Onset time of ischemic events and antiplatelet therapy after intracranial stent-assisted coil embolization

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Grant support: None

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Key words: intracranial aneurysm, stent-assisted coil embolization, ischemic event,
antiplatelet therapy

Running Title: Ischemic events and stent-assisted coiling
Abstract

**Background:** Stent-assisted coil embolization is effective for intracranial aneurysms, especially wide-necked aneurysms; however, the optimal antiplatelet regimens for ischemic events that develop after coil embolization have not yet been established. We aimed to determine the onset time of such postoperative ischemic events and the relationship between these events and antiplatelet therapy.

**Materials and Methods:** We performed coil embolization using a vascular reconstruction stent for 43 cases of intracranial aneurysms and evaluated the incidence of postoperative ischemic events in these cases.

**Results:** Nine patients showed postoperative ischemic events during the follow-up period (13 ± 7 months). Two patients developed cerebral infarction within 24 hours. Five patients developed transient ischemic attack within 40 days while they were receiving dual antiplatelet therapy. In addition, 1 patient showed cerebral infarction 143 days postoperatively during single antiplatelet therapy, and a case of transient visual disturbance was reported 191 days postoperatively (49 days after antiplatelet therapy had been discontinued). We increased the number of antiplatelet agents in 4 of these patients. The other 5 patients were under strict observation with dual antiplatelet therapy. All of these patients were shifted to single antiplatelet therapy 3–13 months postoperatively. No recurrence of ischemic events was noted.

**Conclusion:** Postoperative ischemic events are most likely to occur within 40 days postoperatively. For patients with postoperative ischemic events, additional ischemic events can be prevented by increasing the number of antiplatelet agents; subsequently, they can be shifted to single antiplatelet therapy after the risk of recurrence has decreased.
INTRODUCTION

The use of intracranial stent-assisted coil embolization for treating intracranial aneurysms is associated with increased packing density and decreased coil deviation rates of the parent artery (1). Its use is effective for wide-necked aneurysms (2, 3). However, this procedure is also associated with the adverse complication of thromboembolic events. Previous studies have reported that adverse events occurred in 25% of cases in which this procedure was performed, and ischemic events were specifically found in 4.5–22.2% of cases (4–7). In these earlier studies, two antiplatelet agents were used for periods of 3 weeks to 6 months after the operation, followed by administration of a single antiplatelet agent intended to be administered for the rest of the patients’ lives (4-7). However, administration of multiple antiplatelet agents has been reported to increase the risk of hemorrhagic events (8, 9).

Recently, a 5% risk of ischemic events was observed after a 6-week course of dual antiplatelet therapy (10). The optimal antiplatelet agent regimen for patients who have undergone intracranial stent-assisted coil embolization has not yet been established (10, 11). In the present study, we examined the onset time of postoperative ischemic events following stent-assisted coil embolization and the relationship between these postoperative ischemic events and antiplatelet therapy.

METHODS

We retrospectively analyzed data from 96 patients with unruptured intracranial aneurysms at Fukuoka University Chikushi Hospital between July 2010 and May 2012.
Patients were included for data analysis if they were treated by coil embolization with an intracranial stent and if a follow-up assessment by a neurologist or neurosurgeon was performed at least 3 months after the operation. In Japan, the indications for using a CORDIS ENTERPRISE™ Vascular Reconstruction Device (Cordis Neurovascular, Inc., Miami, FL) include wide-necked intracranial aneurysms (diameter of aneurysmal neck > 4 mm or dome/neck ratio < 2) with a maximum aneurysmal dome diameter of 7 mm and a parent artery diameter between 2.5 and 4 mm. All patients gave their prior informed consent for participation in the study, which was approved by the ethics committee of Fukuoka University Chikushi Hospital.

We used the techniques of standard multi projection cerebral angiography, three-dimensional (3D) digital subtraction angiography (DSA), magnetic resonance imaging (MRI), and time-of-flight magnetic resonance angiography (MRA) for preoperative evaluation measures. Morphologic evaluation and measurement of the aneurysm were done using reconstructed 3D DSA or MRA images.

Our typical dual antiplatelet therapy before the operation was that patients received any 2 of the following 3 antiplatelet agents: aspirin (100 mg/day, first dose at least 3 days before the operation), clopidogrel (75 mg/day, first dose at least 5 days before the operation) or cilostazol (200 mg/day, first dose at least 2 days before the operation). During the operation, patients were administered heparin at a dose that kept activated clotting times longer than 2–2.5 times their baseline values before insertion of the stent. Our typical protocol was to prescribe dual antiplatelet therapy for a period of 3–6 months following the operation; subsequently, we prescribed single antiplatelet therapy after a postoperative investigation which included MRI and/or DSA.

We investigated the relationship between the onset of postprocedural ischemic events
and antiplatelet therapy. Postprocedural ischemic events primarily consisted of cases of cerebral infarction or transient ischemic attack (TIA); however, we also monitored ischemic eye symptoms as potential postoperative ischemic events if the intracranial stent was placed in the internal cerebral artery of the ipsilateral side. The event was defined as a cerebral infarction if the symptoms persisted for more than 24 hours and an abnormal new high intensity area (HIA) was detected by MRI examination with diffusion-weighted imaging (DWI-MRI). If the symptoms disappeared in less than 24 hours and an abnormal new HIA was not detected by MRI-DWI or MRI examination with T2 weighted imaging (T2WI-MRI) after the ischemic event, it was defined as a TIA. In the case of ischemic eye symptoms, detailed examination including the eye ground was performed by ophthalmologists for confirmation.

Fisher’s exact test was used to determine significant differences in gender, presence or absence of hypertension and ischemic heart disease, use of antiplatelet agents, and stent length between the group that experienced postoperative ischemic events and the group that did not. The Mann-Whitney U test was used for assessing all other parameters. $P < 0.05$ was considered to indicate statistical significance.

**RESULTS**

Of the 96 patients treated in our department with endovascular procedures during a 22-month period, 43 patients underwent coil embolization with an intracranial stent. These 43 patients comprised 11 men and 32 women with an average age of $60 \pm 13$ years (mean $\pm$ SD). Of these 43 patients, 16 had hypertension, 2 had diabetes mellitus, 3 had ischemic heart disease, 1 had chronic heart failure and 1 had left subclavian artery
occlusion. None of these 43 patients had a history of cerebral infarction before the operation. In all patients, an angiography performed immediately after coil embolization showed no signs of thromboembolic events.

Two of the 43 cases discontinued antiplatelet therapy postoperatively. In 1 patient, antiplatelet therapy was discontinued due to apparent allergy to all 3 antiplatelet agents, a situation which was discovered on the 10th postoperative day. This patient was administered icosapentaenoic acid and did not experience an ischemic event. In the other patient, antiplatelet therapy was discontinued because of the patient’s low compliance with taking the drug. This patient experienced transient visual disturbance on the 191st postoperative day, 49 days after discontinuation of antiplatelet therapy.

The follow-up period was 13 ± 7 months (mean ± SD; median: 14 months; range: 3–28 months). During this period, 9 of the 43 patients experienced postoperative ischemic events. Of these 9 cases, 4 had hypertension but none showed other cardiovascular risk factors (for example, diabetes mellitus, arterial fibrillation, ischemic heart disease, chronic heart failure, or left subclavian artery occlusion). None of these 9 cases displayed evidence of in-stent stenosis or thrombosis on angiographic follow up.

Although the latest event occurred on the 191st postoperative day, the median time of onset of postoperative events was 12 days. Two patients showed mild hemiparesis on the side opposite to the stented vessel within 24 hours after the operation, and these patients were diagnosed with cerebral infarction in the area of the stented vessel. Their symptoms were mild, and they were able to go home without assistance. Five patients were diagnosed as having experienced TIAAs as evidenced by mild upper arm weakness on the side opposite to the stented vessel. Their symptoms occurred during the 40-day period after the operation during which they were receiving dual antiplatelet therapy.
One additional case of cerebral infarction in the area of the stented vessel occurred on the 143rd postoperative day, 36 days after the number of antiplatelet agents was reduced from 2 to 1. This patient experienced mild ataxia and returned home without assistance. A single case of transient decreased visual acuity caused by branch retinal artery occlusion occurred on the 191st postoperative day, 49 days after antiplatelet therapy had been discontinued. In this case, the stent was placed in the ipsilateral internal carotid artery (ICA), and the origin of the ophthalmic artery was included in the region of stent placement (Table 1).

With respect to these 9 patients who developed postoperative ischemic events, we increased the number of antiplatelet agents in 4 cases, and in the other 5 cases, we kept the patients under strict observation with dual antiplatelet therapy. All the patients who experienced postoperative ischemic events were shifted to single antiplatelet therapy 3–13 months postoperatively. Importantly, no additional ischemic events have been reported in these patients (Figure 1).

We compared several indices between the group that experienced postoperative ischemic events (9 cases) and the remainder of the patient population that did not (34 cases). Notably, postoperative ischemic events occurred only in women, suggesting a significant effect of gender. There was no statistically significant differences between these groups in other parameters, i.e. age, presence or absence of hypertension and ischemic heart disease, neck size of the aneurysm, dome size of the aneurysm, proximal diameter of the parent artery, distal diameter of the parent artery, operation time, antiplatelet agents, and stent length (Table 2).
DISCUSSION

In this study, 77% of the postoperative ischemic events occurred within 40 days of the coil embolization under dual antiplatelet agents. One postoperative ischemic event occurred on the 143rd postoperative day under single antiplatelet therapy and another ischemic event occurred on the 191st postoperative day after discontinuation of antiplatelet therapy. All postoperative ischemic events occurred in the region of the stented vessel. Of the 9 cases in which postoperative ischemic events were observed, 4 had hypertension but none displayed any other cardiovascular risk factors; therefore, the cause of these ischemic events is likely to be thrombosis. Previous reports have indicated the onset time of postoperative ischemic events to be during the 6-month postoperative period (5, 11–13). Kanaan et al. reported that thrombotic events and stent stenosis or occlusion were found in 9 of 133 cases. These events occurred within 35 days of the operation in 6 of the 9 cases, and in 2 of the 6 cases, thrombotic events occurred 5 days after antiplatelet therapy had been reduced (5). Mocco et al. reported that delayed thrombotic events occurred in 3% of the cases, and these events were likewise associated with cessation of dual antiplatelet therapy (11). Rossen et al. reported that a 5% risk of ischemic events was found after a 6-week course of dual antiplatelet therapy (10). These results suggest that postoperative ischemic events are more likely to occur relatively soon after the operation and that the occurrence of postoperative ischemic events is directly influenced by antiplatelet therapy.

The anti-thrombotic property of stents is thought to be associated with neointima formation around the stent. The formation of neointima around the stent has been observed in animal experiments and angioscopic investigation of coronary arteries (14, 15). Asakura et al. observed that the neointima became thicker up until 6
months after stenting and then became thin over a 3-year period as revealed by
angioscopic investigation of coronary arteries. Moreover, luminal diameter was found
to be decreased at 3–6 months, but increased at 3 years after stenting as shown by
angiography (15). Changes in luminal diameter were also found in
intracranial stents for the treatment of intracranial aneurysm (16). This result suggests
that neointimal remodeling develops around stents placed in cerebral arteries for the
treatment of intracranial aneurysm in a similar manner as in stents implanted in
coronary arteries for the treatment of atherosclerotic lesions.

There is clearly good evidence that as neoendothelialization progresses, the
thrombogenicity of intracranial stents decreases over a period of weeks to months.
However, the optimal duration of dual antiplatelet therapy following intracranial stent
insertion has not yet been determined (10). The results of the present study suggest that
patients receiving stent-assisted coil embolization should be kept under strict
observation for at least 40 days after their operation even if they are receiving dual
antiplatelet therapy. Moreover, our finding that a single postoperative ischemic event
occurred 143 days postoperatively while the patient was under single antiplatelet
therapy provides a preliminary indication that dual antiplatelet therapy may be
recommended for at least 5 months after the operation. The postoperative ischemic
event that occurred 191 days postoperatively after antiplatelet therapy had been
discontinued supports our conviction that single antiplatelet therapy should continue for
more than 6 months after the procedure. Future ischemic events may be prevented by
increasing the number of antiplatelet agents; the number of antiplatelet agents can be
reduced later after the risk of recurrence of ischemic events has decreased.

In this study, 2 cases of postoperative ischemic events were found within 24 hours
after the procedure. These could be described as periprocedural ischemic events or operative complications. However, it is difficult to differentiate between periprocedural and early-postoperative ischemic events. We believe that the risk of periprocedural ischemic events may be associated with the number of antiplatelet agents administered during the perioperative period.

Based on our results, we would like to recommend the following revised antiplatelet agent regimen for intracranial stent-assisted coil embolization: triple antiplatelet therapy starting preoperatively until 6 weeks after the operation, followed by dual antiplatelet therapy up until 6 months postoperatively, and single antiplatelet therapy for the rest of the patient’s life.

Obviously, an important consideration is that the administration of multiple antiplatelet agents increases the risk of hemorrhagic events. The incidence of life-threatening hemorrhagic events was reported to be higher with aspirin and clopidogrel than with clopidogrel alone and bleeding complications were observed over time (8). The annual incidence of life-threatening and major bleeding events was reportedly 1.21% with single antiplatelet agent administration and 2% with dual antiplatelet agent administration (9). We, therefore, plan to continue our efforts to determine the ideal timing and dosing for antiplatelet therapy following stent-assisted treatment of intracranial aneurysm.

**Limitations**

Antiplatelet function was not tested by a monitoring system such as the VerifyNow Assay (Accumetrics, San Diego, CA); consequently, the postoperative ischemic events observed in this study might have occurred due to low response to antiplatelet agents. In
previous studies, the incidence of aspirin resistance was 8–45% (17), and the proportion of non-responders and low responders to clopidogrel was 28–55% (18). These numbers indicate that resistance to antiplatelet agents should always be taken into consideration in the case of ischemic events. False positives might result from antiplatelet insensitivity in this study. However, the majority of the postoperative stroke events occurred during dual antiplatelet therapy, and there were no statistically significant differences between the combinations of antiplatelet agents used in this study.

In this study, all the postoperative ischemic events occurred in women, resulting in a statistically significant difference for gender. Since we evaluated only 43 cases for postoperative ischemic events, it is quite possible that the statistical power of this study is insufficient to detect small differences.

In order to circumvent these limitations, we plan to use larger patient populations and to include monitoring of antiplatelet function as we continue our investigations.

**CONCLUSION**

Postoperative ischemic events are most likely to occur within 40 days postoperatively even when patients were receiving dual antiplatelet agents. Our results indicate that when postoperative events occur, future ischemic events may be prevented by increasing the number of antiplatelet agents, and that the patients can be shifted to single antiplatelet therapy later after the risk of recurrent ischemic events has decreased.

We aim to continue our investigations with our proposed antiplatelet agent regimen: triple antiplatelet therapy starting preoperatively until 6 weeks after the operation, followed by dual antiplatelet therapy until the 6-month postoperative time point, and
continuing single antiplatelet therapy throughout the patient’s life. We hope that these studies will help to optimize antiplatelet therapies for surgical patients at risk for ischemic events.

ACKNOWLEDGMENTS

We are grateful to Hidenori Yoshida, Hiromichi Oishi, Taichiro Mizokami, Hosei Eto, Ritsuro Inoue, Yasuyuki Nomoto, Kimiya Sakamoto, and Shuko Hamaguchi for their help with this study.
REFERENCES


Figure Legend

Figure 1. Onset time of postoperative ischemic events