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Delayed thromboembolic events more than 30 days after self expandable intracranial stent-assisted embolization of unruptured intracranial aneurysms

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ABSTRACT

Objective: The Enterprise stent is used for endovascular treatment of complex intracranial aneurysms. The purpose of this study was to evaluate delayed thromboembolic events (DTEs) that developed more than 30 days after Enterprise stent-assisted embolization (SAC) and its associated risk factors.
Methods: There were 125consecutive patients (90 women and 35 men; mean age, 56.1 years) who received endovascular treatment for126 complex intracranial aneurysms using the Enterprise stent during December 2008 to May 2011. A DTE was defined as a symptomatic or asymptomatic ischemic stroke with positive findings on brain magnetic resonance imaging in the territory of the treated aneurysm and transient ischemic attack. Asymptomatic in-stent stenosis and occlusion were excluded.
Results: During a mean follow-up of 32.4 months, DTEs occurred in 10 patients (7.93%). DTEs occurred on antiplatelet therapy (dual medication, $n=2$, 2 months after embolization; single medication, $n=6$, 10–20 months after SAC) or after discontinuation of antiplatelet therapy ($n=2$, 14 months after embolization). Multivariate analysis showed that current smoking ($p=0.005$) and maximum parent artery diameter >4.5 mm ($p=0.003$) were associated with DTE.
Conclusions: SAC with the Enterprise stent poses a considerable risk of DTE. Our results suggest that a longer duration of antiplatelet therapy and clinical follow-up may be warranted for cases with suggested risk factors. The protocol for antiplatelet therapy after SAC should be determined in a large prospective trial.

1. Introduction

Stent-assisted coil embolization (SAC) is increasingly being applied for wide-necked, blister type, and dissecting cerebral aneurysms. Neurovascular stents provide mechanical protection against coil protrusion into the parent artery [1,2] and create a mesh for neo-endothelialization. Such stents also divert blood flow from the aneurysm inflow zone and promote intra-aneurysmal stasis and thrombosis to reduce coil compaction [2].

The Enterprise stent was approved by the Food and Drug Administration for coil embolization of intracranial aneurysms with wide necks (≥4 mm) or poor dome-to-neck ratios (≤2) [3]. It has a fixed closed-cell design and shows a high rate of successful navigation, more accurate stent deployment, and low morbidity and mortality [4]. Long-term angiographic and clinical outcome data were also reported for the Enterprise stent. However, a major drawback of stent-assisted techniques is the propensity for acute and delayed thromboembolic events (DTE) [5]. The use of dual antiplatelet treatment (DAT) with aspirin (ASA) and clopidogrel (CLOPI) reduces the rate of symptomatic thromboembolic complications by counteracting platelet aggregation upon contact with the stent construct and also decreases direct shear-mediated platelet activation [6]. There are no established, unifying guidelines about antiplatelet medication; therefore, previous multicenter series with Neuroform (Boston Scientific/Target, Fremont, CA, USA) or Enterprise (Cordis Neurovascular/Johnson & Johnson, Bridgewater, NJ, USA) were performed using different antiplatelet protocols at different centers [4,5]. Recent data from the International Collaboration of

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Enterprise Stent-coiling registry demonstrate a correlation between the timing of cessation of DAT and DTE, highlighting the importance of continuing antiplatelet therapy in certain cases [3]. The purpose of this study was to report delayed thromboembolic complications that developed more than 30 days after Enterprise stent-assisted embolization and its associated risk factors at a single center.

2. Materials and methods

2.1. Patient selection

There were 151 consecutive patients with 152 aneurysms treated with stent-assisted embolization for intracranial aneurysms at Samsung Medical Center between December 2008 and April 2011. We included 143 patients who were treated with Enterprise stents. We excluded patients who were lost to follow-up within 30 days after treatment ($n=4$), had ruptured aneurysms ($n=7$), died of early rebleeding ($n=1$), experienced aneurysmal ruptures or vessel perforations during procedures ($n=2$), had moyamoya disease ($n=1$), or had another possible source of thromboembolism, such as heart disease ($n=2$) or malignancy ($n=1$). Data were collected from 125 patients (90 women and 35 men; mean age, 56.1 years) with 126 procedures. Patient age, sex, aneurysm location, and aneurysm size were retrospectively analyzed in addition to comorbid conditions, including smoking, hypertension, diabetes, dyslipidemia, and coronary artery disease. We also examined the use and duration of medications, including peri-procedural antiplatelet treatments. This study was approved by institutional review board at our center. The requirement to obtain written informed consent to participate in this study was waived.

2.2. Image assessment and follow up

In addition to standard cerebral angiography, three-dimensional rotational, digital subtraction angiography (3D-DSA) of the vessel bearing the aneurysm was acquired in all patients. Morphologic evaluation and measurements were performed from reconstructed 3D-DSA images. The D_{max} of the parent artery was defined as the maximal diameter of the stent-deployed segment internal carotid artery (ICA) and was measured using 2D-DSA images. The number and size of the Enterprise stent was also reviewed. Patients received diffusion-brain magnetic resonance imaging (MRI) and gadolinium-enhanced magnetic resonance angiography on the day after treatment to detect acute complications. Follow-ups occurred at 6 and/or 12 months after treatment and then annually thereafter to identify delayed thromboembolism or recanalization.

An acute thromboembolic event (ATE) was defined as any hyperintense signal change on a diffusion-weighted image, which was routinely taken within 24 h after SAC. A DTE was defined as a symptomatic and asymptomatic ischemic stroke with positive findings on brain MRI in the territory of the treated aneurysm or a transient ischemic attack (TIA) which occurred more than 30 days after SAC. Ischemic stroke was traditionally defined as a new focal neurological deficit of sudden onset that lasted at least 24 h and was not caused by hemorrhage. TIA was defined as an acute onset of a focal neurological deficit lasting less than 24 h. We only counted the DTEs which were occurred at the ipslateral side and were anatomically remote from the stent deployment site. We did not count as DTEs if the patient has another source of embolism after thorough stroke work up. In-stent restenosis (ISR), one of the major risk factors of thromboembolic event, was not included in the definition of DTE because only 37 patients were evaluated with catheter-based angiography. Clinical outcomes were assessed by a modified Rankin Scale.

2.3. Detailed procedure and anticoagulation/antiplatelet regimen

All procedures were performed under general anesthesia in a single stage. All coil embolizations were performed by using detachable bare platinum coils (GDC, Stryker Neurovascular, Fremont, Calif; MicroPlex, MicroVention, Aliso Viejo, Calif; Trufill-DCS, Cordis, Miami Lakes, Fla; Axium, Covidien, Irvine, Calif) coils and modified coils (Matrix, Stryker Neurovascular; Hydro-Coil, MicroVention; Hydrosoft, MicroVention). The stent was compatible with a 0.021-in. Prowler Plus microcatheter (Codman Neurovascular) and measured 4.5 mm in diameter with different stent lengths of 22, 28, and 37 mm. Some patients received multiple stents to treat multiple aneurysms, aneurysms requiring Y-shaped reconstruction, or suboptimal positioning of the original stent. Stent-assisted coiling was performed for 126 aneurysms. Three aneurysms were managed by stent placement alone. Multiple stents were applied for 11 aneurysms according to their morphology and location, including five aneurysms that received Y-stents.

Patients with unruptured aneurysms were premedicated with 100 mg of ASA and 75 mg of CLOPI daily for 5–7 days before the procedure or loaded with 300 mg of ASA and CLOPI the day before the procedure. Patients received heparin during the procedure to maintain an activated clotting time of 250–350 and continued for 24 h. After the procedure, dual antiplatelet therapy was provided with 100 mg ASA and 75 mg CLOPI for a period of six months (mean, range 1–12 months). And then mono-antiplatelet therapy (MAT) was administered with 100 mg of ASA or 75 mg of CLOPI for additional periods of time according to physician's decision (mean duration of MAT, 23.6 ± 14.5 months, range 1–54 months).

2.4. Statistical analysis

Values are reported as mean (SD) or number (percentage) of subjects. Baseline characteristics were compared for statistical differences using χ^2 tests for categorical variables and independent sample t test for continuous variables. Odds ratios were calculated using multivariate logistic regression analysis. Factors predictive of DTE in univariate analysis ($p<0.10$) were entered into a stepwise multivariate logistic regression analysis. The following variables were tested as predictors for DTE: age, sex, hypertension, diabetes, dyslipidemia, smoking, coronary artery disease, ATE, maximum diameter of parent artery, paraclinoid location, stent length, and total number of stents per person, which may be related to the prognosis of patients. Statistical significance was established at $p<0.05$. Statistical analyses were performed using the SPSS software for Windows, version 18.0.

3. Results

3.1. Onset time of delayed thromboembolic events and antiplatelet status

During a mean follow-up of 32.4 ± 5 months with 126 aneurysms, 10 DTEs occurred. Table 1 summarizes the clinical information and course of all 10 patients. Baseline characteristics were compared between two groups in Table 2. Two patients experienced DTEs within 6 months despite receiving DAT. Four patients developed DTEs after 6–12 months on MAT, and 4 patients showed DTEs more than 12 months after SAC (two were on MAT, and two temporarily discontinued medication). With respect to these 10 patients, we increased the number of antiplatelet drugs in six cases, changed to another drug in two patients, or maintained the medication with strict observation (Fig. 1). Patient 1 was on DAT and