Preliminary Experience of Preoperative Modification of Platelet Aggregation

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Objective: Antiplatelet drugs are frequently used to prevent ischemic complications of endovascular therapy, but patients who showed poor responses to these drugs have been reported. We have adjusted antiplatelet drugs based on platelet aggregation activity before endovascular therapy. The objective of this study was to investigate the association between platelet aggregation test-based modification of antiplatelet drugs and perioperative complications.

Methods: In this study, we enrolled 146 patients who received elective endovascular therapy between October 2015 and December 2016. All patients received administration of aspirin 100 mg and clopidogrel 75 mg from 2 weeks before endovascular therapy and platelet aggregation activity was measured 1–2 days before the procedure. Cilostazol was additionally administered to patients who poorly responded to aspirin, or the drug was switched to prasugrel in patients who poorly responded to clopidogrel. Thereafter, platelet aggregation activity was re-tested on the following morning.

Results: On the initial test, 52 (35.6%) and 57 (39.0%) patients showed poor responses to aspirin and clopidogrel, respectively, and these rates were higher than those previously reported. After antiplatelet drug modification, 31 (21.2%) and 20 (13.7%) patients showed poor responses to aspirin and clopidogrel, respectively, showing significant decreases (p = 0.012 and <0.0001, respectively). Perioperative ischemic complication developed in five patients (3.4%), being lower than that (4.6%) previously reported.

Conclusion: The rate of patients with poor responses to antiplatelet drugs on the platelet aggregation test was higher than those previously reported, but their responses were improved by drug modification. Platelet aggregation test-based drug modification may be effective to prevent perioperative complications and further investigation is necessary.

Keywords ▶ prasugrel, poor metabolizer, clopidogrel, platelet aggregation test, endovascular treatment

Introduction

Dual antiplatelet therapy (DAPT) is generally performed to prevent perioperative ischemic complications of cerebral endovascular therapy, such as carotid artery stenting and coil embolization of cerebral aneurysm. However, there are many patients not responding to clopidogrel in East Asians, including Japanese, compared with those in Western people,1,2) and the association with ischemic complications is of concern. Actually, it has been reported that the incidence of thromboembolism in cerebral endovascular therapy was significantly higher in clopidogrel non-responder patients.3) Regarding countermeasures against unresponsiveness to antiplatelet drugs, a significant reduction of ischemic complications in clopidogrel non-responder patients by increasing the aspirin dose to 300 mg or addition of cilostazol 200 mg before cerebral endovascular therapy4) and the effectiveness of switching to prasugrel have been reported.5,6)

Although various countermeasures have been tried, optimal method to prevent periprocedural complications in antiplatelet non-responders treated with endovascular therapy has not yet been clarified. The objective of this study
was to clarify the association between the drug modification method for low responsiveness to antiplatelet drugs employed by us based on the platelet aggregation test and perioperative complications.

## Subjects and Methods

We enrolled 146 consecutive patients (mean age: 65 ± 11 years old, 95 [65.1%] were females) who received elective cerebral endovascular therapy at our hospital between October 1, 2015 and December 31, 2016, and they were retrospectively investigated. The therapy performed was coil embolization of cerebral aneurysm in 46 patients (31.5%), stent-assisted coil embolization in 43 (29.5%), flow diverter placement in 20 (13.7%), and carotid artery stenting in 37 (25.3%).

In our hospital, DAPT with aspirin 100 mg and clopidogrel 75 mg is administered to patients scheduled for elective cerebral endovascular therapy from 2 weeks before therapy and platelet aggregation activity is measured 1 or 2 days before the procedure by nephelometry using MCM Hematracer 712 (Tokyo Photoelectric, Tokyo, Japan) with collagen (final concentration: 2.0 and 5.0 μg/mL) and adenosine diphosphate (ADP) (final concentration: 1.0 and 10.0 μM) as aggregation inducers to detect transmitted light detection to adjust drugs. The platelet aggregation activity level was evaluated based on the area under the aggregation curves acquired using the aggregation inducer at two concentrations following the classification into nine classes for simple judgment of the effect of antiplatelet therapy: Classes 1–3, 4–6, and 7–9 were regarded as promoted, appropriate, and non-responder, respectively (Fig. 1).

DAPT was continued in enhanced or appropriate cases (Group D), triple antiplatelet therapy (TAPT) with additional cilostazol 200 mg administration was performed in aspirin non-responders (collagen Classes: 7–9; Group T), and clopidogrel was switched to prasugrel (20 mg loading dose followed by 3.75 mg/day maintenance dose from the following day) in clopidogrel non-responders (ADP Classes: 7–9; Group P). The platelet aggregation activity was re-tested on the following morning (Fig. 2). For patients resistant to both aspirin and clopidogrel, intervention for a higher class was performed (when the collagen class >ADP class, the patient was included in Group T, and when the collagen class <ADP class, the patient was included in Group P). Perioperative complications were retrospectively investigated in Group D (81 patients), Group T (26 patients), and Group P (39 patients).

The primary endpoint was set to antiplatelet drug-associated perioperative complications, which defined as hemorrhagic or ischemic events unrelated to the procedure (e.g., gastrointestinal bleeding, ischemic stroke, and transient ischemic attack). Since no group without switching of the antiplatelet drug serving as a control was set in this study, the same primary endpoint as that in a nationwide survey (JR-NET) previously performed in Japan was set to compare the perioperative complications with those in JR-NET, that is, the primary endpoint of this study was set to ‘antiplatelet drug-associated complications’ excluding clearly procedural complications, such as subcutaneous hematoma and false aneurysm in the punctured region and ruptured aneurysm and subarachnoid hemorrhage caused by arterial perforation. Of perioperative complications, only symptomatic ischemic lesions were regarded as ischemic complications excluding asymptomatic cerebral infarction on imaging. Hemorrhagic complication was specified to ‘significant bleeding’ in the Thrombolysis in Myocardial Infarction (TIMI) hemorrhage criteria.

Statistical analysis was performed using JMP 9 (SAS Institute Inc., Cary, NC, USA). Significance of differences among the groups was analyzed using the Tukey–Kramer Honestly Significant Difference (HSD) test. For comparison of rates, Fisher’s exact test was performed, and \( p < 0.05 \) was regarded as significant.

## Results

On the platelet aggregation test before drug modification, 52 (35.6%) and 57 (39.0%) patients poorly responded to aspirin (collagen Classes: 7–9) and clopidogrel (ADP...
Preoperative Modification of Platelet Aggregation

Classes: 7–9), respectively. After drug modification, the number of collagen Classes 7–9 and ADP Classes 7–9 patients were 31 (21.2%) and 20 (13.7%), respectively, showing significant decreases (collagen, \( p = 0.012 \); ADP, \( p < 0.0001 \); \textbf{Fig. 3}).

No significant difference was noted in the age (\( p = 0.94 \)), sex ratio (\( p = 0.23 \)), therapy procedure (\( p = 0.31 \)), anesthesia method (\( p = 0.30 \)), past medical history (hypertension [\( p = 0.39 \)], diabetes [\( p = 0.45 \)], dyslipidemia [\( p = 0.77 \)]), cigarette smoking habit (\( p = 0.41 \)), or concomitant anticoagulant treatment (\( p = 0.67 \)) among Groups D, T, and P (\textbf{Table 1}).

Regarding the primary endpoint (antiplatelet drug-associated perioperative complications), ischemic complications occurred in five patients (3.4%) and hemorrhagic

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\textbf{Table 1} Demographic and cerebrovascular characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 146))</th>
<th>Group D ((n = 81))</th>
<th>Group T ((n = 26))</th>
<th>Group P ((n = 39))</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y.o.)</td>
<td>65 ± 11</td>
<td>65 ± 12</td>
<td>66 ± 9</td>
<td>67 ± 11</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>95 (65.1%)</td>
<td>52 (64.2%)</td>
<td>14 (53.8%)</td>
<td>29 (74.4%)</td>
<td>0.23</td>
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<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>CE</td>
<td>46 (31.5%)</td>
<td>28 (34.6%)</td>
<td>7 (26.9%)</td>
<td>11 (28.2%)</td>
<td></td>
</tr>
<tr>
<td>SACE</td>
<td>43 (29.5%)</td>
<td>26 (32.1%)</td>
<td>5 (19.2%)</td>
<td>12 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>FDP</td>
<td>20 (13.7%)</td>
<td>9 (11.1%)</td>
<td>3 (11.5%)</td>
<td>8 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>CAS</td>
<td>37 (25.3%)</td>
<td>18 (22.2%)</td>
<td>11 (42.3%)</td>
<td>8 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td>0.30</td>
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<td></td>
<td></td>
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<tr>
<td>General</td>
<td>76 (52.1%)</td>
<td>44 (54.3%)</td>
<td>10 (38.5%)</td>
<td>22 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>70 (47.9%)</td>
<td>37 (45.7%)</td>
<td>16 (61.5%)</td>
<td>17 (43.6%)</td>
<td></td>
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<tr>
<td>Past history</td>
<td>83 (56.8%)</td>
<td>42 (51.9%)</td>
<td>16 (61.5%)</td>
<td>25 (64.1%)</td>
<td>0.39</td>
</tr>
<tr>
<td>HT</td>
<td>22 (15.1%)</td>
<td>11 (13.6%)</td>
<td>6 (23.1%)</td>
<td>5 (12.8%)</td>
<td>0.45</td>
</tr>
<tr>
<td>DM</td>
<td>65 (44.5%)</td>
<td>36 (44.4%)</td>
<td>13 (50.0%)</td>
<td>16 (41.0%)</td>
<td>0.77</td>
</tr>
<tr>
<td>DL</td>
<td>58 (39.7%)</td>
<td>35 (43.2%)</td>
<td>11 (42.3%)</td>
<td>12 (30.8%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (8.2%)</td>
<td>8 (9.9%)</td>
<td>2 (7.7%)</td>
<td>2 (5.1%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

\( AC \): anticoagulant; \( CAS \): carotid artery stenting; \( CE \): coil embolization; \( DL \): dyslipidemia; \( DM \): diabetes mellitus; \( FDP \): flow diverter placement; \( HT \): hypertension; \( SACE \): stent-assisted coil embolization
complications occurred in three (2.1%). The ischemic complication was symptomatic cerebral infarction in three patients (2.1%), central retinal artery occlusion in one patient (0.7%), and amaurosis fugax in one patient (0.7%). The hemorrhagic complication was gastrointestinal hemorrhage in all three patients (Table 2). No significant difference was noted in the incidence of antiplatelet drug-associated perioperative complications among the three groups.

The five patients who developed ischemic complications belonged to Classes 4–6 for both ADP and collagen after drug modification (Table 3). On the other hand, the incidence of hemorrhagic complications was high in Classes 1–3, but the difference was not significant. No significant association was noted between the perioperative complications and therapy procedures (Table 4).

### Discussion

Antiplatelet drug administration is recommended to prevent perioperative ischemic complications for patients undergoing cerebral endovascular therapy. DAPT is considered especially useful for carotid artery stenting, stent-assisted coil embolization, and flow diverter placement. Generally, aspirin and thienopyridine drugs (clopidogrel exhibiting less adverse effects is currently the first choice) are frequently used.

Since clopidogrel is mostly metabolized to the active form by liver CYP2C19 and then exhibits the antiplatelet action, the effect varies among the CYP2C19 gene polymorphisms. The rate of people with the metabolic dysfunction type of CYP2C19 is 3%–5% in Western people, whereas it is higher (12%–23%) in East Asians including...
Japanese and the presence of many clopidogrel non-responders in East Asians has been reported. The rate of clopidogrel non-responders (ADP Classes 7–9) was 39.0%, being higher than those in previous reports, but switching to prasugrel significantly decreased the rate to 13.7% (Fig. 3A).

Regarding aspirin non-responders, it is considered that it is not simply due to COX-1 but various factors are involved, such as complication by diabetes, intestinal absorption rate, and interactions with other drugs. Aspirin non-responders accounted for 35.6% in our study, but the frequency markedly varied from 5.2% to 60% in previous reports. Only an increase in the dose of aspirin is ineffective for non-responders and combination with other drugs was recommended in a report. In the present study, the addition of cilostazol significantly decreased the rate of collagen Classes 7–9 patients to 21.2% (Fig. 3B).

Although a novel thienopyridine antiplatelet drug, prasugrel, is a prodrug, similar to clopidogrel, platelet aggregation activity of prasugrel is less influenced by the CYP2C19 gene polymorphism because it is activated by several types of CYP. Prasugrel is used at a loading dose of 60 mg and maintenance dose of 10 mg in the standard treatment. In a randomized study with Japanese subjects, the incidence of ischemic and hemorrhagic complications of PCI was similar between patients treated with prasugrel at a 20-mg loading dose and 3.75-mg maintenance dose and clopidogrel. Based on these findings, prasugrel with a 20-mg loading dose and 3.75-mg maintenance dose have been approved in patients undergoing PCI in Japan.

It has been reported that ischemic complications frequently develop in clopidogrel non-responders treated with percutaneous coronary intervention (PCI) for coronary artery disease. In addition, it has been reported that in acute coronary syndrome patients treated with PCI, prasugrel inhibited ischemic events compared with clopidogrel, but the risk of massive hemorrhage including fatal hemorrhage increased. However, in its sub-analysis, prasugrel inhibited ischemic events without increasing the risk of hemorrhage in clopidogrel non-responders. It was investigated whether dose elevation of clopidogrel and switching to prasugrel decrease complications of PCI in clopidogrel non-responders, but no effect was noted in two randomized studies.

The use of prasugrel for cerebral endovascular therapy has been reported. On the other hand, combination of aspirin and prasugrel significantly increased hemorrhagic complications compared with those caused by combination of aspirin and clopidogrel (19.4% vs. 3.6%). According to previous studies, the incidence of thrombotic complications increased to 16.7%–17.4% after cerebral endovascular therapy in clopidogrel non-responders, but it could be reduced to 2.7% by switching to appropriate drugs.

Regarding antiplatelet drug-associated perioperative complications in the present study, ischemic and hemorrhagic complications occurred only in five (3.4%) and three (2.1%) patients, respectively. In JR-NET 1&2 (limited to unruptured cerebral aneurysm), the incidences of ischemic and hemorrhagic complications were 4.6% and 2.0%, respectively. Although direct comparison is not possible because the conditions were different, it is possible that ischemic complications could be prevented without increasing hemorrhagic complications by drug modification.

However, the five patients who developed ischemic complications belonged to Classes 4–6 after modification on both tests with ADP and collagen (Table 3), showing that the incidence of complications is not necessarily high in non-responders after drug modification. It is possible that ischemic complications were not accurately evaluated because therapy was postponed in some patients because of non-responsiveness even after drug modification during the study period and the number of non-responders was small because no non-responder group without intervention was set.

The incidence of hemorrhagic complications was high in Classes 1–3. Statistical evaluation was difficult because therapy was postponed in some patients due to promoted aggregation and there were only a few promoted cases in Classes 1–3, but it was suggested that hemorrhagic

![Image](https://via.placeholder.com/150)

**Fig. 3** The ratio of the classes of platelet aggregation. Changes in the platelet aggregation activity level in antiplatelet drug non-responders after drug modification: (A) ADP and (B) collagen. ADP: adenosine diphosphate.
complications increase in promoted cases. Additional investigation in a large-scale clinical study is necessary.

There were limitations of this study. First, since it was a single-center retrospective observational study, the number of patients was small and fewer patients developed complications, in which detection of significant difference with regard to complications is difficult. Second, drug modification was performed in all non-responder patients and no group without drug modification (control group) was set. Thus, the efficacy of drug modification could not be directly investigated and only the differences in the incidences of complications were compared with those in previous studies with a different background. To solve these problems and investigate the true efficacy of antiplatelet drug modification before therapy based on the platelet aggregation test, it is necessary to perform a large-scale controlled study setting a control group without drug modification.

Conclusion

More patients showed poor responses to the drugs based on the platelet aggregation test compared with those in previous reports, but platelet aggregation activity was favorably controlled by drug modification. Since the incidence of non-procedural complications was lower than those in previous reports, drug modification based on platelet aggregation activity may contribute to decreasing perioperative complications. To investigate the effect of platelet aggregation activity-based antiplatelet drug modification on perioperative complications, it is necessary to perform a large-scale randomized controlled study.

Disclosure Statement

None of the first and co-authors has conflict of interest to be disclosed in this study.

References

Preoperative Modification of Platelet Aggregation


