attention paid to antiaggregation. Since the etiology of strokeinvolves certain mechanisms like cardiac embolism, vasculopathies, non-thrombotic occlusive atheromatous plaques, iatrogenic causes, hemodynamic deterioration, and arterial vasoconstriction or vasospasm, the role of platelets in vascular events appliesonly to a limited group of patients (45).

In conclusion, a personalized therapy for preventing secondary stroke aimsat using the most appropriate drug at the right dose,considering the patient's clinical condition and associated risk factors. We suggest investigatingfor resistance, particularly among patients over 67 years of age, females, and those with low Hb levels. The foremost measure should be to reduce the probability of a stroke by preventive therapy against risk factors.

Limitations: Our research included a relatively small group of patients. Also, ASA and clopidogrel resistance was measured once; a second measurement could have been performed for further confirmation. Finally, medication adherence was only questioned verbally.

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Ethics

Ethics Committee Approval: The study was approved by Clinical Research Ethics Committee of the Health Sciences University, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 13.12.2021, No: 126/10).

Informed Consent: The authors declared that informed consent was not obtained from the patients because of the retrospective study design.

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