Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part I

Current Perioperative Management of Anticoagulant and Antiplatelet Use in Neuroendovascular Therapy: Analysis of JR-NET1 and 2

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Abstract

To evaluate current perioperative antithrombotic management in neuroendovascular therapy in Japan, we analyzed perioperative anticoagulant and antiplatelet use in various procedures and examined their relationships with periprocedural adverse events. Patient’s data from nationwide surveys administered by the Japanese Registry of Neuroendovascular Therapy (JR-NET) between January 2005 and December 2007 (JR-NET1) and January 2008 and December 2009 (JR-NET2) were retrospectively analyzed. Compared to JR-NET1, the frequency of perioperative antiplatelet therapy and dual or triple therapy were increased for either aneurysm coiling and percutaneous transluminal angioplasty or stenting in JR-NET2. Although ischemic complications were significantly decreased (4.2% vs. 2.1%, p < 0.001), hemorrhagic complications (2.1% vs. 5.3%, p < 0.001), severe adverse events (1.5% vs. 2.1%, p < 0.001), and total perioperative complications (8.3% vs. 10.3%, p < 0.001) were significantly increased in JR-NET2. The rate of hemorrhagic complications was significantly higher in patients with triple or more perioperative antiplatelet therapy (preoperative: 5.3% vs. 9.2%, p < 0.0001, postoperative: 5.7% vs. 12.7%, p < 0.0001). Perioperative antithrombotic therapy was performed more frequently and intensively in neuroendovascular therapy in Japan. While ischemic complications were decreased, hemorrhagic complications and severe adverse events were increased. These results suggest that intensive antithrombotic therapy has a potential risk of hemorrhagic complications for Japanese patients.

Key words: neuroendovascular therapy, antiplatelet, anticoagulant

Introduction

Anticoagulants and antiplatelet agents are widely prescribed to lower the rate of perioperative thromboembolic events in neuroendovascular treatments. Endovascular procedures are associated with a risk of immediate or delayed thromboembolic and ischemic complications. At the site of flow stagnation in catheters, a red thrombus consisting of red blood cells and fibrin can form due to activation of coagulation, which is preventable with anticoagulants such as heparin. Thus, use of perioperative anticoagulants represents a critical management strategy in endovascular therapy. However, anticoagulants cannot prevent formation of platelet-rich white thrombi. For example, carotid artery stenting (CAS) can cause intimal injury of the arterial vessel, and implanted thrombogenic foreign devices may trigger activation of platelets and subsequent formation of white thrombi. Antiplatelet agents are essential to prevent thrombotic ischemic event by such mechanism. Dual antiplatelet therapy for at least four days prior to surgery is...
currently recommended by five academic societies in the United States as perioperative antithrombotic treatment at the time of CAS.\textsuperscript{1} Aneurysm coiling or parent artery occlusion requires thrombosis of the aneurysmal sac for complete obliteration. Immature embolization of the aneurysmal sac, protrusion of coils, or balloon-assisted maneuvers may lead to acute thrombus formation by platelet activation. Antiplatelet therapy prior to procedures has been shown to lower thromboembolic complications in elective coil embolization of cerebral aneurysms.\textsuperscript{2} While perioperative antithrombotic therapy can reduce ischemic complications, there is a potential risk of hemorrhagic complications. Although several antithrombotic therapeutic options are available, optimized management in neuroendovascular therapy is not well defined. Appropriate antiplatelet agents, anticoagulants, dosing, and duration of treatment have not been adequately determined.

To evaluate current perioperative antithrombotic management in neuroendovascular therapy, we retrospectively analyzed patient’s data from two Japanese Registry of Neuroendovascular Therapy (JR-NET) studies.

Methods

I. Study population
JR-NET1 and 2 are retrospective surveys conducted between January 2005 and December 2007 and January 2008 and December 2009, respectively, in Japan regarding neuroendovascular therapy. A total of 23,757 patients registered in JR-NET1 and 2 who received perioperative antithrombotic therapy were retrospectively analyzed for the following parameters: aneurysm coiling (n = 3,902 in JR-NET1, n = 7,723 in JR-NET2), parent artery occlusion for dissecting aneurysm (n = 313 in JR-NET1, n = 818 in JR-NET2), percutaneous transluminal angioplasty (PTA) or stenting of the external carotid artery (n = 2,013 in JR-NET1, n = 5,462 in JR-NET2), extracranial artery (n = 563 in JR-NET1, n = 615 in JR-NET2), or intracranial artery (n = 400 in JR-NET1, n = 647 in JR-NET2), or recanalization therapy for acute stroke (n = 504 in JR-NET1, n = 797 in JR-NET2). Patients with incomplete medical records were excluded from analysis (lack of detailed information: n = 1,304; classification mistake: n = 793, others: n = 8).

To determine the relationship between antithrombotic therapy and perioperative complications, the rates of ischemic, hemorrhagic, and groin-site complications for each procedure in patients from the JR-NET2 survey were calculated. Ischemic and hemorrhagic complications were defined as procedure-related intracranial complications within 24 hours following a procedure. Severe adverse events were defined as death or severe disability with a deterioration of ≥ 2 points based on the modified Rankin scale 30 days after a procedure.

II. Statistics
The chi-square test was used for two-group analyses between JR-NET1 and JR-NET2. The impact of each variable on four perioperative complications (ischemic, hemorrhagic, groin-site hematoma, and severe adverse events) was determined by multivariate logistic regression analysis. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA).

Results

I. Comparison of perioperative antithrombotic therapy between JR-NET1 and 2
In aneurysm coiling, including ruptured and unruptured coiling and parent artery occlusion with

Table 1 Antithrombotic therapy in aneurysm coiling

| Variables | Ruptured n (%) | p value | Unruptured n (%) | p value |
|-----------|----------------|---------|-----------------|---------|
|           | JR-NET1        | JR-NET2 |                 |         |
| Total number of patients | n = 2,004 | n = 3,978 | n = 2,211 | n = 4,563 |
| Pre-AP | | | | |
| Yes | 119 (5.9%) | 532 (13.4%) | < 0.001 | 1,574 (71.2%) | 3,857 (84.5%) | < 0.001 |
| Mono | 90 (4.5%) | 384 (9.7%) | < 0.001 | 1,033 (46.7%) | 1,566 (34.3%) | < 0.001 |
| Dual | 27 (1.4%) | 137 (3.4%) | < 0.001 | 509 (23.0%) | 2,128 (46.6%) | < 0.001 |
| Triple | 0 (0%) | 4 (0.1%) | 0.373 | 2 (0.1%) | 30 (0.7%) | < 0.01 |
| None | 1,624 (81.0%) | 3,290 (82.7%) | 0.112 | 523 (23.7%) | 536 (11.7%) | < 0.001 |
| Unknown | 261 (13.0%) | 89 (2.2%) | < 0.001 | 114 (5.2%) | 80 (2.0%) | < 0.001 |

(Continued)
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Table 1 (Continued)

| Variables | Ruptured n (%) | p value | Unruptured n (%) | p value |
|-----------|----------------|---------|------------------|---------|
|           | JR-NET1 | JR-NET2 |       | JR-NET1 | JR-NET2 |       |
| Total number of patients | n = 2,004 | n = 3,978 | | n = 2,211 | n = 4,563 | |
| Post-AP |       |         |       |         |         |         |
| Yes | −* | 2,175 (54.7%) | −* | 3,863 (84.7%) |
| Mono | −* | 1,749 (44.0%) | −* | 1,837 (40.3%) |
| Dual | −* | 318 (8.0%) | −* | 1,650 (36.2%) |
| Triple | −* | 25 (0.6%) | −* | 236 (5.2%) |
| None | −* | 1,574 (39.6%) | −* | 560 (12.3%) |
| Unknown | −* | 162 (4.1%) | −* | 50 (1.1%) |
| Post-AC |       |         |       |         |         |         |
| Yes | −* | 1,659 (41.7%) | −* | 2,997 (65.7%) |
| Heparin | 356 (17.8%) | 477 (12.0%) | < 0.001 | 808 (36.5%) | 1,264 (27.7%) | < 0.001 |
| Argatroban | 313 (15.6%) | 712 (17.9%) | < 0.05 | 658 (29.8%) | 1,868 (40.9%) | < 0.001 |
| Ozagrel | 423 (21.1%) | 536 (13.5%) | < 0.001 | 78 (3.5%) | 104 (2.3%) | < 0.01 |
| None | −* | 2,118 (53.2%) | −* | 1,391 (30.4%) |
| unknown | −* | 134 (3.4%) | −* | 85 (1.9%) |

*Indicates postoperative antithrombotic therapy data that were not provided in the JR-NET survey. AC: anticoagulant, AP: antiplatelet, JR-NET: Japanese Registry of Neuroendovascular Therapy.

Next, we reviewed perioperative antithrombotic therapy and compared the results of JR-NET1 and JR-NET2 surveys (Table 1). Compared to JR-NET1, preoperative antiplatelet therapy was more frequently performed in JR-NET2 patients (5.9% vs. 13.4% in the ruptured group, p < 0.001; 71.2% vs. 84.5% in the unruptured group, p < 0.001). The frequency of dual therapy was also higher (1.4% vs. 3.4% in the ruptured group, p < 0.001; 23.0% vs. 46.6% in the unruptured group, p < 0.001). Regarding postoperative anticoagulants, use of heparin therapy was decreased and argatroban therapy was increased in both the ruptured and unruptured groups. The most frequently used postoperative antiplatelet therapy for ruptured aneurysm was mono therapy with aspirin, this result was the same also in JR-NET1 and 2. For the unruptured aneurysm, the most frequently used preoperative antiplatelet regimen changed from aspirin-ticlopidine (44% in JR-NET1) to aspirin-clopidogrel dual therapy (36.6% in JR-NET2) (Table 4).

Next, we reviewed perioperative antithrombotic therapy in PTA or stenting, including PTA or stenting of the external carotid artery (CAS), extracranial artery, or intracranial artery, and compared the results of JR-NET1 and JR-NET2 surveys (Table 3). The frequency of preoperative antiplatelet therapy was not significantly different between JR-NET1 and JR-NET2 (96.6% and 96.3%, respectively, p = 0.474). However, compared to JR-NET1, the mono therapy frequency was significantly decreased (17.2% vs. 6.6%, p < 0.001) and dual or triple therapy was significantly increased (74.8% vs. 84.5%, p < 0.001) in JR-NET2. Regarding postoperative anticoagulants, use of heparin therapy was decreased (37.8% vs. 21.8%, p < 0.001) in JR-NET2 compared to JR-NET1.

The most frequently used preoperative antiplatelet regimen changed from aspirin-ticlopidine (44% in JR-NET1) to aspirin-clopidogrel dual therapy (36.6% in JR-NET2) (Table 4).

II. Relationship between perioperative antithrombotic therapy and complications

Perioperative complication rates were compared between 7,695 JR-NET1 patients and 16,062 JR-NET2 patients. Ischemic complications were significantly decreased (4.2% vs. 2.1%, p < 0.001), whereas hemorrhagic complications (2.1% vs. 5.3%, p < 0.001) and severe adverse events (1.5% vs. 2.1%, p < 0.001) were significantly increased. The rate of groin-site complications was similar between the two groups (0.6% vs. 0.7% p = 0.219). The incidence of all perioperative complications was significantly higher in JR-NET2 patients compared to JR-NET1 (8.3% vs. 10.3%, p < 0.001).

Next, we evaluated the relationship between perioperative antithrombotic therapy and complications from the JR-NET2 survey. For postoperative
operative anticoagulant therapy (2.7% vs. 1.8%, or 4.172 [95% CI 2.478–7.023], p < 0.01).

For preoperative antiplatelet therapy, ischemic complications (4.0% vs. 1.2%, p < 0.0001) and severe adverse events (3.8% vs. 1.4%, p < 0.0001) were significantly higher in patients who were not treated with anticoagulant therapy compared to patients with antiplatelet therapy. Hemorrhagic (9.2% vs. 5.3%, p < 0.0001) and groin-site complications (2.4% vs. 0.6%, p < 0.0001) were significantly higher in patients treated with three or more antiplatelet agents compared to other patients. The rate of ischemic complications decreased based on the number of preoperative antiplatelet agents used (4.0%, 1.9%, 0.7%, 0.3%, 0.1%, 0.0%, p = 0.483).

Table 2  Antiplatelet agent use in aneurysm coiling

|                | Ruptured |     | Unruptured |     |
|----------------|----------|-----|------------|-----|
|                | JR-NET1  |     | JR-NET2    |     |
|                | p value  |     | p value    |     |
| Preoperative   |          |     |            |     |
| Mono therapy   |          |     |            |     |
| Aspirin        | 78 (3.9%)|     | 885 (40.0%)|     |
|                | 327 (8.2%)|     | 1,013 (22.2%)|     |
|                | < 0.001 |     | 0.001      |     |
| Ticlopidine    | 5 (0.3%) |     | 107 (4.8%) |     |
|                | 5 (0.1%) |     | 31 (0.68%) |     |
|                | 0.269    |     | 0.422      |     |
| Cilostazol     | 1 (0.1%) |     | 35 (1.6%)  |     |
|                | 19 (0.5%)|     | 61 (1.3%)  |     |
|                | < 0.05   |     |            |     |
| Clopidogrel    | 0        |     | 5 (0.2%)   |     |
|                | 31 (0.8%)|     | 460 (10.1%)|     |
|                | < 0.001  |     | 0.001      |     |
| Others         | 6 (0.3%) |     | 1 (0.1%)   |     |
|                | 2 (0.1%) |     | 1 (0.0%)   |     |
|                | < 0.05   |     | 0.818      |     |
| Dual therapy   |          |     |            |     |
| ASA-TCL        | 14 (0.7%)|     | 274 (12.4%)|     |
|                | 9 (0.2%) |     | 113 (2.5%) |     |
|                | < 0.01   |     | 0.001      |     |
| ASA-CLP        | 4 (0.20%)|     | 51 (2.3%)  |     |
|                | 85 (2.1%)|     | 1,253 (27.5%)|     |
|                | 0.054    |     | < 0.001    |     |
| ASA-CSZ        | 9 (0.45%)|     | 180 (8.1%) |     |
|                | 36 (0.9%)|     | 672 (14.7%)|     |
|                | < 0.001  |     | < 0.001    |     |
| CSZ-CLP        | 0 (0%)   |     | 0 (0%)     |     |
|                | 7 (0.2%) |     | 81 (1.8%)  |     |
|                | 0.139    |     | 0.001      |     |
| Others         | 0        |     | 4 (0.2%)   |     |
|                | 0        |     | 9 (1.7%)   |     |
|                | 0.879    |     |            |     |
| Postoperative  |          |     |            |     |
| Mono therapy   |          |     |            |     |
| Aspirin        | 201 (10.0%)|     | 229 (10.4%)|     |
|                | 1,259 (31.6%)|     | 1,319 (28.9%)|     |
|                | < 0.001 |     | < 0.001    |     |
| Ticlopidine    | 16 (0.8%)|     | 57 (2.6%)  |     |
|                | 16 (0.4%)|     | 35 (0.8%)  |     |
|                | < 0.05   |     | < 0.001    |     |
| Cilostazol     | 34 (1.7%)|     | 12 (0.5%)  |     |
|                | 298 (7.5%)|     | 157 (3.4%) |     |
|                | < 0.001  |     | < 0.001    |     |
| Clopidogrel    | 1 (0.1%) |     | 2 (0.1%)   |     |
|                | 172 (4.3%)|     | 323 (7.1%) |     |
|                | < 0.001  |     | < 0.001    |     |
| Others         | –*       |     | –*         |     |
|                | 4 (0.1%) |     | 3 (0.1%)   |     |
|                | 0.879    |     |            |     |
| Dual therapy   |          |     |            |     |
| ASA-TCL        | 28 (1.4%)|     | 250 (11.3%)|     |
|                | 26 (0.7%)|     | 105 (2.3%) |     |
|                | < 0.001  |     | < 0.001    |     |
| ASA-CLP        | 32 (1.60%)|     | 253 (11.4%)|     |
|                | 126 (3.2%)|     | 535 (11.7%)|     |
|                | < 0.001  |     | 0.734      |     |
| ASA-CSZ        | 2 (0.10%)|     | 29 (1.3%)  |     |
|                | 147 (3.7%)|     | 928 (20.3%)|     |
|                | < 0.001  |     | < 0.001    |     |
| CSZ-CLP        | 0 (0%)   |     | 1 (0.1%)   |     |
|                | 12 (0.3%)|     | 68 (1.5%)  |     |
|                | < 0.05   |     | < 0.001    |     |
| Others         | –*       |     | –*         |     |
|                | 7 (1.31%)|     | 14 (2.6%)  |     |
|                | 0.879    |     |            |     |

*indicates postoperative antplatelet therapies that were not mentioned in the JR-NET1 survey. ASA: aspirin, CSZ: cilostazol, JR-NET: Japanese Registry of Neuroendovascular Therapy, TCL: ticlopidine.
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rate of symptomatic thromboembolic complications was significantly lower in patients who received antiplatelet therapy (2% with and 16% without antiplatelet agents). For CAS, McKevitt et al. reported that dual antiplatelet therapy showed lower incidences of both ischemic complications (0% vs. 25%, respectively) and hemorrhagic complications (9% vs. 17%, respectively) compared to aspirin mono therapy plus anticoagulant therapy. Dalainas et al. also reported similar results. From the results of reported studies, it is convinced that dual (or more) antiplatelet therapy was more effective to

Discussion

Thromboembolic events appeared to be the most common adverse events in neuroendovascular therapy. Antithrombotic therapy is prescribed to lower the rate of thromboembolic complications. For aneurysm coiling, Yamada et al. reported that the

Table 3 Antithrombotic therapy in PTA or stenting

| Variables          | PTA or stenting | p value |
|--------------------|-----------------|---------|
|                    | JR-NET1  | JR-NET2 |         |
| Total number of patients | n = 2,976 | n = 6,724 |         |
| Pre-AP              |         |         |         |
| Yes                 | 2,834 (96.6%) | 6,473 (96.3%) | 0.474 |
| Mono                | 514 (17.2%) | 446 (6.6%) | < 0.001 |
| Dual                | 2,090 (70.2%) | 5,080 (75.6%) | < 0.001 |
| Triple              | 137 (4.6%) | 598 (8.9%) | < 0.001 |
| None                | 116 (3.9%) | 62 (0.9%) | < 0.001 |
| Unknown             | 26 (0.9%) | 189 (2.8%) | < 0.001 |
| Post-AP             |         |         |         |
| Yes                 | −*  | 6,519 (97.0%) |         |
| Mono                | −*  | 382 (5.7%) |         |
| Dual                | −*  | 5,229 (78.9%) |         |
| Triple              | −*  | 567 (8.4%) |         |
| None                | −*  | 27 (0.4%) |         |
| Unknown             | −*  | 178 (2.6%) |         |
| Post-AC             |         |         |         |
| Yes                 | −*  | 4,051 (60.2%) |         |
| Heparin             | 1,125 (37.8%) | 1,468 (21.8%) | < 0.001 |
| Argatroban          | 1,086 (36.5%) | 2,570 (38.2%) | 0.105 |
| Ozagrel             | 97 (3.3%) | 192 (2.9%) | 0.281 |
| None                | −*  | 2,399 (35.7%) |         |
| Unknown             | −*  | 274 (4.1%) |         |

*Indicates postoperative antithrombotic therapy data that were not described in the JR-NET1 survey. AP: antiplatelet, AC: anticoagulant, JR-NET: Japanese Registry of Neuroendovascular Therapy, PTA: percutaneous transluminal angioplasty.

Table 4 Antiplatelet agents used in PTA or stenting

| Variables          | PTA or stenting | p value |
|--------------------|-----------------|---------|
|                    | JR-NET1  | JR-NET2 |         |
| Preoperative       |         |         |         |
| Mono therapy       |         |         |         |
| Aspirin            | 281 (9.4%) | 169 (2.5%) | < 0.001 |
| Ticlopidine        | 133 (4.5%) | 34 (0.5%) | < 0.001 |
| Cilostazol         | 71 (2.4%) | 65 (1.0%) | < 0.001 |
| Clopidogrel        | 11 (0.4%) | 130 (1.9%) | < 0.001 |
| Others             | 21 (0.7%) | 7 (0.1%) | < 0.001 |
| Dual therapy       |         |         |         |
| ASA-TCL            | 1,308 (44.0%) | 697 (10.4%) | < 0.001 |
| ASA-CLP            | 128 (4.3%) | 2,462 (36.6%) | < 0.001 |
| ASA-CSZ            | 590 (19.8%) | 1,352 (20.1%) | 0.749 |
| CSZ-CLP            | 6 (0.2%) | 505 (7.5%) | < 0.001 |
| Others             | 58 (1.9%) | 83 (1.2%) | < 0.001 |
| Postoperative      |         |         |         |
| Mono therapy       |         |         |         |
| Aspirin            | 48 (1.6%) | 170 (2.5%) | < 0.01 |
| Ticlopidine        | 33 (1.1%) | 19 (0.3%) | < 0.001 |
| Cilostazol         | 11 (0.4%) | 71 (1.1%) | < 0.001 |
| Clopidogrel        | 5 (0.2%) | 121 (1.8%) | < 0.001 |
| Others             | −*  | 14 (0.2%) |         |
| Dual therapy       |         |         |         |
| ASA-TCL            | 1,217 (40.9%) | 1,022 (15.2%) | < 0.001 |
| ASA-CLP            | 120 (4.0%) | 2,608 (38.8%) | < 0.001 |
| ASA-CSZ            | 590 (19.8%) | 1,354 (20.1%) | < 0.001 |
| CSZ-CLP            | 10 (0.3%) | 472 (7.0%) | < 0.05 |
| Others             | −*  | 281 (4.2%) |         |

*Indicates postoperative antiplatelet therapies that were not mentioned in the JR-NET1 survey. ASA: aspirin, CSZ: cilostazol, JR-NET: Japanese Registry of Neuroendovascular Therapy, PTA: percutaneous transluminal angioplasty, TCL: ticlopidine.
prevent perioperative complications.

Although intensive antithrombotic therapy reduces the risk of ischemic complications, there are concerns that it may increase the risk of hemorrhagic complications. A prospective study on antiplatelet therapy for preventing thrombotic events in cerebrovascular patients showed that the rate of bleeding events was higher with dual than with single antiplatelet therapy.5,6) The bleeding with antithrombotic therapy (Bat) study in Japanese patients showed that the incidence of bleeding events was 2.0% in the dual antiplatelet therapy group compared to 1.21% in the single therapy group.7)

In the present study, we found that perioperative antithrombotic therapy has changed to be more frequently performed preoperatively with multiple agents in Jr-nEt2 compared to Jr-nEt1. In aneurysm coiling, preoperative antiplatelet therapy for coiling of unruptured aneurysm was shifted to dual antiplatelet therapy. We can speculate that this result may be influenced by introduction of new techniques, such as balloon assist techniques or stent assist techniques. Such complicated procedures increase the risk of thromboembolic complications or severe adverse events and require intensive antithrombotic therapy as preventative measures.8)

In PTA and stenting, dual antiplatelet therapy had been widely recognized as the “gold standard.”1) The percentage of dual antiplatelet therapy was high enough in Jr-nEt1. However, while ischemic complications significantly decreased, hemorrhagic complications, severe adverse events, and total perioperative complications significantly increased in Jr-nEt2. The present study demonstrated several relationships between perioperative antithrombotic therapy and complications. For postoperative anticoagulant therapy, ischemic complication was significantly higher but hemorrhagic complication was significantly lower in patients treated with postoperative anticoagulant therapy. This inconsistency may be because treatment with postoperative anticoagulant therapy depends on the onset of intraoperative ischemic or hemorrhagic complications.

Table 5 Relationship between postoperative anticoagulants and complications

| Variables          | Anticoagulant | Heparin | Argatroban | Ozagrel |
|--------------------|---------------|---------|------------|---------|
|                    | Used Not used | p value | Used Not used | p value |
| Total number of patients | 9,312 6,060 | 0.001 0.001 | 5,353 9,997 | 0.001 0.001 |
| Ischemic complications | 191 604 | 0.001 0.001 | 383 416 | 0.001 0.001 |
| Hemorrhagic complications | 39 286 | 0.001 0.001 | 27 54 | 0.001 0.001 |
| Groin-site complications | 27 81 | 0.001 0.001 | 48 48 | 0.001 0.001 |
| Severe adverse events | 67 267 | 0.001 0.001 | 101 101 | 0.001 0.001 |

Table 6 Relationship between perioperative complications and antiplatelet therapy

| Preoperative antiplatelet therapy | None Mono Dual ≥ Triple |
|----------------------------------|-------------------------|
| Number of patients              | 3,888 2,396 7,345 632 |
| Ischemic                        | 156 (4.0%) 46 (1.9%) 75 (1.0%) 4 (0.6%) |
| Hemorrhagic                     | 221 (5.7%) 132 (5.5%) 375 (5.1%) 58 (9.2%) |
| Groin-site                      | 8 (0.2%) 20 (0.8%) 57 (5.0%) 15 (2.4%) |
| Severe adverse event            | 148 (13.8%) 42 (1.8%) 95 (1.3%) 8 (1.3%) |

| Postoperative antiplatelet therapy | None Mono Dual ≥ Triple |
|-----------------------------------|-------------------------|
| Number of patients                | 606 4,124 7,340 844 |
| Ischemic                          | 179 (6.9%) 88 (2.1%) 46 (0.6%) 6 (0.7%) |
| Hemorrhagic                       | 93 (3.6%) 195 (4.7%) 395 (5.4%) 107 (12.7%) |
| Groin-site                        | 8 (0.3%) 22 (0.5%) 60 (0.8%) 20 (2.4%) |
| Severe adverse event              | 146 (5.6%) 71 (1.7%) 100 (1.4%) 10 (1.2%) |

*Significant differences (p < 0.01) between variables with asterisks and the other three groups.
complications. The rate of severe adverse events was significantly higher in patients who were not treated with postoperative anticoagulant therapy. For perioperative antiplatelet therapy, although ischemic complications and severe adverse events were significantly higher in patients who were not treated with antiplatelet therapy, hemorrhagic and groin-site complications were significantly higher in patients treated with three or more antiplatelet agents. Japanese individuals tend to have a smaller physique than Westerners. We speculate that conventional antithrombotic therapy protocols may lead to overdose in Japanese patients. In particular, it was reported that there is a higher incidence of intracerebral hemorrhage in Asian patients compared to patients of other ethnicities.9)

This study has several limitations. It was conducted retrospectively and courses of treatment were decided independently at each facility. These two factors may have influenced complication rates. Because postoperative use of anticoagulants depends on the occurrence of intraoperative adverse events, the rate of ischemic complications in patients with postoperative anticoagulant therapy was higher, but the rate of hemorrhagic complications was lower. A prospective study should be performed to identify the actual effects of perioperative antithrombotic therapy on perioperative complications.

Conclusion

In the present study, perioperative antithrombotic therapy was shown to be more frequently performed using multiple agents in neuroendovascular therapy in Japan. Although the rate of ischemic complications was decreased, the rate of hemorrhagic complications or severe adverse events was increased. Caution should be taken when prescribing three or more antiplatelet agents due to an increased risk of hemorrhagic complications. Additional considerations regarding suitable antithrombotic agents, doses, and duration of perioperative antithrombotic therapy are necessary in Japanese patients.

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Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest except for S. Yoshimura and N. Sakai. S. Yoshimura received Speakers’ Bureau/Honoraria from Sanofi and Otsuka Pharmaceutical Co. N. Sakai received Speakers’ Bureau/Honoraria from Sanofi and Otsuka Pharmaceutical Co. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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