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The Impact of Smoking on Post-Clopidogrel Platelet Reactivity in Patients With Acute Myocardial Infarction

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ABSTRACT

Background and Objectives: Smoking increases inhibition of clopidogrel-induced platelet reactivity in patients undergoing elective coronary stenting. However, an association between pre-admission smoking (PS) and post-clopidogrel platelet reactivity in patients with acute myocardial infarction (AMI) has not been determined. **Subjects and Methods**: Study cohorts were recruited from a pool of patients at our hospital who were undergoing coronary stenting for AMI (n=134). Immediately after arrival at the emergency room (ER), all patients received a 600 mg loading dose of clopidogrel followed by a maintenance dose of 75 mg/day. Platelet aggregation was measured with light transmittance aggregometry (LTA) after addition of 5 or 20 μmol/L adenosine diphosphate (ADP). **Results**: Maximal platelet aggregation (Agg_{max}) was lower in PS patients after 5 μmol/L ADP (43.6±15.7% vs. 48.4±12.5%, p=0.096) and 20 μmol/L ADP stimuli (56.2±15.6% vs. 61.3±11.6%, p=0.073) compared with non-smoking (NS) patients. However, there were no differences in 5 μmol/L (42.6±16.3% vs. 43.8±15.6%, p=0.776) and 20 μmol/L ADP-induced Agg_{max} (54.8±14.3% vs. 56.5±15.9%, p=0.692) between PS patients <0.5 pack/day and ≥0.5 pack/day. Although more PS patients met the criteria for low post-clopidogrel platelet reactivity (LPPR) (≤37%; the lowest quartile of 5 μmol/L ADP-induced Agg_{max}) than NS patients (30.9% vs. 13.5%, p=0.048), advancing age was the only independent predictor of LPPR {odds ratio (OR) 0.960, 95% confidence interval (CI) 0.929 to 0.993, p=0.019}. **Conclusion**: PS is significantly not associated with decreased residual platelet reactivity in AMI patients. **(Korean Circ J 2010;40:119-124)**

KEY WORDS: Smoking; Post-clopidogrel platelet reactivity; Acute myocardial infarction.

Introduction

Clopidogrel is metabolized into an active metabolite by 2 consecutive steps involving cytochrome P450 (CYP), and inhibits platelet aggregation through an irreversible blockade of adenosine diphosphate (ADP) P2Y12 receptors.[1] Therefore, various factors that interfere with CYP activity can reduce antiplatelet responses to clopidogrel.[2-5] On the contrary, cigarette smoking, an inducer of CYP1A2 activity, can increase concentrations of the active metabolite of clopidogrel.[6] Recently, Bliden et al.[7] reported that smoking, in a dose-related manner, increases platelet inhibition by clopidogrel compared with non-smoking (NS). An analysis of patients on chronic clopidogrel therapy (n=120) showed significantly lower platelet aggregation in patients currently smoking ≥0.5 pack/day compared with patients of NS and currently smoking <0.5 pack/day (p<0.05). The study of Bliden used the results of platelet aggregation in the setting of elective coronary stenting.

However, acute myocardial infarction (AMI) is associated with enhanced platelet reactivity, and the impact of pre-admission smoking (PS) on post-clopidogrel platelet reactivity in AMI patients can be different from platelet reactivity in patients on chronic clopidogrel th-

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erapy. In addition, there is no clear data for the role of smoking on clopidogrel-induced platelet inhibition in AMI patients.[8)9)] Accordingly, the aim of the present study was to determine if there is an association between smoking and clopidogrel-induced platelet inhibition in AMI patients.

Subjects and Methods

Subjects

Subjects were prospectively recruited from the population of patients who underwent, between October 2007 and May 2008, coronary stenting for AMI in the Department of Cardiology of the Gyeongsang National University Hospital. Consecutive patients admitted for AMI were enrolled if they were ≥18 years of age and had undergone uneventful coronary stenting. AMI was defined as clinical symptoms compatible with acute myocardial ischemia within 12 hours before admission with a subsequently documented increase in markers of AMI. ST-segment elevation myocardial infarction (STEMI) patients were treated with primary stenting less than 12 hours after the onset of pain; non-STEMI (NSTEMI) patients received coronary stenting within 24 hours after admission. Exclusion criteria were a history of active bleeding and bleeding diatheses, oral anticoagulation therapy with warfarin, contraindications to antiplatelet therapy, left ventricular ejection fraction <30%, leukocyte count <3,000/mm^3 and/or a platelet count <100,000/mm^3, aspartate aminotransferase or alanine aminotransferase levels ≥3 times upper normal, serum creatinine level ≥2.5 mg/dL, and non-cardiac disease with a life expectancy <1 year. The Institutional Review Board approved the study protocol, and the patients provided written informed consent for participation.

Study design

Immediately after emergency room (ER) arrival, all patients received a 600 mg loading dose of clopidogrel followed by a maintenance dose of 75 mg/day. Low-molecular-weight heparin (enoxaparin) or unfractionated heparin was used at the physician's discretion before the procedure, and tirofiban, which has a short half-life, was administered if needed. Pre-discharge post-clopidogrel platelet reactivity was assessed 1) 3 or more days after coronary stenting not treated with tirofiban or 2) 5 or more days after the procedure in patients treated with tirofiban.

Platelet function assays and definition

Platelet aggregation was assessed with light transmittance aggregometry (LTA) according to standard protocols.[10)] The results of LTA were validated in our laboratory and reported.[11)] Blood samples were drawn though a 21-gauge needle into vacutainer tubes containing 0.5 mL sodium citrate 3.2% (Becton-Dickinson, San Jose, CA, USA) and processed within 60 minutes. Platelet-rich plasma (PRP) was obtained as a supernatant fluid after centrifuging blood at 120 g for 10 minutes. The remaining blood was further centrifuged at 1,200 g for 10 minutes to prepare platelet-poor plasma (PPP). PRP was adjusted to platelet counts of 250,000/μL by adding PPP as needed. Platelet aggregation was assessed at 37℃ using an AggRAM aggregometer (Helena Laboratories Corp., Beaumont, TX, USA). Light transmission was adjusted to 0% with PRP and to 100% with PPP for each measurement. Platelet functions were measured after addition of 5 or 20 μmol/L ADP, and curves were recorded for 10 minutes. Platelet aggregation was measured at peak (Agg_{max}) and at 5 minutes (Agg_{late}) by laboratory personnel blinded to the study protocol. Agg_{max} is considered to reflect the activity of both P2Y1 and P2Y12 ADP receptors, whereas Agg_{late} may be more reflective of P2Y12 receptor activity.

We defined the criteria for low post-clopidogrel platelet reactivity (LPPR) as the lowest quartile of 5 μmol/L ADP-induced platelet reactivity (Agg_{max} ≤37%).[7)]

Statistical analysis

Continuous variables are presented as means±SD. They were compared using Student's unpaired t-tests or Mann-Whitney U-tests. Categorical variables are presented as numbers or percentages and were compared using the chi-square tests or Fisher's exact tests (if an expected frequency was <5). Platelet function measurements of the 3 groups were analyzed by one-way analysis of variance (ANOVA) on ranks. To determine predictors of LPPR, multivariate regression analyses were performed using the dependent variables that exhibited at least a modest effect ($p<0.20$). A $p<0.05$ was considered to indicate a significant difference. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 13 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

We identified 134 AMI patients (73 STEMI and 61 NSTEMI patients) who underwent uneventful coronary stenting. The 134 included 97 PS patients (smoking within 2 weeks of the procedure and 37 NS patients (no smoking within 1 year of the Procedure). The PS patients were younger, more often men, and less likely to have diabetes, hypertension or anemia than the NS patients (Table 1).

Platelet function assays

There was no difference between STEMI and NSTEMI patients with regard to post-clopidogrel platelet

Table 1. Clinical and procedural characteristics

Variables, n (%)	Pre-admission smoking (n=97)	Non-smoking (n=37)	p
Age (years)	58.7±12.3	66.1±9.0	0.001
Male	91 (93.8)	10 (27.9)	<0.001
BMI (kg/m^2)	24.1±2.5	24.9±2.5	0.179
Indication for intervention			0.847
STEMI	52 (53.6)	21 (56.8)	
NSTEMI	45 (46.4)	16 (43.2)	
Pre-procedural hemodynamics			
Systolic blood pressure (mmHg)	129±29	125±29	0.551
Diastolic blood pressure (mmHg)	80±17	76±19	0.168
Heart rate (bpm)	79±22	81±26	0.510
Risk factor			
Diabetes mellitus	21 (21.6)	17 (45.9)	0.009
Hypertension	34 (35.1)	22 (59.5)	0.018
Hypercholesterolemia	32 (33.0)	14 (37.8)	0.685
Chronic kidney disease	9 (9.3)	8 (21.6)	0.079
History			
Previous myocardial infarction	2 (2.1)	0 (0)	0.523
Previous PCI	1 (1.0)	0 (0)	0.724
Previous CABG	0 (0)	0 (0)	1.000
Previous stroke	1 (1.0)	0 (0)	0.724
Concomitant medications			
Statin			0.557
CYP 3A4 pathway metabolized	90 (92.8)	34 (91.9)	
Non-CYP 3A4 pathway metabolized	7 (7.2)	3 (8.1)	
Beta blocker	88 (90.7)	31 (83.8)	0.200
ACEI	25 (25.8)	9 (24.3)	1.000
ARB	71 (73.2)	26 (70.3)	0.829
Nitrate	85 (87.6)	33 (89.2)	0.533
Calcium channel blocker	9 (9.3)	3 (8.1)	0.567
LV ejection fraction (%)	56±9	56±12	0.959
Hemoglobin (g/dL)	14.7±1.4	13.9±1.4	0.002
Platelet count ($\times 10^3$/mm^3)	277±63	277±79	0.993
Hb_{A1C} (%)	6.2±1.2	6.8±1.6	0.019
Creatinine clearance (mL/min)	85±24	76±29	0.054
Total cholesterol (mg/dL)	192±41	197±43	0.502
Total ischemic time (minutes) (STEMI patients)	220±180	179±179	0.575
DTB time (minutes) (STEMI patients)	68±32	62±30	0.745
Infarct-related vessel			0.731
Left anterior descending	45 (46.4)	15 (40.5)	
Left circumflex artery	23 (23.7)	11 (29.7)	
Right coronary artery	29 (29.9)	11 (29.7)	
Left main	0 (0)	0 (0)	
Initial TIMI flow grade			0.249
0 or 1	60 (61.8)	25 (69.4)	
2	28 (28.9)	10 (27.8)	
3	9 (9.3)	1 (2.8)	
Thrombus present	25 (25.8)	4 (10.8)	0.065
Pre-dilatation	93 (95.9)	35 (94.6)	0.530
Aspiration thrombectomy	22 (22.7)	4 (10.8)	0.147
Administration of GPI	8 (8.2)	1 (2.7)	0.232

Table 1. Continued

Variables, n (%)	Pre-admission smoking (n=97)	Non-smoking (n=37)	p
Stent diameter (mm)	3.1±0.7	3.0±0.8	0.421
Stents per patient	1.5±0.8	1.7±0.9	0.200
Total stent length (mm)	35.9±20.7	41.7±25.8	0.183
Final TIMI flow grade 3	97 (100)	36 (97.3)	0.276

BMI: body mass index, STEMI: ST-elevation myocardial infarction, NSTEMI: non-ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CYP 3A4: cytochrome P450 3A4 isoenzyme, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, LV: left ventricular, Hb: hemoglobin, DTB: door-to-balloon, TIMI: thrombolysis in myocardial infarction, GPI: glycoprotein IIb/IIIa inhibitor

Table 2. The rate of LPPR and platelet reactivity according to smoking status

	Non-smoking (n=37)	Smoking <0.5 pack/day (n=16)	Smoking ≥0.5 pack/day (n=81)	p
Rate of LPPR, n (%)	5 (13.5)	5 (31.3)	25 (30.9)	0.058
Maximal platelet aggregation (%)				
5 μmol/L ADP	48.4±12.5	42.6±16.3	43.8±15.6	0.240
20 μmol/L ADP	61.3±11.6	54.8±14.3	56.5±15.9	0.185
Late platelet aggregation (%)				
5 μmol/L ADP	38.1±17.3	31.0±20.2	34.3±19.5	0.404
20 μmol/L ADP	51.0±18.6	42.1±21.2	46.1±22.8	0.334

Low post-clopidogrel platelet reactivity indicates the lowest quartile of 5 μmol/L ADP-induced maximal platelet aggregation (≤37%). LPPR: low post-clopidogrel platelet reactivity, ADP: adenosine diphosphate

reactivity (data not shown). When platelet reactivity was compared according to clinical risk factors, there were no significant differences in terms of the presence of diabetes mellitus, hypertension and hypercholesterolemia, except for higher values in patients with chronic kidney disease (5 μmol/L ADP-induced Agg_{max}; 52.6±11.0% vs. 43.8±15.2%, p=0.023 and 20 μmol/L ADP-induced Agg_{max}; 63.6±10.4% vs. 56.7±15.1%, p=0.074). The PS patients showed a trend toward lower Agg_{max} after 5 μmol/L (43.6±15.7% vs. 48.4±12.5%, p=0.096) and 20 μmol/L ADP stimuli (56.2±15.6% vs. 61.3±11.6%, p=0.073) compared with NS patients (Table 2). However, Agg_{late} did not differ between PS and NS patients (5 μmol/L ADP: 33.8±19.5% vs. 38.1±17.3%, p=0.234 and 20 μmol/L ADP: 45.5±22.5% vs. 51.0±18.6%, p=0.187). In contrast to the results of Bliden et al.,[7] our results did not show significant differences in 5 μmol/L (Agg_{max}: p=0.776 and Agg_{late}: p=0.540) and 20 μmol/L ADP-induced platelet aggregation (Agg_{max}: p=0.692 and Agg_{late}: p=0.517) between PS patients <0.5 pack/day and ≥0.5 pack/day (Table 2).

Predictor of low post-clopidogrel platelet reactivity

More PS patients met the criteria for LPPR than NS patients (30.9% vs. 13.5%, p=0.048). To identify significant predictors of LPPR, a logistic regression analysis was used to evaluate the impact of the same analytic variables as Bliden et al.[7] evaluated (age, body mass index, diabetes, history of myocardial infarction, hypertension, smoking status, and use of calcium antagonists, angiotensin-converting enzyme inhibitors, beta blockers, and statins). Age was the only variable that was inversely correlated with LPPR {odds ratio (OR) 0.904, 95% confidence interval (CI) 0.845 to 0.968, p=0.004}. In another model of multivariate analyses including variables with p<0.2 in univariate analyses for differences between LPPR vs. non-LPPR groups, age was also the only independent predictor of LPPR (OR 0.960, 95% CI 0.929 to 0.993, p=0.019) (Table 3).

Table 3. Multivariate analysis of predictors for LPPR

Variables	p	OR	95% CI
Age	0.019	0.960	0.929-0.993
Male	0.932	1.073	0.216-5.319
Pre-admission smoking	0.245	1.916	0.640-5.747
Hemoglobin	0.384	1.179	0.813-1.710
Beta blocker	0.192	2.882	0.588-14.085
Glycoprotein IIb/IIIa inhibitor	0.476	0.586	0.135-2.547
Presence of thrombus	0.845	0.902	0.321-2.535
Stents per patient	0.102	1.555	0.916-2.646

Low post-clopidogrel platelet reactivity indicates the lowest quartile of 5 μmol/L ADP-induced maximal platelet aggregation (≤37%). LPPR: low post-clopidogrel platelet reactivity, OR: odds ratio, CI: confidence interval

Discussion

Our study showed that smoking before admission is not significantly associated with decreased residual platelet reacti-vity in AMI patients. In addition, we could not find a dose-related relationship between smoking and postclopidogrel residual platelet reactivity.

Clopidogrel is a prodrug and can be converted to its active metabolite by CYP isoenzymes. Of these, CYP isoenzyme 1A2 is activated by the polycyclic aromatic hy-

drocarbons in cigarette smoke and induced by plasma nicotine.[6)12)] Therefore, cigarette smoking induces CYP1A2 activity and contributes to the increased metabolite of clopidogrel in a dose-related manner.[13)] Interestingly, some reports suggested that smoking might have a good effect on short-term clinical outcomes after coronary stenting.[14)15)]

However, this suggestion is in opposition to common knowledge of smoking's harmfulness. Most epidemiologic studies have strongly supported the conclusion that smoking increases the incidence of fatal coronary artery diseases (CAD), especially AMI.[16-20)] The magnitude of the risk has been linearly related to the number of cigarettes smoked, with even low levels of smoking being associated with a considerable risk of AMI. Increased risk of CAD due to smoking is associated not only with vasomotor dysfunction but also with inflammatory reactions. Thrombosis due to smoking has been associated with alterations in platelet function, antithrombotic/prothrombotic factors, and fibrinolytic factors.[21-23)] Cigarette smoking induces hyperaggregability, decreases the availability of platelet-derived nitric oxide (NO), and decreases platelet sensitivity to exogenous NO. Alterations in tissue factors and a consequent increase in thrombotic potential have also been documented. Furthermore, higher fibrinogen, higher red blood cell counts, higher hematocrits, and higher blood viscosity potentiate the prothrombotic process associated with exposure to smoke. Decreased plasma tissue plasminogen activator activity was observed in smokers. Therefore, smoking is associated with dysfunctional thrombotic mechanisms that promote the initiation and/or propagation of thrombus formation. Compared to chronic CAD, these effects of smoking may play a greater role in the setting of AMI.

Although we could ascertain that smoking may enhance clopidogrel-induced platelet inhibition in AMI patients, the association seems weaker than the association between and elective coronary stenting. In addition, we did not observe a relationship between the number of cigarettes and post-clopidogrel platelet reactivity. Enhanced platelet reactivity may be a main feature in the early phase of AMI[24)] and correlate with the amount of smoking. Because CYP is associated with conversion to the active metabolite of clopidogrel, the activity of CYP subtypes may be related to the amount of the active form of clopidogrel. CYP2C19 contributes to both of the two sequential oxidative metabolic steps of clopidogrel activation. The polymorphism of this subtype can induce loss-of-function to a considerable extent.[25)26)] Because CYP1A2 affects only the first oxidative step of clopidogrel, induction of CYP1A2 by smoking may have a relatively weak impact on clopidogrel activation.[25)26)] Furthermore, we assessed residual platelet reactivity at least 3 days after emergency stenting, which may be related to a decrease in smoking-induced CYP1A2 activity. This can explain why smoking did not achieve significant suppression of enhanced platelet hyperaggregability in this study.

In the present study, advancing age predicted higher post-clopidogrel platelet reactivity in AMI patients. Like diabetes mellitus, advancing age shows higher pre-treatment platelet reactivity,[27)] which is related to high residual platelet reactivity. Geisler et al.[28)29)] also found that patients aged 65 years or older had significantly increased residual platelet aggregation at least 6 hours after clopidogrel loading.

A study of the PREDICT score demonstrated that various clinical factors influence residual platelet reactivity (acute coronary syndrome, age >65 years, diabetes mellitus, renal failure, and reduced left ventricular function).[28)29)] Because the PS patients showed lower prevalence of clinical risk factors in this study, a lower platelet reactivity in PS patients might not be explained by the effect of smoking alone. However, the presence of diabetes mellitus and hypertension did not induce increased residual platelet reactivity in this study, which may be related to the fact that we only enrolled AMI patients and we enrolled a small number of subjects.

Limitations

Our study has several limitations. First, the number of study subjects was relatively small. Because there were differences in clinical risk factors between PS and NS patients, a decreased trend towards maximal platelet reactivity in PS patients could not be explained by the effect of smoking alone. Second, the study group was heterogeneous: it contained both STEMI and NSTEMI patients. However, there was no difference in platelet reactivity between these groups. Finally, the time point of platelet function measurements can be criticized. Although post-clopidogrel platelet reactivity may change dynamically during the early phase of AMI, Matetzky et al.[9)] showed that there may be no significant changes of post-clopidogrel platelet reactivity from days 3 to 5 in AMI patients after coronary stenting. Because we assessed platelet reactivity from 3 to 5 days after coronary stenting, our patients' results may principally reflect pre-discharge residual platelet reactivity.

Conclusions

Smoking before admission is not significantly associated with decreased residual platelet reactivity in AMI patients. In addition, PS of $\geq$0.5 pack/day can not induce a significant reduction in post-clopidogrel platelet reactivity compared with NS.

Acknowledgments

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