Predictors of clopidogrel hyper-responsiveness in neuro-interventional procedures

Abstract

Background: Hyper-responsiveness to clopidogrel abnormally inhibits platelet aggregation and increases hemorrhagic complications. The present study investigated clinical factors related to clopidogrel hyper-responsiveness in neuro-interventional procedures.

Methods: Two hundred twenty-four patients receiving clopidogrel for coil embolization to treat unruptured cerebral aneurysm or carotid artery stenting to treat carotid artery stenosis at the internal carotid artery origin were retrospectively reviewed for their P2Y12 reactivity unit (PRU) values and clinical characteristics. Hyper-responsiveness to clopidogrel was defined as a PRU of <95.

Results: The mean PRU was 218.2 ± 77.8. Hyper-responsiveness to clopidogrel was observed in 12 patients (5.4%). Hyper-responsiveness was observed in younger patients, patients with a lower concentration of hemoglobin A1c, and patients with a higher low-density lipoprotein cholesterol (LDL-C) concentration compared with non-hyper-responsive patients ($P = 0.01$, $P < 0.01$, $P < 0.01$, respectively). On analysis of concomitant drugs, the patients in the hyper-responsive group were less frequently

administered calcium channel blockers (CCBs) compared with the non-hyper-responsive group ($P = 0.01$). No significant differences in the usage of proton pump inhibitors or statins were observed. A LDL-C concentration of >120 mg/dL and no usage of CCBs were significant independent predictors of hyper-responsiveness to clopidogrel with a multivariate analysis (OR; 6.16, 95% CI, 1.57–26.64, $P = 0.01$, OR; 0.09, 95% CI, 0.01–0.82, $P = 0.03$, respectively).

Conclusion: The present study shows that a higher LDL-C concentration and no usage of CCBs are independent predictors of clopidogrel hyper-responsiveness. These results are useful to predict perioperative hemorrhagic complications. Considering dose reduction of clopidogrel or alternative drugs in high risk cases is necessary to prevent perioperative hemorrhagic complications.

Introduction

Antiplatelet therapy is commonly used to reduce the risk of thromboembolic complications during and after neuro-interventional procedures when foreign intraluminal material is inserted in the vessel. Dual antiplatelet therapy with aspirin and clopidogrel is now widely used because aspirin monotherapy had previously emerged as insufficient.[1] Dual antiplatelet therapy reduces the risk of thromboembolic complications during neuro-interventional[2] and cardiovascular procedures[3]; in contrast, there is risk of intracranial hemorrhage associated with cardiovascular procedures.[4] With antiplatelet therapy, individual variability in antiplatelet responsiveness to clopidogrel is widely recognized,[2,5] which are due to genetic polymorphisms in the cytochrome P450 family 2 subfamily C member 19 (*CYP2C19*) allele. Genetic polymorphisms are strongly associated with variable responsiveness to clopidogrel.[6-8] Variability in the responsiveness to clopidogrel correlates with age,[9] diabetic status,[10,11] renal function,[12] drug interaction with concomitant drugs (e.g., calcium channel blockers [CCBs] use,[13] statins use,[14] and proton pump inhibitors [PPIs] use.[15,16])

Multiple technologies are available to assess hyper-responsiveness to clopidogrel; the VerifyNow system (Accumetrics, San Diego, California) is one of the most common.[17] While predictors of

clopidogrel hypo-responsiveness have been well-investigated, there are few reports that have investigated predictors of clopidogrel hyper-responsiveness. Hyper-responsiveness to clopidogrel increases the risk of hemorrhagic complications during neuro-interventional[18, 19]and cardiovascular procedures.[20]

The aim of the present study is to investigate the incidence of clopidogrel hyper-responsiveness and to identify its predictors, which lead to a reduction in the risk of hemorrhagic complications during and after neuro-interventional procedures.

Methods and materials

A retrospective single-center study was performed in all patients receiving clopidogrel who underwent coil embolization to treat unruptured cerebral aneurysm or carotid artery stenting to treat carotid artery stenosis at the internal carotid artery origin from November 2012 to April 2018. Patients were evaluated for their P2Y12 reactivity unit (PRU) values using the VerifyNow system. The inclusion criteria were as follows: 1) ≥18 years of age, 2) receiving clopidogrel for more than seven days, 3) undergoing a neuro-interventional procedure for unruptured aneurysm, or 4) patients with carotid artery stenosis undergoing carotid artery stenting. Patients with a ruptured aneurysm or patients in the acute phase of symptomatic carotid artery stenosis were excluded.

With the VerifyNow system, citrate-anticoagulated whole blood samples were automatically dispensed from a blood collection tube into the assay device and adenosine-5'-disphosphate was incorporated into the assay channel to induce platelet activation. Light transmittance increased as activated platelets bound to and aggregated with fibrinogen-coated beads; the instrument measured this change using an optical signal and the results were reported in PRU. PRU measurement using VerifyNow was performed on the day before the procedure. Hyper-responsiveness to clopidogrel was defined as a PRU of <95 in line with

previous reports.[21,22,23] Hypo-responsiveness to clopidogrel was defined as a PRU of >240 in line with previous reports.[18,23] To investigate related factors of clopidogrel hyper-responsiveness, clinical characteristics were analyzed between the hyper-responsive group and the non-hyper-responsive group. The clinical characteristics included age, sex, body weight, primary disease (unruptured aneurysm or carotid artery stenosis), concomitant drug use (CCBs, statins, PPIs, angiotensin II receptor blockers [ARBs], oral hypoglycemic agents, or insulin), hemodialysis, and laboratory variables (hemoglobin [Hb], HbA1c, estimated glomerular filtration rate [eGFR], platelet count, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglyceride [TG]) were reviewed using medical records.

The study was approved by the local ethics committee of our hospital and all patients provided informed consent.

Statistical analysis

Statistical analysis was performed using SPSS for Mac (version 24.0 IBM Corp., Armonk, New York, USA). Continuous variables are presented by mean with standard deviation. The χ^2test, Fisher's exact test, and the Student's t-test were used to compare the hyper-responsive group with the non-hyper-responsive group. Related clinical factors of hyper-responsiveness with p value of < 0.1 in univariate analysis were evaluated using multivariate logistic regression analysis. In addition, we investigated the association between continuous variables (LDL-C, HDL-C, HbA1c and eGFR) and PRU using receiver operating characteristic curves, and the optimal cut-off value was determined. A p value of <0.05 was considered statistically significant.

Results

Two hundred twenty-four patients were enrolled; 95 males and 129 females with a mean age of 63.9 ± 12.0 years. Patients constituted 182 cases of unruptured aneurysm and 42 cases of carotid artery stenosis. Thirty-five (15.6%) patients were smokers. Concomitant use of other antiplatelet drugs (aspirin or cilostazol) was observed in 175 cases (78.1%), anticoagulants in 4 cases (1.9%), CCBs in 95 cases (42.4%), ARBs in 89 cases (40%), PPIs in 139 cases (62.1%), oral hypoglycemic agents in 25 cases (11.2%), insulin in 4 cases (1.9%), and statins in 77 cases (34.4%). The mean PRU value was 218.2 ± 77.8, the mean baseline PRU value was 315.3 ± 60.1, and the percentage of platelet inhibition was 31.3 ± 21.6%. Hyper-responsiveness was observed in 12 cases (5.4%) and hypo-responsiveness was observed in 86 cases (38.4%). The mean duration of clopidogrel administration was 35.9 ± 150.4 days.

The clinical characteristics of the hyper-responsive and non-hyper-responsive groups are summarized in Table 1. There was no significant intergroup difference in baseline PRU values (302.8 ± 61.5 vs. 316.0 ± 59.9, $P = 0.96$), but the percentage of platelet inhibition was significantly higher in the hyper-responsive group (75.4 ± 11.1 vs. 28.8 ± 19.3, $P < 0.01$). The mean age of the hyper-responsive group (54.75 ± 13.77 years) was significantly younger than that of the non-hyper-responsive group (64.37

± 11.71 years) (P = 0.01). There was no significant difference in sex, primary disease, smoking habit, body weight, and hemodialysis between the two groups. In the analysis of concomitant drugs, patients treated with CCBs were less frequently observed in the hyper-responsive group (8.3% in the hyper-responsive group vs. 44.3% in the non-hyper-responsive group, P = 0.01). Use of other concomitant drugs did not relate to the incidence of hyper-responsiveness to clopidogrel. An influence on the PRU value by PPIs was not observed in this study. The laboratory variables are summarized in Table 2. Lower HbA1c levels were frequently observed in the hyper-responsive group (5.5% in the hyper-responsive group vs. 5.8% in the non-hyper-responsive group, P < 0.01). A higher LDL-C concentration was frequently observed in the hyper-responsive group (123.9 mg/dL in the hyper-responsive group vs. 113.3 mg/dL in the non-hyper-responsive group, P < 0.01). Other laboratory variables did not show significant differences between the two groups.

Predictors of clopidogrel hyper-responsiveness in multivariate analysis are summarized in Table 3. the cut off value of predictors were determined using receiver operating characteristic curves (LDL:120 mg/dL, HDL, 58 mg/dL, eGFR: 74 ml/min/1.73 m^2, HbA1c: 5.8%). In multivariate analysis that included factors such as age, HbA1c, eGFR, HDL-C concentration; LDL-C concentration of >120 mg/dL (P =

0.01, odds ratio [OR]: 6.16, 95% confidence interval [CI] 1.57–26.64) and no usage of CCBs (P = 0.03, OR: 0.09, 95% CI 0.01–0.82) were significant predictors of clopidogrel hyper-responsiveness.

Two patients (16.7%) of the 12 who presented with clopidogrel hyper-responsiveness also presented with perioperative hemorrhagic complications. One patient with unruptured aneurysm had asymptomatic intracranial hemorrhage after the procedure. The other patient had carotid artery stenosis, femoral subcutaneous hematoma, and retroperitoneal hematoma at the puncture site; this patient required a blood transfusion. Alternatively, among the 212 patients presenting with clopidogrel non-hyper-responsiveness, 9 (4.2%) presented with perioperative hemorrhagic complications.

DISCUSSION

The second generation thienopyridine, clopidogrel, inhibits the binding of adenosine-5'-diphosphate to platelets via the P2Y12 receptor. The first generation thienopyridine, ticlopidine, has been associated with serious side effects such as liver dysfunction, agranulocytosis, and thrombotic thrombocytopenic purpura; therefore, clopidogrel is preferable. Clopidogrel is a prodrug metabolized by *CYP450* enzymes and is converted to its active form in the liver. The active metabolite inhibits platelet aggregation. From this pharmacological activity, genetic polymorphisms in the *CYP* allele lead to individual variability in the responsiveness to clopidogrel.[7, 24] *CYP2C19* is a highly polymorphic human gene, having more than 25 known variant alleles.[25] Genetic polymorphisms in the *CYP2C19* allele have been implicated as a mechanism for both hyper-responsiveness and hypo-responsiveness to clopidogrel, but the mechanism of hyper-responsiveness to clopidogrel is unclear. *CYP2C19* 17* variant allele, which increases the concentration of active metabolite and the subsequent function of clopidogrel, was reported. [26,27] However, the impact on ischemic events and clinical outcome is not known yet.[26]

Although light transmittance aggregometry still remains the gold standard to assess platelet function

during antiplatelet therapy with clopidogrel, the effectiveness of the VerifyNow system used in this study has been confirmed.[23] In addition, the simplified procedure of the VerifyNow system is useful as it can be used as a daily medical examination.

The optimal PRU value for neuro-interventional procedures has not been established yet.[28] Further, no clear guidelines have been shown in the cut-off value of hyper-responsiveness to clopidogrel in Japan, and we defined hyper-responsiveness to clopidogrel as a PRU of <95 in this study, which was referred to ACCF/AHA 2011 guidelines and past reports.[21,22,23] The occurrence of hyper-responsiveness to clopidogrel is 14%–33% in cardiovascular procedures[29] and 15%–38% in neuro-interventional procedures.[24~~2~~25] Clopidogrel resistance was associated with genetic polymorphisms in the *CYP* allele has been frequently reported in the Asian population.[7, 24] Hypo-responsiveness to clopidogrel was more frequent in the Asian population; however, the difference in the incidence of hyper-responsiveness to clopidogrel between ethnicities is not well known.

Hyper-responsiveness to clopidogrel increases the risk of hemorrhagic complications during neuro-interventional procedures.[18, 19] In addition, incidences of life-threating bleeding, minor bleeding, and transfusion were significantly higher among the clopidogrel hyper-responsiveness group in

cardiovascular procedures.[29] The usefulness of dose adjustment of clopidogrel to normalize PRU values has been reported in studies investigating clopidogrel hyper-responsiveness.[30] We reduced the dose of clopidogrel from 75 mg/day to 25 mg/day or 50 mg/day in our institution. Although we reduced the clopidogrel dose, hemorrhagic complications were observed in two cases. Therefore, we need to re-evaluate for their PRU values using the VerifyNow system after reduction the clopidogrel dose and alternative drugs should be considered.

The platelet response to clopidogrel correlates with age, diabetic history, and renal dysfunction.[9,10,11,12] The present study showed that age and a low HbA1c concentration were predictors of clopidogrel hyper-responsiveness with a univariate analysis. Old age[9] and a higher HbA1c concentration[11] are predictors of hypo-responsiveness to clopidogrel. These two factors may drive PRU values to increase, which results in fewer hyper-responders in old patients and/or in patients with a higher HbA1c concentration. The platelet response to clopidogrel is influenced by concomitant drugs, which inhibit the CYP2C19 enzyme.[15] The competing action of statins[14] and CCBs[13] has been reported and is similar for PPIs. All of these reports noted that concomitant drug use leads to hypo-responsiveness to clopidogrel. Few reports have described the correlation between concomitant drug use and hyper-responsiveness to

clopidogrel. This study is the first to identify significantly more clopidogrel hyper-responsiveness in patients that do not use CCBs. This result implies that CCBs mediate a certain effect as inhibitors of clopidogrel even in hyper-responsive patients. An association between PPIs and hypo-responsiveness to clopidogrel is widely known. The metabolic product of clopidogrel was decreased by competitive inhibition of CYP2C19 during concomitant use of PPIs and clopidogrel. Although concomitant use of PPIs increases clopidogrel hypo-responsiveness, the presence of PPIs does not affect the PRU value in the hyper-responsive group in this study. It is thought that the degree of CYP450 inhibition varies according to the PPI used. CYP inhibition was strong with use of omeprazole in particular, and combined usage of omeprazole decreases the effect of clopidogrel.[31] CYP inhibition is observed as follows: omeprazole > esomeprazole > lansoprazole > dexlansoprazole[32] and their influence on the PRU value was not seen in this study because lansoprazole and esomeprazole, for which CYP inhibition is relatively weak, were mainly used in this study.

In laboratory variables, a higher LDL-C concentration was observed in the hyper-responsive group in this study, and a LDL-C concentration of >120 mg/dL was a statistically significant predictor of hyper-responsiveness to clopidogrel. A few reports have observed an association between the LDL-C

concentration and clopidogrel; all of these studies showed that the LDL-C concentration did not affect the pharmacological effect of clopidogrel.[6,33] Wadowski et al.[33] showed that a low HDL concentration increased PRU values, indicating that it is a predictor of hypo-responsiveness to clopidogrel, whereas no relationship was detected between PRU values and LDL-C/TG concentrations. Several studies have shown that a higher LDL-C concentration elevates platelet activity[34] and causes aspirin resistance.[35] However, the mechanism by which a higher LDL-C concentration affects platelet aggregation is still unknown.

The PRU value obtained using the VerifyNow system has not been part of our daily practice because of difficulty and impracticality of laboratory testing[36] in Japan and its high measurement cost. Therefore, it is difficult to apply this in all cases of neuro-interventional procedures. Our results are useful to predict clopidogrel hyper-responsiveness before neuro-interventional procedures.

Study Limitations

First, this study had a retrospective design, and the patient groups were heterogenous, including those with unruptured aneurysms and carotid artery stenosis. Second, even though hyper-responsiveness of

clopidogrel showed some hemorrhagic complications, it was not powered statistically to show that the clopidogrel response does not directly affect clinical outcomes. Third, this investigation did not analyze CYP450 genetic polymorphisms.

Conclusions

In the present study, we investigated predictors of clopidogrel hyper-responsiveness using the VerifyNow system. A higher LDL-C concentration and no usage of CCBs were significant independent predictors of hyper-responsiveness to clopidogrel. These results are useful to predict perioperative hemorrhagic complications. Considering dose reduction of clopidogrel or alternative drugs in high risk cases is necessary to prevent perioperative hemorrhagic complications.

Acknowledgments: None

Funding: No funding was received for this research.

Conflict of Interest: The authors certify that they have no affiliations.

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