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Original Article

Aspirin Resistance in Patients with Ischemic Stroke

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Keywords: Aspirin resistance; ischemic stroke; Multiplate analyzer.

ABSTRACT

Objective: Aspirin is the basic agent of antithrombotic treatment in ischemic cerebrovascular disease (CVD). Patients who do not respond to the treatment are described as aspirin-resistant. Recent studies have reported an incidence of aspirin resistance among CVD patients of between 3% and 85%. The aim of this study was to determine the frequency of aspirin resistance in CVD patients and evaluate any relationship with demographic characteristics, risk factors, or stroke subtypes.

Methods: A total of 163 (106 male, 57 female) acute ischemic stroke patients from a 6-month period treated with aspirin (100 mg, 300 mg daily) were evaluated. Aspirin resistance was measured using a Multiplate platelet analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland). Potential correlations between aspirin resistance and stroke subtypes, age, sex, weight, height, hypertension, diabetes mellitus, history of CVD, tobacco use, alcohol use, hyperlipidemia, and fasting blood glucose level were analyzed.

Results: Aspirin resistance was determined in 16 male patients and 9 female patients in the group: a total of 25 (15.3%) of 163 patients. There was no statistically significant relationship between aspirin resistance and stroke-related clinical and laboratory parameters.

Conclusion: Additional, large, prospective, randomized studies are needed to clarify which patients with ischemic stroke should be tested and how to treat patients with resistance.

INTRODUCTION

Acetyl salicylic acid (ASA; aspirin) is widely used worldwide in the primary treatment of vascular diseases as well as in the secondary treatment of atherothrombotic risk factors associated with vascular diseases. The low cost and high reliability of aspirin treatment have contributed to its prevalence. Aspirin has been reported to reduce the risk of non-fatal stroke by 25% and mortality by 18%.[1] Many clinical studies have shown that 30% to 40% of patients with ischemic cerebrovascular disease (CVD) follow an aspirin regimen.[2] Yet despite its efficacy, aspirin cannot completely preclude recurrent vascular events in some patients and may not produce the same effect in every patient. The ineffectiveness or insufficiency of aspirin to inhibit platelet (PLT) production has been described as aspirin resistance.

Various mechanisms have been proposed as having a role in the development of aspirin resistance, including genetic differences, patient inadaptability, drug interactions, and thromboxane A2 production from aspirin-independent pathways.[3] The incidence of aspirin resistance in ischemic CVD has been reported as 5% to 67%.[4–8] Clarifying mechanisms that may cause aspirin resistance would be useful in determining treatment strategies. Studies on aspirin resistance have mostly been related to cardiovascular diseases.

The number of studies on ischemic CVD has grown in recent years. However, a lack of sufficient studies with large patient series is the likely reason why PLT function tests are not routinely included in treatment guidelines. Although prevention of aspirin resistance is partly understood, it is not clear whether it is even necessary to treat it. Patients with aspirin resistance may require stronger PLT inhibition. Increased doses or a different group of antiaggregant agents are treatment options. Different forms of the same molecule (for example, exchanging the enteric coated form for the tablet form) are among the methods that can be pursued to break aspirin resistance.

This study was an investigation of relationships between the frequency of aspirin resistance in ischemic CVD and clinical and laboratory parameters related to stroke, such as stroke type, age, gender, hypertension (HT), diabetes (DM), and coronary artery disease (CAD).

MATERIAL AND METHODS

A total of 163 patients (106 males, 57 females) aged 18 to 90 years who were treated with aspirin (100-300 mg/day) and were in follow-up with the neurology clinic with the diagnosis of ischemic CVD between May 1, 2014 and October 15, 2014 were investigated for aspirin resistance. Exclusion criteria included a history of bleeding, renal dysfunction (serum creatinine level >1.4 mg/dL), severe anemia (hemoglobin <9 mg/dL), thrombocytopenia (PLT <150,000/µl), thrombocytosis (PLT >500,000/µl), myeloproliferative disease, use of nonsteroidal anti-inflammatory drugs for the previous week, use of oral anticoagulants, long-term use of statin or proton pump inhibitors, acute infection, non-regulated history of HT or DM, and use of dual antiplatelet drugs.

In vitro aspirin sensitivity was tested with a Multiplate platelet analyzer (Roche Diagnostics, Risch-Rotkreuz, Switzerland). This is a quick and modern method in which platelet function in whole blood (a physiological environment) is measured using the impedance method. Impedance aggregometry was developed by Flower and Cardinal in the 1980s. The Multiplate analyzer is an automated system of measurement using multiple electrode aggregometry technology. Measurement is easy and can be accomplished within 5 minutes. Blood samples are drawn from the aspirin- user into hirudin-containing tubes. The cartridges and plates are disposable and therefore do not need to be cleaned before each test.

A 0.3 mL sample of hirudinated blood is diluted and incubated for 3 minutes. The cartridge containing the agonist of the drug to be measured is sent to the medium. Throughout the process, sensors record changes in the resistance patterns induced by platelets that adhere to the electrodes. Increased resistance due to platelets adhering to the sensor wires is converted by the device into aggregation units (AU) and a graph is produced. Sensitivity can also be tested by adding aspirin to the plate. Therefore, the test can also be used safely in patients who do not use aspirin. Three parameters are determined: the area under the curve (AUC), AUs, and speed (AUs/second). The most important diagnostic parameter is the AUC.[9]

Relationships between aspirin sensitivity and ischemic CVD risk factors (age, sex, HT, diabetes, hyperlipidemia (HL), smoking, history of ischemic CVD, history of ischemic CVD in family history) were analyzed. The statistical analysis was performed using NCSS 2007 software (NCSS, LLC, Kaysville, UT, USA). In addition to descriptive statistical methods (mean, SD), an independent t-test was used to compare paired groups, and a chi-square, Fisher's exact test, and relative proportion (odds ratio; OR) were used for comparisons of qualitative data. The results were evaluated at $p<0.05$ significance level and within a 95% confidence interval.

RESULTS

Of the 163 patients, 65% (n=106) were male and 34.9% (n=57) were female. The mean age was 64.51±13.85 years. Aspirin resistance was determined in 15.3% (n=25) of the 163 patients, who were evaluated within the first 72 hours after the aspirin dose. Aspirin resistance was seen in 66.7% (16/106) of the male and 33.3% (9/57) of the female patients. The mean age of the resistant patients was 67.5±10.7 years. There was no statistically significant relationship between the mean age, sex, and aspirin resistance ($p>0.05$). Aspirin resistance was determined in 76% (n=19) of the patients receiving a daily dose of 300 mg ASA (n=19) and in 24% (n=6) of the patients using a daily dose of 100 mg ASA (Table 1).

When the 25 patients in the aspirin resistance (+) group were evaluated in terms of systemic diseases, HT was present in 14 (53.6%), DM in 10 (40%) CAD in 3 (12%) congestive heart failure (CHF) in 2 (8%), HL in 1 (4%), and CVD in 2 (8%). Although there was an increased risk of HT and DM in patients with aspirin resistance, the intergroup difference was not statistically significant ($p>0.05$) (Table 1).

The distribution of levels of fasting blood glucose (FBG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; height-weight; and use of tobacco and alcohol were investigated in both the aspirin resistance (-) and aspirin resistance (+) groups, and the incidence of FBG >106 mg/dL was found to be slightly higher in the group with aspirin resistance but without any statistically significant intergroup difference ($p>0.05$) (Table 1).

This study also examined the reasons underlying aspirin resistance and the relationship between aspirin resistance and stroke phenotype. Stroke subtypes were determined according to the TOAST classification.[10] When the 25 patients with aspirin resistance were classified according to stroke etiology, atherosclerosis of major arteries was observed in 60% (n=15), followed by small vessel occlusion (lacunar) in 28% (n=7), cardioembolism in 8% (n=2), and transient ischemic attack (TIA) in 4% (n=1). None of the patients with aspirin resistance were included in the group of other etiologies or unknown etiologies. There was no statistically significant difference between aspirin resistance and etiological factors.

DISCUSSION

Aspirin is widely used but it does not demonstrate the same protective effect in all patients. The development of recurrent vascular events under aspirin therapy has raised issues surrounding the therapeutic efficacy of aspirin and aspirin resistance. Aspirin resistance affects primary treat-

Table 1. The relationship between aspirin resistance, demographic characteristics, and stroke-related risk factors

	Aspirin resistance (–)	Aspirin resistance (+)	p	Odds ratio
Total	138 (84.66%)	25 (15.34%)	0.926	1.04 (0.41–2.61)
Gender				
Male	90 (65.69%)	16 (66.67%)		
Female	48 (34.31)	9 (33.33%)		
Acetyl salicylic acid				
100 mg	19 (13.77%)	6 (24.00%)		
300 mg	119 (86.23%)	19 (76.00%)	0.315	1.97 (0.7–5.58)
Age (Mean±SD)	63.9±14.3	67.5±10.7	0.253	
Height (m), (Mean±SD)	1.67±0.06	1.65±0.08	0.143	
Weight (kg), (Mean±SD)	75.34±10.8	73.29±10.58	0.391	
Body mass index (kg/m^2), (Mean±SD)	27.09±3.97	27.17±5.04	0.931	
Fasting blood glucose >106 mg/dL	71 (52.59%)	17 (73.91%)	0.816	0.75 (0.26–2.18)
Low-density lipoprotein >130 mg/dL	45 (39.13%)	8 (36.36%)	0.996	0.88 (0.34–2.29)
High-density lipoprotein <60 mg/dL	117 (95.12%)	21 (95.45%)	0.946	1.07 (0.12–9.41)
Cholesterol >200 mg/dL	57 (46.72%)	10 (45.45%)	0.913	0.95 (0.38–2.36)
Hypertension	74 (53.62%)	14 (56.00%)	0.998	1.1 (0.47–2.59)
Diabetes mellitus	42 (30.43%)	10 (40.00%)	0.477	1.52 (0.63–3.66)
Hyperlipidemia	8 (5.80%)	1 (4.00%)	0.717	0.68 (0.08–5.66)
Coronary artery disease	24 (17.39%)	3 (12.00%)	0.707	0.65 (0.17–2.34)
Congestive heart failure	8 (5.80%)	2 (8.00%)	0.761	1.28 (0.02–6.43)
Past stroke	20 (14.49%)	2 (8.00%)	0.578	0.51 (0.11–2.34)
Tobacco use	36 (26.09%)	5 (20.00%)	0.692	0.71 (0.24–2.02)
Alkol	8 (5.80%)	3 (12.00%)	0.481	2.22 (0.54–9.01)
Systolic blood pressure >130 mmHg	77 (57.89%)	14 (58.33%)	0.968	1.01 (0.42–2.45)
Diastolic blood pressure >85 mmHg	45 (33.83%)	10 (41.67%)	0.611	1.39 (0.57–3.39)

SD: Standard deviation.

ment and secondary prophylaxis of cardiovascular and CVD. Therefore, aspirin resistance screening in patients is useful in planning appropriate treatment.

Several methods have been used to evaluate aspirin resistance. It has been reported that the frequency of aspirin resistance varies between 6% and 27% in the general population.[11,12] An evaluation of the meta-analysis results of over 40 studies indicated that the average prevalence of aspirin resistance was 24%.[11]

In this study, impedance aggregometry using whole blood samples was employed to test for aspirin sensitivity in vitro. Platelet aggregation can be tested directly with the Multiplate analyzer. Other commonly used techniques are PFA100, LTA and verify NOW. Using the PFA100, rates of aspirin resistance have been reported as 3.4% to 62%, while 6.5% to 44% with LTA, and 11.5% to 30% with verifyNOW.[13] Harrison et al. evaluated aspirin resistance in 100 patients after TIA and stroke, and calculated the frequency of resistance using 3 different techniques with findings of 12%, 17% and 22%. The frequency of aspirin resistance in ischemic CVD has been reported to range between 3% and 85%, depending on the analysis method used.[14] Bennett et al.[15] found a rate of aspirin resistance of 30% in stroke patients. In our study, the frequency of aspirin resistance was found to be 15.3%.

We examined the relationship between pharmacological resistance and clinical, demographic, and etiological features in a stroke population under aspirin treatment and no statistically significant relationship was found between sex and aspirin resistance. In a study conducted by Lee et al.[16] in an ischemic stroke patient group, platelet sensitivity to aspirin was reported to be higher in female patients.

No significant relationship between age and aspirin resistance has been reported. Berrouschot et al.[5] evaluated recurrent stroke patients and reported no significant relationship with age. Similarly, we found no significant relationship between age and aspirin resistance.

In a large number of patients who had ischemic stroke when using aspirin, it was determined that the etiology was not expected to respond to aspirin therapy due to the pathophysiology of the event, and it was stated that this was independent of the pharmacological activity of aspirin.[17] The first choice for cardiogenic cerebral embolism is an anticoagulant agent.[18] In our study, the inclusion of patients with atrial fibrillation and therefore not receiving anticoagulant therapy may explain the low rate of association between aspirin resistance and cardioembolic stroke.

It has been proposed that in diabetic patients, 2 pathways in which aspirin is not effective (thromboxane A2 production via the COX-2 pathway and the thromboxane A2-like

isoprostanes produced from arachidonic acid) may become activated and thereby increase aspirin resistance.[19] Dichiara et al.[20] reported that the rate of aspirin resistance in diabetic patients ranged between 13% and 37%. Fateh-Moghadam et al.[21] found an aspirin resistance in 21% of patients with DM who regularly used aspirin at daily doses of 100 mg daily for 6 to 12 months. In our study, DM was found in 40% of the patients with aspirin resistance, and in 30.4% of those without resistance. Although the incidence of DM in patients with aspirin resistance was higher than that of other studies, there was no statistically significant relationship between aspirin resistance and DM.

Aspirin has been reported to be less effective in patients with a systolic blood pressure greater than 145 mmHg.[22] It has been suggested that the interaction between platelets and red blood cells may increase aspirin resistance by creating a prothrombotic effect. The majority of studies have investigated a relationship between HT and aspirin resistance in cardiovascular disease; however, no significant relationship has been found. Fong et al.[23] analyzed stroke patients and found no significant relationship between aspirin resistance and HT.

In another study examining aspirin and blood pressure, the relative risk of stroke was 1.42 in the group with high blood pressure and 0.41 in the low blood pressure group.[22] This complex relationship cannot be explained on the basis of aspirin resistance alone, factors such as the positive effect of blood pressure control on cardiovascular events and the risk of less bleeding in the control group with HT and aspirin use play a role in this relationship.[24] In our study, the incidence of HT was 56% in patients with aspirin resistance and 53.6% in those without. The fact that the incidence of HT was similar in both groups suggested that there may be no significant relationship between HT and aspirin resistance. In our study, systolic and diastolic blood pressure values and aspirin resistance rates were examined. There was no statistically significant difference between systolic blood pressure (>130 mmHg) and diastolic blood pressure (>85 mmHg) values in the aspirin resistance (-) and aspirin resistance (+) groups ($p>0.05$). Cardiac risk factors, such as CAD, CHF, and HL, which are among the etiological risk factors for ischemic stroke, were also evaluated in our study. Different patient populations and methods used in studies of the relationship between CAD and aspirin resistance conducted between 1993 and 2006 led to various results.

Fong et al.,[23] who investigated antiplatelet markers in stroke patients, found no significant relationship between CAD and CHF and aspirin resistance. In our study, in aspirin resistance group, CAD and CHF were 12% and 8%, respectively.

Zheng et al.[25] compared aspirin-resistant and non-resistant groups of patients who experienced stroke under aspirin treatment and determined that the HL rate was higher in the aspirin-sensitive group.[25] Luzak et al.[26] reported that in hypercholesterolemic patients taking aspirin, statin therapy led to an increased sensitivity of platelets to aspirin, and that aspirin resistance decreased.[26] Similarly, in our study, when groups with and without aspirin resistance were compared, no statistically significant correlation was observed with regard to LDL cholesterol (>130 mg/dL), HDL cholesterol (<60 mg/dL) and total cholesterol (>200 mg/dL)

The role of smoking in aspirin resistance is controversial. Studies have not demonstrated a statistically significant correlation between aspirin resistance and smoking.[27] In one study investigating causes of aspirin resistance in ischemic CVD patients in our country, no significant relationship was found between tobacco use and aspirin resistance.[28] Similarly, both smoking and alcohol use were evaluated separately in our study and there was no statistically significant difference in aspirin resistance.

We investigated the frequency of aspirin resistance in ischemic CVD and clinical factors that might be associated. There was no statistically significant difference in the clinical or demographic factors between groups with and without aspirin resistance in our study patients. Aspirin resistance was determined in 15.3% of 163 ischemic stroke patients, which eliminated the typical antiaggregant effect. Though evidence-based data related to aspirin-resistant patients are sparse, we have transitioned to using treatments with different mechanisms of action.

Nonetheless, whether or not the preference for another antiaggregant is a good approach in clinical practice should be clarified with further randomized studies.

In conclusion, the possibility of existing aspirin treatment underlying ischemic CVD or cardiovascular diseases should be kept in mind. This condition is not rare, and may be observed as an element of a primary or recurrent event. Questions remain regarding the patient groups that should be suspected of aspirin resistance, the standard diagnostic method to be used in the measurement of aspirin resistance, and the optimal effective treatment strategies as alternatives to aspirin therapy. Additional prospective, randomized trials are needed to address these questions, including assessment of cost- effectiveness and risk/benefit.

Ethics Committee Approval

Retrospective study approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: A.B., S.Ç., M.Ç., S.Ş.; Design: A.B., S.Ç., M.Ç., S.Ş.; Data collection &/or processing: A.B., S.Ç., M.Ç., S.Ş.; Analysis and/or interpretation: A.B., S.Ç., V.Y.; Literature search: A.B., S.Ç.; Writing: A.B., S.Ç., V.Y.; Critical review: A.B., S.Ç., V.Y.

Conflict of Interest

None declared.

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İskemik İnme Hastalarında Aspirin Direnci

Amaç: Aspirin, iskemik serebrovasküler hastalıklarda (SVH) antitrombosit tedavinin temelini oluşturur. Bazı hastalarda aspirin tedavisine yeterli yanıt alınamaz, bu durum son zamanlarda aspirin direnci kavramının doğmasına neden olmuştur. Çalışmalarda SVH'da aspirin direnci sıklığı %3–85 oranında değişmektedir. Bu çalışmada, iskemik SVH tanısıyla takip edilen aspirin tedavisi altındaki hastalarda aspirin direnci sıklığı, demografik özellikleri, risk faktörleri, inme alt gruplarıyla ilişkisini araştırmak amaçlandı.

Gereç ve Yöntem: İskemik SVH tanısıyla altı aylık sürede izlenen, düzenli aspirin 100–300 mg/gün tedavisi almış ve Multiplate platelet fonksiyon analizatörüyle aspirin direncine bakılmış 163 hasta (106 erkek, 57 kadın) değerlendirilmiştir. Bu hastalarda inme alt tipleri, yaş, cinsiyet, boy, kilo, hipertansiyon (HT), diyabetes mellitus (DM), geçirilmiş SVH, hiperlipidemi (HL), sigara ve alkol kullanımı, açlık kan şekeri düzeyi gibi durumlarla aspirin direnci ilişkisi gözden geçirilmiştir.

Bulgular: İskemik SVH tanılı 163 hastanın 25'inde (16 erkek, 9 kadın) aspirin direnci saptandı (%15.3). Aspirin direnci ve inme ile ilişkili klinik ve laboratuvar parametreleri arasında istatistiksel anlamlı herhangi bir ilişki bulunmadı.

Sonuç: İskemik inme geçiren hastalardan hangilerine test uygulanması gerektiğinin ve direnç saptanan hastalarda tedavide nasıl bir yol izleneceğinin netliğe kavuşması için daha fazla sayıda ileriye yönelik, randomize çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Sözcükler: aspirin direnci; iskemik inme; Multiplate analizör.