ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Clopidogrel responsiveness in chronic kidney disease patients with acute coronary syndrome

Akut koroner sendromlu kronik böbrek hastalarında klopidogrel cevabı

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ABSTRACT

Objective: Cardiovascular diseases are the leading cause of death in patients with chronic kidney disease (CKD). There is conflicting evidence about effect of CKD on clopidogrel responsiveness. We aimed to evaluate the clopidogrel responsiveness in CKD patients with acute coronary syndrome (ACS).

Methods: A total of 101 patients; 55 with moderate to severe CKD and 46 with normal renal function or mild CKD, hospitalized with ACS were included in our study. Multiplate test was used to determine clopidogrel responsiveness. Platelet aggregation results were presented as aggregation unit (AU)*min and values over 470 AU*min were accepted as clopidogrel low responders.

Results: The 101 patients (mean age 64.76±8.67 years; 61 [60.4%] male) were grouped into the two study groups as follows: group 1; 55 patients with eGFR<60 ml/min/1.73 m2 and group 2; 46 patients with eGFR>60 ml/min/1.73 m2. 35 patients (34.7%) of the study population were found to have low response to clopidogrel (16 [34.8%] patients in group 1 and 18 [33.3%] patients in group 2, p=0.879) . There was no significant difference between group 1 and 2 for Multiplate test results (414.67±281.21 vs 421.56±316.19 AU*min, p=0.909). Clopidogrel low responsiveness were independently related to Multiplate test results of aspirin responsiveness (OR=1.004, CI 1.002–1.007, p=0.001) and hemoglobin (OR=0.727, CI 0.571–0.925, p=0.010). Multiplate results were also independently related to Multiplate test results of aspirin responsiveness (β=0.402, p<0.0001) and hemoglobin (β=-0.251, p=0.007).

Conclusion: Platelet response to clopidogrel does not differ between patients with eGFR < 60 ml/min/1.73 m² and eGFR>60 ml/min/1.73 m².

Key words: Acute coronary syndrome, chronic kidney disease, clopidogrel response

ÖZET

Amaç: Kardiyovasküler hastalıklar, kronik böbrek hastalığı (KBH) olanlarda önde gelen ölüm sebebidir. KBH' nın klopidogrel cevabı üzerine olan etkisi hakkında çelişkili kanıtlar vardır. Bu çalışmada, akut koroner sendromlu kronik böbrek hastalarında klopidogrel yanıtını değerlendirmeyi amaçladık.

Yöntemler: Akut koroner sendrom ile hospitalize edilen; orta ileri KBH olan 55, normal böbrek fonksiyonu olan veya hafif KBH bulunan 46; toplamda 101 hasta çalışmaya dahil edildi. Klopidogrel yanıtını değerlendirmek için Multiplate testi kullanıldı. Trombosit agregasyon sonuçları agregasyon birimi (AU)*dak olarak verildi ve 470 AU*dak üzerindeki değerler klopidogrele düşük cevaplılar olarak kabul edildi.

Bulgular: Çalışmaya dahil edilen 101 hasta (ortalama yaş 64.76±8.67, 61 [60.4%]' i erkek) şu şekilde iki çalışma grubuna ayrıldı: grup 1; eGFH<60 ml/dak/1.73 m2 olan 55 hasta, grup 2; eGFH>60 ml/dak/1.73 m2 olan 46 hasta. Çalışma populasyonundaki 35 hastada (34.7%) klopidogrele düşük yanıt bulundu (grup 1'den 16 [34.8%] hasta; grup 2'den 18 [33.3%] hasta, p=0.879). Multiplate test sonuçları açısından grup 1 ve 2 arasında anlamlı fark yoktu (414.67±281.21 vs 421.56±316.19 AU*dak, p=0.909). Klopidogrele düşük yanıt, aspirin cevabının Multiplate test sonuçları ile (odds ratio [OR]=1.004, confidence interval [CI] 1.002–1.007, p=0.001) ve hemoglobin ile (OR=0.727, CI 0.571–0.925, p=0.010) bağımsız olarak ilişkili idi. Yine Multiplate sonuçları; aspirin yanıtının Multiplate test sonuçları (β=0.402, p<0.0001) ve hemoglobin (β=-0.251, p=0.007) ile bağımsız olarak ilişkili idi.

Sonuç: Klopidogrele trombosit yanıtı; eGFH < 60 ml/dak/1.73 m2 ve eGFH>60 ml/dak/1.73 m2 olan hastalar arasında değişmiyor.

Anahtar kelimeler: Akut koroner sendrom , kronik böbrek hastalığı, klopidogrel cevabı

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INTRODUCTION

Clopidogrel is a thienopyridine that irreversibly inhibits platelet adenosine diphosphate P2Y12 receptor, which is a key signaling pathway of the platelet activation. Clopidogrel is widely used in patients with coronary artery disease. Dual antiplatelet treatment is the standard therapy for patients after acute coronary syndromes (ACS) and undergoing percutaneous coronary interventions (PCI). Guidelines recommend 1 year dual antiplatelet treatment in patients with ACS [1].

Interindividual variability of response to clopidogrel therapy has been demonstrated in some studies [2]. The clinical importance of this situation has been demonstrated in different clinical conditions such as ACS and after PCI [3-5]. Although clopidogrel resistance is used in clinical practice; in fact it is a low responsiveness to clopidogrel. It is a multifactorial phenomenon. Variability of platelet response to clopidogrel is likely to develop as a result of a decreased bioavailability of the active metabolite, due to genetic variation or concomitant drug treatment [2].

Cardiovascular diseases are the leading cause of death in patients with chronic kidney disease (CKD). Patients with all stages of CKD experience higher rates of atherothrombotic disease manifestations than the general population [6-8]. This underlies the importance of antithrombotic therapy in these patients. There is conflicting evidence about effect of CKD on clopidogrel responsiveness. Some studies demonstrated high rates of clopidogrel low responsiveness (CLR) in CKD patients [9,10] whereas someone did not showed any relation [11].

The aim of our study was to evaluate the clopidogrel responsiveness in CKD patients with ACS.

METHODS

This study was approved by the local ethics committee, and all participants gave written informed consent before participating.

Estimated glomerular filtration rate (eGFR) of 312 consecutive patients hospitalized with ACS was calculated by using the Modification of Diet in Renal Disease Study Formula [12]. 46 of these patients with normal renal function or mild CKD and 55 with moderate to severe CKD, total 101 patients were included in the study. We classified the 101 patients into two study groups according to their eGFR values. Group 1 included 55 patients with moderate to severe CKD (eGFR< 60 ml/min/1.73 m2) and group 2 included 46 patients with mild CKD or normal renal function (eGFR> 60 ml/min/1.73 m2). Aspirin and clopidogrel responsiveness were assessed after 7 days of regular 100 mg acetyl salicylic acid (ASA) and clopidogrel 75 mg once a day prescription. The discharged patients during this period were called for the test and their drug compliance were determined by patient interviews.

Patients taking an antiplatelet therapy other than ASA and clopidogrel (ticlopidine, dipyridamole, nonsteroidal anti-inflammatory drugs, pentoxyphillin, cilostazol), previous treatment with glycoprotein IIb/IIIa inhibitors within 10 days, active malignancy, hemorrhagic diathesis, thrombolytic treatment within the last month, liver disease, platelet counts <100,000/ml, and noncompliant with medical therapy were not included in the study.

Information on diabetes, hypertension, hyperlipidemia, smoking, and medication history of the patients were recorded. Fasting blood samples were obtained to determine creatinine, blood urea nitrogen (BUN), uric acid, blood glucose, lipid profile, hemoglobin, mean platelet volume (MPV), leucocyte, and platelet count. We used the multiplate test (Dynabyte Medical, Munich, Germany) to determine clopidogrel responsiveness.

Assessment of clopidogrel responsiveness

Whole blood was obtained via standard venipuncture at an antecubital vein. Blood was collected in tubes containing the anticoagulant hirudin. The ADP-induced platelet aggregation in whole blood was assessed with multiple electrode aggregometry using an impedance aggregometer called Multiplate analyzer within two hours of sampling after two to four hours of drug ingestion. Details of this method have been reported previously [13]. In brief, after 1:1 dilution of whole blood with 0.9% NaCl solution and stirring for 3 min in the test cuvettes at 37°C, 6.4 μmol/l ADP was added. Platelet aggregation was continuously recorded for 5 min. Impedance with Multipl electrode aggregometry is transformed to arbitrary aggregation units (AU) that are plotted against time (AU*min). Aggregation mea-

sured is quantified as AU and area under the curve of arbitrary units (AU*min) and values over 470 AU*min were accepted as CLR.

Assessment of aspirin responsiveness

Whole blood aggregation was performed with the multiplate analyzer, an impedance aggregometer that is based on the principle that activated platelets expose receptors on their surface that allow them to attach to artificial surfaces. After two to four hours of aspirin ingestion, whole blood samples were collected in test tubes containing hirudin (25 mcg/ml) as anticoagulant. Arachidonic acid was used as the aggregation agonist, and all samples were analyzed within 2 hours of collection. The aggregation measured with this device is quantified as area under the curve, aggregation degree, and aggregation velocity. Platelet aggregation results were presented as aggregation unit (AU)*min, and values over 500 AU*min were accepted as aspirin resistance (AR) [14].

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. The unpaired Student's t-test for continuous variables and $\chi 2$-test for categorical variables was performed to compare the study groups in relation to eGFR levels and patients groups with and without CLR. Correlations between the multiplate test results and CLR status with other parameters were analyzed using Spearman's or Pearson's correlation analysis. Multivariate associations of the multiplate test results were determined by using multiple stepwise linear regression analysis with parameters having significant correlations in the univariate analysis. For the determination of the influential factors on CLR, multivariate logistic regression analysis was also performed on variables with a p value of <0.05 derived from the univariate analysis. The receiver-operating characteristics (ROC) curve was used to test the predictive accuracy of eGFR with respect to the presence of CLR based on Multiplate test results. Significant prediction was accepted when the area under the ROC curve was significantly different from 0.5. p<0.05 was accepted as statistically significant. All analyses were performed using SPSS 15.0 statistical software.

RESULTS

The 101 patients (mean age 64.76±8.67 years; 61 [60.4%] male) included in the study were grouped into the two study groups as follows: group 1; 55 patients with eGFR<60 ml/min/1.73 m², and group 2; 46 patients with eGFR>60 ml/min/1.73 m². Group 1 were included 47 patients with an eGFR between 30 and 59 ml/min/1.73 m² (Stage 3 CRF) and 8 patients with eGFR between 15 and 29 ml/min/1.73 m² (Stage 4 CRF). Group 2 were included 21 patients with an eGFR >90 ml/min/1.73 m² without renal disease history and 25 patients with an eGFR between 60 and 89 ml/min/1.73 m² (Stage 2 CRF). Demographic and clinical features of these two groups are listed in Table 1.

35 patients (34.7%) of the study population were found to have CLR (aggregation >470 AU*min). Multiplate test results and CLR status of the study groups were also shown in Table 1 and Figure-1.
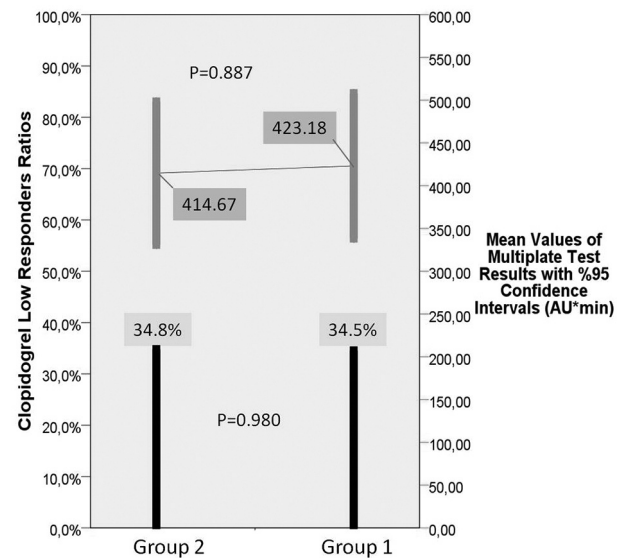

Figure1. Multiplate test results and aspirin resistance ratios in the study groups

The mean value of the multiplate test results was 760.05±240.74 (range 475–1232) AU*min in the 35 patients with CLR and 238.61±102.13 (range 25–459) AU*min in the 66 patients with normal clopidogrel response. Demographic and clinical features of clopidogrel low responders and clopidogrel sensitive patients are presented in Table 1.

Table 1. Demographic Characteristics and Laboratory Values of the Study Groups

	Group I (n=55)	Group II (n= 46)	p value
Age, years	67.83 ± 8.29	61.08 ± 7.71	<0.0001
Male, n (%)	27 (49.1)	34 (73.9)	0.011
Hypertension, n (%)	49 (89.1)	30 (65.2)	0.004
Diabetes mellitus, n (%)	32 (58.2)	11 (23.9)	0.001
Hypercholesterolemia, n (%)	45 (81.8)	34 (73.9)	0.338
Smoking, n (%)	13 (23.9)	22 (47.8)	0.011
Body mass index, kg/m^2	29.13 ± 4.39	29.02 ± 5.73	0.418
Medication			
β-blockers, n (%)	43 (78.2)	39 (84.8.6)	0.398
RAS blockers, n (%)	44 (80.0)	34 (73.9)	0.468
Calcium antagonists, n (%)	18 (32.7)	10 (21.7)	0.219
Statins, n (%)	47 (85.5)	37 (80.4)	0.502
Diuretics, n (%)	11 (20.0)	8 (17.4)	0.738
Laboratory values			
Creatinine, mg/dL	1.71 ± 0.96	0.92 ± 0.21	<0.0001
BUN, mg/dL	31.98 ± 17.84	17.06 ± 5.72	<0.0001
Glucose, mg/dL	150.31 ± 85.17	135.51 ± 69.33	0.358
Uric acid, mg/dL	7.15 ± 1.81	5.81 ± 1.69	<0.0001
Total cholesterol, mg/dL	177.34 ± 56.76	161.04 ± 44.72	0.119
LDL, mg/dL	106.74 ± 46.54	95.65 ± 36.55	0.194
HDL, mg/dL	42.82 ± 11.10	40.67 ± 10.97	0.333
Triglyceride, mg/dL	172.83 ± 93.61	161.56 ± 86.22	0.535
WBC, × 10^3/μl	8.37 ± 3.14	7.74 ± 2.83	0.293
Hemoglobin, g/dL	11.60 ± 1.84	13.43 ± 1.59	<0.0001
Platelet count , × 10^3/μl	239.31 ± 62.69	238.46 ± 60.45	0.945
MPV, fL	8.45 ± 1.01	8.37 ± 1.59	0.667
Aspirin Response			
Multiplate, AU*min	242.31 ± 262.87	251.95 ± 233.72	0.847
AR, n (%)	7 (12.7)	6 (13.0)	0.962
Clopidogrel response			
Multiplate, AU*min	423.18 ± 313.48	414.67 ± 281.21	0.887
CLR, n (%)	19 (34.5)	16 (34.8)	0.980
Both AR and CLR, n (%)	4 (7.3)	5 (10.9)	0.728

CKD, chronic kidney disease; eGFR, estimated Glomerular filtration rate; RAS, renin–angiotensin system; BUN, blood urea nitrogen; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell; MPV, mean platelet volume; AR, aspirin resistance.

CLR status was weakly correlated with hemoglobin (r=–0.201, p=0.044), platelet count (r=0.283, p=0.004), LDL (r=0.207, p=0.039), total cholesterol (r=0.211, p=0.027), AR status (r=0.279, p=0.005) and Multiplate test results of aspirin responsiveness (r=0.303, p=0.002). When these parameters which had significant correlation with CLR status were included in the multivariate analysis, CLR status was independently related to Multiplate test results of aspirin responsiveness (odds ratio [OR]=1.004, confidence interval [CI] 1.002–1.007, p=0.001) and hemoglobin (OR=0.727, CI 0.571–0.925, p=0.010). Multiplate test results of clopidogrel responsiveness were also weakly correlated with sex (r=-0.223, p=0.025) , hemoglobin (r=-0.233, p=0.019) , platelet count (r=0.377, p<0.0001), LDL (r=0.223, p=0.026), total cholesterol (r=0.227, p=0.013), AR status (r=0.273, p=0.006) and Multiplate test results of aspirin responsiveness (r=0.340, p=0.001). When these parameters which had significant correlation with Multiplate test results were included in the multivariate analysis, Multiplate test results of clopidogrel responsiveness were also independently related to Multiplate test results of aspirin responsiveness (β=0.402, p<0.0001) and hemoglobin (β=-0.251, p=0.007).

GFR were not correlated with CLR status (r=–0.127, p=0.207) and also showed no significant discriminatory capacity between clopidogrel low responder and clopidogrel sensitive patients, having an area under the ROC curve of 0.577 (CI 0.458-0.695), p=0.205 (Figure 2).
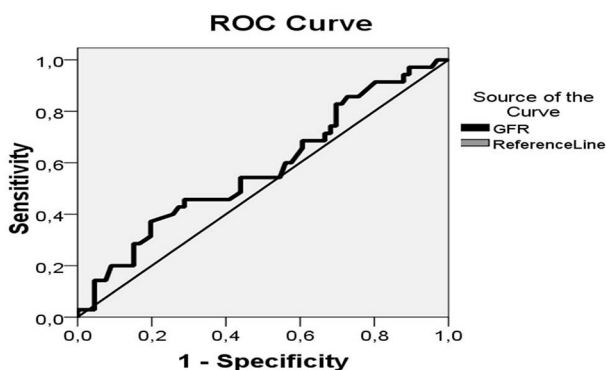

Figure 2. The receiver-operating characteristics (ROC) curve of the estimated glomerular filtration rate (eGFR) for detecting clopidogrel low responsiveness (an area under the ROC curve of 0.577 (CI 0.458-0.695), p=0.205)

DISCUSSION

In the present study, we did not observe any significant differences of clopidogrel responsiveness between the patients with normal renal function or mild CKD (eGFR > 60 ml/min/1.73 m^2) and moderate to severe CKD and not on chronic hemodialysis treatment. CLR was independently related to only Multiplate test results of aspirin responsiveness and hemoglobin. eGFR was not related to CLR and could not predict it.

In large randomized controlled trials, CKD has been linked with a lower efficacy of clopidogrel [15] and there are papers with different results about effects of CKD on clopidogrel responsiveness. Park et al [10] reported that platelet responsiveness to clopidogrel decreased more in patients with CKD than in those with normal renal function and this decreased response was not improved by increased dosage. They included severe CKD patients (patients had CKD for > 6 months and with a serum creatinine concentration > 3 mg/dl) in their CKD group and the sample size of the study was smaller. Their study included both patients with stable angina pectoris and unstable angina pectoris in contrast to our study group with ACS. Clopidogrel responsiveness was also determined by VerifyNow, not Multiplate method. Angiolillo et al showed impaired renal function was associated with reduced clopidogrel-induced antiplatelet effects in diabetic patients with coronary artery disease taking maintenance aspirin and clopidogrel therapy. Their study group was only diabetics and clopidogrel responsiveness was assessed by light transmittance aggregometry method.

Like our study results; Cuiset et al also did not find any significant effect of CKD on clopidogrel responsiveness assessed by PRI VASP, neither for acute response, nor for chronic response with high dose [11] in the patients with ACS .

The mechanisms leading to variability in clopidogrel responsiveness are not fully understood, but likely to be multifactorial. It is caused by genetic and nongenetic causes. Increased baseline platelet reactivity; commonly observed in some clinical scenarios such as ACS, diabetes mellitus and increased body mass index may lead to decreased clopidogrel responsiveness. [16-19]. Differences in individual absorption of clopidogrel and levels of its active

metabolite may also lead to clopidogrel response variability [20]. Also drugs that are substrates or inhibit the CYP isoenzyme 3A4 can lead to reduced antiplatelet effects [21].

Cardiovascular diseases are the leading cause of death in patients with CKD. These patients are at increased risk for both thrombosis and hemorrhage. Morel et al reported low platelet response to clopidogrel was associated with worse outcomes after PCI in patients with CKD [22]. Also in their study degree of P2Y12 inhibition by clopidogrel was not significantly different in the CKD and non-CKD groups. Htun et al also demonstrated low response to clopidogrel was an additional risk factor for the poorer post-PCI outcomes in patients with moderate to severe CKD patients [23]. So it is important to highlight if aspirin and clopidogrel responsiveness are lower in CKD patients and to decide the management of this situation without increasing hemorrhagic complications. As the patients with CKD also prone to hemorrhagiac complications it is important to avoid high dose of antithrombotic treatments without any evidence.

We did not include patients with end-stage renal disease and on chronic hemodialysis. This is the limitation of our study and large studies with all stages of CKD patients including hemodialysis patients with both predialysis and postdialysis tests are needed to clear the relation between CKD and antiplatelet responsiveness.

In conclusion, Platelet response to clopidogrel does not differ between patients with mild CKD or normal renal function and patients with moderate to severe CKD.

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