Effectiveness of Antiplatelet Drug Loading before Acute-phase Coil Embolization of Ruptured Cerebral Aneurysms

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Objective: The hemostatic/coagulation capacity is enhanced in the acute phase of ruptured cerebral aneurysms, and the risk of thromboembolic complications during endovascular surgery is high. We examined the usefulness of antiplatelet drug loading (LD) before acute-phase coil embolization of ruptured cerebral aneurysms.

Methods: The subjects were 117 patients who underwent acute-phase coil embolization of ruptured cerebral aneurysms in our hospital between June 2009 and October 2016. They were divided into three groups (non-administration, clopidogrel LD, and dual LD groups) based on the presence or absence of preoperative antiplatelet drug administration, and the incidence of thromboembolic events (TEEs), influence of combined adjunctive techniques (ATs), and incidence of hemorrhagic events were compared.

Results: In the clopidogrel LD group, there was no significant decrease in the incidence of TEEs in comparison with the non-administration group. However, the incidence of TEEs was significantly lower in the dual LD group. Similarly, combined ATs significantly decreased the incidence of TEEs in the dual LD group. In LD groups, there was no increase in the incidence of hemorrhagic complications.

Conclusion: The results suggest that dual LD decreases the incidence of TEEs. In the future, its effects should be further investigated.

Keywords: endovascular treatment, ruptured intracranial aneurysm, acute-phase coiling, antiplatelet drug, loading dose

Introduction

Since the results of the International Subarachnoid Aneurysm Trial (ISAT) were reported,1,2) endovascular treatment (EVT) has been increasingly performed as acute-phase treatment for ruptured cerebral aneurysms.3) The incidence of perioperative thromboembolic complications in patients treated by EVT is reportedly 2.4–28%,4,5) and most complications develop during EVT.6) As the administration of a thrombolytic agent for intraoperative thrombosis may cause serious complications,1) perioperative thrombus prevention is important. Many studies reported the preventive effects of perioperative antiplatelet drug administration on thromboembolic complications in patients undergoing intra-aneurysmal coil embolization for unruptured cerebral aneurysms. However, few studies have reported perioperative antiplatelet drug administration to patients undergoing acute-phase coil embolization for subarachnoid hemorrhage.3)

In the future, endovascular surgery for ruptured cerebral aneurysms will be increasingly performed, and more complex procedures/devices may increase the risk of thromboembolic complications;1,3) strategies to prevent them may become more important.

In our hospital, antiplatelet drug loading (LD) before acute-phase coil embolization for ruptured cerebral aneurysms has been positively introduced since 2015. We examined whether the preoperative administration of an antiplatelet drug influences the frequency or grade of thromboembolic/hemorrhagic complications in comparison with LD-free treatment.
Subjects and Methods

The subjects were consecutive 117 patients who underwent acute-phase coil embolization of ruptured cerebral aneurysms in our hospital between June 2009 and October 2016, with a mean age of 61.7 years (45 males and 72 females). They were divided into three groups (non-administration, clopidogrel LD [clopidogrel: 300 mg], and dual LD [aspirin: 200 mg + clopidogrel: 300 mg] groups) based on the presence or absence of preoperative antiplatelet drug administration. Concerning administration methods, diagnostic imaging was performed under local anesthesia after a diagnosis of subarachnoid hemorrhage was made. When EVT was selected, a gastric tube was inserted after the induction of general anesthesia in the angiography room, and the antiplatelet drug was infused through the gastric tube before the start of the procedure. As intraoperative anticoagulant therapy, heparin was intravenously administered to all patients after first-coil insertion to maintain the activated clotting time (ACT) at 200–250 seconds. The following contents were compared among the groups: 1) total number of patients per group, annual changes, and influence of device changes; 2) localization of aneurysms (internal carotid/anterior communicating/anterior cerebral/middle cerebral arteries, posterior circulation system); 3) incidence of intraoperative thromboembolic events (TEEs); 4) incidence of TEEs in the presence of adjunctive techniques (ATs: double-catheter, balloon-assist, distal access catheter); and 5) incidence of intraoperative extravasation and its influence.

All patients with contrast-enhanced defects of the endovascular space on intraoperative angiography regardless of the presence or absence of signs and those with defects at the periphery were regarded as having TEEs. We retrospectively collected data from angiographic images, postoperative CT findings, records on surgery, and medical records. Statistical analysis was performed using the chi-square and Fisher’s exact tests.

Results

The total number of patients in the non-administration, clopidogrel LD, and dual LD groups was 78, 22, and 17, respectively. Concerning annual changes, EVT has been performed without administering an antplatelet drug in most cases since 2009, when data collection was started, as shown in Fig. 1. For a small number of patients, clopidogrel LD has been conducted. As dual LD has been positively introduced since 2015, patients belonging to the dual LD group were treated during the past year. As a change in therapeutic strategies during this period, a guiding system was switched from a 5 Fr or 6 Fr guiding catheter to a 5 Fr or 6 Fr guiding sheath (GS; ultra-long sheath) (Table 1). In the non-administration, clopidogrel LD, and dual LD groups, patients for whom a GS was adopted accounted for 51.3 (40/78), 77.3 (17/22), and 82.4% (14/17), respectively; the percentages were significantly higher in the LD groups (p = 0.0124, Table 1). We examined guiding-system-switching-related changes in the incidence of TEEs in the non-administration group. The incidence after the use of a guiding catheter was 10.5% (4/38), and that after the use of a GS was 27.5% (11/49); there was no significant difference (p = 0.052).

We investigated the incidence of TEEs with respect to aneurysmal sites. The incidences in patients with internal carotid artery (ICA) aneurysms, those with aneurysms in the posterior circulation system, those with middle cerebral artery aneurysms, and those with anterior communicating/anterior cerebral artery aneurysms were 10.0%, 22.2%, and 23.5%, respectively; the values were slightly higher in those with middle/anterior cerebral artery aneurysms. However, there was no specific tendency of the localization of ruptured aneurysms in each group (p = 0.545), as shown in Fig. 2.

The incidences of TEEs in the non-administration, clopidogrel LD, and dual LD groups were 19.2 (15/78), 13.6 (3/22), and 0% (0/17), respectively. In the clopidogrel LD group, it was slightly lower than in the non-administration group, but there was no significant difference (non-administration group vs. clopidogrel LD group: p = 0.4). In the dual LD group, the incidence of TEEs was significantly lower (Fig. 3, non-administration group vs. dual LD group: p = 0.0396).

ATs were combined in 42.3 (33/78), 68.2 (15/22), and 76.5% (13/17) of the patients in the non-administration,
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selected was 13.3% (6/45), and that in those in whom ATs were combined was 27.3% (9/33), showing a slight increase (Fig. 5). In the clopidogrel LD group, it decreased from 28.6% (2/7) to 6.7% (1/15), but there was no significant difference. On the other hand, both patients showed an incidence of 0% (0/4, 0/5, respectively) in the dual LD group; the incidence of TEEs in the presence of ATs was significantly lower than in the non-administration group (Fig. 5, non-administration group vs. dual LD group: \( p = 0.035 \)).

During EVT, extravasation was noted in 10.3 (8/78), 0 (0/22), and 5.9% (1/17) of the patients in the non-administration, clopidogrel LD, and dual LD groups, respectively; the percentages were higher in the LD groups (\( p = 0.00945 \), Fig. 4). In the non-administration group, the incidence of TEEs in patients for whom a simple technique was

![Table 1](image)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. of patients</th>
<th>Clopidogrel LD</th>
<th>Dual LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>n = 78</td>
<td>n = 22</td>
<td>n = 17</td>
</tr>
<tr>
<td>Ave. age (yrs)</td>
<td>61.5</td>
<td>61.3</td>
<td>63.4</td>
</tr>
<tr>
<td>Female</td>
<td>47 (60.1)</td>
<td>15 (68.2)</td>
<td>12 (70.6) ( p = 0.902 )</td>
</tr>
<tr>
<td>Aneurysm site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>24 (30.7)</td>
<td>7 (33.3)</td>
<td>9 (52.9) ( p = 0.545 )</td>
</tr>
<tr>
<td>AcomA/ACA</td>
<td>31 (39.7)</td>
<td>6 (28.5)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>MCA</td>
<td>5 (6.4)</td>
<td>3 (14.2)</td>
<td>1 (5.8)</td>
</tr>
<tr>
<td>PC</td>
<td>18 (23)</td>
<td>5 (23.8)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Guiding system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6F Catheter</td>
<td>38 (48.7)</td>
<td>5 (22.7)</td>
<td>3 (17.6) ( p = 0.0124 )</td>
</tr>
<tr>
<td>5/6F Guiding sheath</td>
<td>40 (51.3)</td>
<td>17 (77.3)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>Adjunctive technique</td>
<td>33 (42.3)</td>
<td>16 (72.7)</td>
<td>14 (82.4) ( p = 0.00945 )</td>
</tr>
<tr>
<td>Balloon assist</td>
<td>26</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Double catheter</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Balloon + double catheter</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Distal access catheter</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Extravasation</td>
<td>8 (10.3)</td>
<td>0 (0)</td>
<td>1 (5.9) ( p = 0.26 )</td>
</tr>
</tbody>
</table>

Raw values are reported in each cell. Percentage is in parentheses. ACA: anterior cerebral artery; AcomA: anterior communicating artery; Admin.: administration; F: French; ICA: internal cerebral artery; LD: drug loading; MCA: middle cerebral artery; No.: number; PC: posterior circulation.

![Fig. 2](image)

Fig. 2 Distribution of aneurysm locations. ACA: anterior cerebral artery; AcomA: anterior communicating artery; ICA: internal cerebral artery; LD: drug loading; MCA: middle cerebral artery; PC: posterior circulation.

![Fig. 3](image)

Fig. 3 Rates of thromboembolic events. * statistically significant compared to the non-administered group (\( p = 0.0396 \)). LD: drug loading.

![Fig. 4](image)

Fig. 4 Rates of adjunctive technique combinations. LD: drug loading.

 clopidogrel LD, and dual LD groups, respectively; the percentages were higher in the LD groups (\( p = 0.00945 \), Fig. 4). In the non-administration group, the incidence of TEEs in patients for whom a simple technique was
When performing acute-phase coil embolization of ruptured cerebral aneurysms, preoperative antiplatelet drug loading (dual LD) significantly decreased the incidence of TEEs, and the effect was more marked when the procedure was combined with ATs. LD with clopidogrel alone inhibited TEEs although there was no significant difference.

Etiological factors for EVT-related thrombus formation include blood-flow stagnation, intimal injury, various devices (catheters/coils/stents) in contact with blood, and intra-aneurysmal thrombus dispersion.3,7 As there is a positive feedback relationship between the platelet aggregation response and blood coagulation cascade, it is difficult to prevent thrombus formation by anticoagulant therapy with heparin alone when a potent platelet aggregation response involving GPIIb/IIIa receptors expressed on platelets as a starting point occurs through the appearance of either response.7 Therefore, for TEE prevention, it may be necessary to inhibit platelet aggregation in addition to anticoagulant therapy.7,8

A meta-analysis showed that anticoagulant therapy with heparin decreased the incidence of TEEs, and that it did not increase the incidence of hemorrhagic complications.9 Therefore, heparin, which has been positively introduced, has the following characteristics: 1) intravenously administered heparin exhibits immediate, stable effects; 2) the drug efficacy can be quantitatively evaluated based on the ACT; and 3) a neutralizing agent, protamine, is present.7 On the other hand, clopidogrel is absorbed in vivo, and metabolized in the liver, acquiring a drug activity; therefore, a specific period is required until the appearance of its effects.7 LD-related immediate effects are obtained, but 6 and 2 hours are required at 300 and 600 mg, respectively, and there is no time reduction at a higher dose.10 Furthermore, poor responders (5%–11%) are present due to the gene polymorphism of metabolic enzymes.7 On the other hand, aspirin exhibits more immediate effects compared with clopidogrel. However, a delay in effect appearance is observed in 5%–40%. Dose elevation to obtain a fast-acting property is limited due to an aspirin dilemma.7 For acute-phase EVT, sufficient inhibitory effects on platelet aggregation may not be achieved by LD with these antiplatelet drugs, but these drugs were demonstrated to prevent thromboembolic complications in patients undergoing percutaneous coronary intervention (PCI).11,12 With respect to pre-/intraoperative administration to patients undergoing coil embolization of cerebral aneurysms, Yamada et al.13 reported that the preoperative administration of antiplatelet drugs for unruptured aneurysms decreased the incidence of TEEs from 16% to 1.9%. Ries et al.14 indicated that the intravenous injection of acetylsalicylic acid (ASA) after first-coil insertion in patients who underwent coil embolization in the acute phase of subarachnoid hemorrhage significantly decreased the incidence of intraoperative TEEs (from 20% to 10.1%). In our study, LD with clopidogrel alone did not significantly decrease the incidence of TEEs in comparison with the non-administration group, but dual LD significantly decreased it. Furthermore, the balloon-assist technique is a risk factor for TEEs related to coil embolization.15 In the dual LD group, the rate of patients in whom a balloon was used was higher than in the non-administration group (92.9% vs. 79.4%, respectively), but the incidence of TEEs significantly decreased. Thus, dual LD may have contributed to a decrease in the incidence of TEEs during coil embolization. As monotherapy with aspirin or clopidogrel (oral preparations) exhibits inaccurate properties, combination therapy with the two drugs may increase the accuracy of effects.

Another serious complication related to coil embolization of cerebral aneurysms is intraoperative rupture. It is diagnosed based on intraoperative extravasation.3 The most
frequent cause of this complication is aneurysmal perforation. The incidence of perforation during coil embolization of ruptured cerebral aneurysms is reportedly 2.3%–4.3%.\(^{3,7,9}\) A study indicated that the pre- or intraoperative administration of aspirin did not increase the incidence of perforation.\(^{9,18}\) In our study, there was also no increase. If intraoperative perforation occurs, exacerbation can be avoided through blood pressure control, heparinization reversion, hemostasis with a balloon, and countermeasures for the continuation of embolization procedures,\(^{13}\) and there may be no exacerbation of hemorrhagic complications.\(^{7}\) However, some studies reported that the incidence of additional or intracerebral hemorrhage increased after EVT.\(^{13,16}\) Tumialán et al.\(^{17}\) recommended that ventricular drainage should be performed before EVT when administering antiplatelet drugs. It is necessary to recognize the possibility that an increase in the dose may induce a delayed, excessively platelet-aggregation-suppressed state after EVT, leading to serious hemorrhagic complications.

In the future, stents may be increasingly used to treat ruptured aneurysms.\(^{9,18}\) In such cases, the risk of TEEs may further increase, and preventive strategies are important.\(^{9,18}\) In the future, TEEs may be prevented by introducing an adenosine diphosphate receptor inhibitor with immediate/stable effects, prasugrel, or a GPIIb/IIIa inhibitor, Abciximab.\(^{9,19}\) However, there is no neutralizer for either drug; therefore, when introducing these drugs, the risk of serious intra-/postoperative hemorrhagic complications must be considered.

As the case accumulation period differed among the three groups compared in this study, we compared guiding systems, which most markedly differed, considering the influence of changes in procedures/strategies during this period on the results. In the LD groups, the rate of patients in whom a GS was used was higher than in the non-administration group. It was assumed that an increase in the guiding system diameter might reduce intra-catheter interferences related to the use of several devices, improving the operability and decreasing the incidence of TEEs. However, actually, the incidence of TEEs was higher than in patients in whom a guiding catheter was used (10.5%). This may have been related to a transient increase in the incidence of TEEs in the initial phase of GS introduction. The causes of the increase in the incidence of TEEs were speculated as follows: 1) the timing of GS introduction was consistent with the initial phase of the positive introduction of ATs with a balloon in patients with subarachnoid hemorrhage, 2) a wide GS facilitates wedging to the ICA, and 3) wide-GS-guided procedures may cause spasm or dissection of the ICA. These factors may lead to a reduction in the flow velocity, becoming risk factors for the development of TEEs. As strategies to prevent this, ATs were improved and stabilized, and the following points were concretely corrected: 1) to prevent accordion phenomenon or spasm of the extra-cranial ICA, a wedge-tendency-related reduction in the flow velocity was avoided, paying attention to GS-guiding operations and the tip position in reference to vascular torsion; and 2) an inner catheter for guiding a GS was switched from a 6 Fr catheter to a catheter consisting of 6 Fr (hand to 15 cm on this side from the tip) and 4 Fr (tapering) at the tip. These strategies gradually decreased the incidence of TEEs, and there was no significant difference in comparison with patients in whom a guiding catheter was used during the study period. However, in our series, the incidence of TEEs was relatively high although it ranged from 2.5 to 28% when evaluating angiography findings according to several studies;\(^{4,5}\) therefore, to further decrease the incidence of TEEs, we introduced dual loading with antiplatelet drugs.

For coil embolization, the incidence of TEEs is higher than that of intraoperative perforation, and the preventive effects of LD on TEEs may be advantageous.\(^{3,7,13}\) In this study, the number of patients in the LD groups was small, and other conditions were not consistent with those in the non-administration group. To establish the optimal drug type, dose, and timing of administration and investigate the influence on hemorrhagic events, a larger number of patients should be examined.

## Conclusion

Dual LD with antiplatelet drugs before acute-phase coil embolization of ruptured cerebral aneurysms significantly inhibited the development of TEEs. Although neither the drug type nor dose has been established, the introduction of dual LD in acute-phase treatment for ruptured aneurysms should be considered.

## Disclosure Statement

There is no conflict of interest regarding this article for the first author or coauthors.

## References


