Ultra-early endovascular embolization of ruptured cerebral aneurysm and the increased risk of hematoma growth unrelated to aneurysmal rebleeding

Clinical article

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Object. Hematoma growth unrelated to aneurysmal rebleeding is recognized as a somewhat common complication following endovascular embolization of ruptured aneurysms, but it is scarcely studied. The aim of this study is to elucidate the possible risk factors for this phenomenon.

Methods. Included in this study were 101 consecutive patients with subarachnoid hemorrhage (SAH) who underwent endovascular embolization for saccular aneurysms at the authors’ institution within 72 hours of symptom onset. All endovascular procedures were conducted under intraprocedural systemic anticoagulation. Age, sex, hypertension, type 2 diabetes, preoperative antplatelet or anticoagulation use, neurological grade, Fisher grade, location and size of the aneurysm, grade of aneurysm occlusion, and timing of the endovascular procedure were retrospectively analyzed to determine the risk factors for hematoma growth unrelated to aneurysmal rebleeding. To determine the clinical significance of this complication, the authors also investigated the risk factors for poor clinical outcome (modified Rankin Scale Scores 3–6 at 30 days after onset).

Results. This series included 32 men (31.7%) and 69 women (68.3%) with a mean age ± SD of 65.5 ± 14.0 years. The mean time from onset to endovascular procedure was 12.1 ± 4.0 hours. After the procedure, hematoma growth unrelated to aneurysmal rebleeding occurred in 14 patients (13.9%), 10 of whom required surgical removal of the hematoma and/or ventriculostomy to control intracranial pressure. All 14 patients had an anterior circulation aneurysm and had Fisher Grade 3 or 4 SAH. Ultra-early embolization (conducted within 6 hours after onset), female sex, history of hypertension, and poor neurological grade (World Federation of Neurosurgical Societies Grades IV and V) were significant risk factors for hematoma growth (p < 0.05 for all, univariate logistic analysis). In multivariate analysis, ultra-early embolization (OR 18.0 [95% CI 3.26–338], p < 0.001) and female sex (OR 9.83 [95% CI 1.73–187], p = 0.007) were independent risk factors for this phenomenon. Anterior circulation aneurysms and Fisher Grade 3 or 4 SAH were also revealed to be significant risk factors (p = 0.02 for each, chi-square test). Furthermore, hematoma growth without aneurysmal rebleeding was determined as an independent risk factor for poor clinical outcome by multivariate logistic analysis (OR 11.8 [95% CI 2.31–87.1], p = 0.002).

Conclusions. Ultra-early endovascular embolization for ruptured cerebral aneurysms under systemic anticoagulation increases the risk of growth of hematomas unrelated to aneurysmal rebleeding. It is important to recognize the risk of this complication and to either reduce the amount of heparin or to refer the patient for direct clipping if appropriate.

KEY WORDS • anticoagulation • complication • vascular disorders • endovascular embolization • hematoma growth • ruptured aneurysm • interventional neurosurgery

Endovascular embolization using detachable coils is widely accepted as a valuable therapeutic alternative to surgical clip placement for aneurysmal SAH.11 Several reports have suggested that early aggressive endovascular treatment of ruptured aneurysms improved patient outcomes, even in patients in poor neurological grades8,15,17,22 or in the presence of intracerebral hematoma.13 On the other hand, hematoma growth unrelated to aneurysmal rebleeding has been scarcely studied, but is recognized as a somewhat common complication in patients with aneurysmal SAH.21 Because the major concern for endovascular embolization of ruptured aneurysms is intra- or postoperative aneurysmal rebleeding, many previous reports have described postprocedural hematoma growth as aneurysmal rebleeding. However, in fact, hematoma growth that is unrelated to aneurysmal rebleeding may occur after successful endovascular procedures.2 The aim of this study was to determine the incidence and possible risk factors for this phenomenon.

Abbreviations used in this paper: ICA = internal carotid artery; ICH = intracerebral hematoma; MCA = middle cerebral artery; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.
Methods

Patient Selection and Neurological Evaluation

A prospectively maintained endovascular database at our institution was searched for patients who had undergone endovascular embolization for ruptured cerebral aneurysms within 72 hours after symptom onset between June 2004 and May 2011. Patients who underwent endovascular parent artery occlusion or who were treated in combination with craniotomy were excluded. Medical and surgical records were retrieved for 101 consecutive patients, and the retrieved data were analyzed retrospectively. Clinical condition was classified using the WFNS grading scale for SAH. We dichotomized the clinical condition before embolization into good (WFNS Grades I–III) and poor (WFNS Grades IV and V). Modified Rankin Scale scores were determined by physicians blinded to the patient’s history at 30 days after symptom onset. Scores of 0–2 were considered favorable outcomes, and scores of 3–6 were considered poor outcomes. Formal approval of the institutional ethics review board was not required because we considered poor outcomes. Formal approval of the institutional ethics review board was not required because we considered favorable outcomes, and scores of 3–6 were considered poor outcomes. Formal approval of the institutional ethics review board was not required because we considered favorable outcomes, and scores of 3–6 were considered poor outcomes.

Radiological Evaluation

All patients underwent CT scanning on admission soon after the endovascular procedure (first follow-up CT scanning study). Patients routinely underwent follow-up CT scanning (second follow-up CT scanning study); 2 patients died of initial brain damage due to a SAH before the second follow-up CT scanning study could be obtained. All CT images were analyzed independently for detection of hematoma growth by an independent neuroradiologist who was blinded to the patient’s history. Initial CT images were classified according to the Fisher CT grading system. Hematoma growth was defined as an increasing subarachnoid or intraparenchymal hematoma that appeared between the first and second follow-up CT scanning studies without clinical signs of aneurysmal rebleeding, such as neurological deterioration or changes in vital signs. Digital subtraction angiograms were retrospectively analyzed by an experienced interventional neuroradiologist for detail and occlusion grade of aneurysms. Occlusion grade after the endovascular treatment was classified as a complete occlusion, a neck remnant, or a residual aneurysm by using a modified Raymond scale. Procedure-related complications were defined as vascular perforations, arterial dissections, thromboembolic occlusions, or any other complications related to the endovascular procedure.

Routine Endovascular Procedure

The treatment method was selected according to the results of the International Subarachnoid Aneurysm Trial and patients with very small or wide-necked aneurysms, MCA aneurysms, or large ICHs were mostly referred for craniotomy. Diagnostic digital subtraction angiography and embolization were performed in an angiography suite (Axiom Artis BA, Siemens). Three-dimensional rotational angiography was used in all 101 patients to determine aneurysm shape. All endovascular procedures were performed under systemic anticoagulation by intravenous administration of heparin. We routinely used heparin with a bolus dose of 5000 U at the beginning of the endovascular procedure, followed by 1000 U at 1-hour intervals to maintain an activated clotting time around 250 seconds. All patients were admitted to the ICU and were closely observed with continuous monitoring of arterial blood pressure and electrocardiography for at least 72 hours after the procedure.

Statistical Analysis

All quantitative variables are expressed as the mean ± SD. Age, sex, hypertension, type 2 diabetes status, preoperative antiplatelet or anticoagulant use, neurological grade, Fisher grade, location and size of the aneurysm, the grade of aneurysm occlusion, and timing of endovascular procedure were analyzed to identify risk factors for hematoma growth. The retrieved clinical variables were interrogated using univariate/multivariate analysis to identify risk factors. Only variables with p < 0.20 in the univariate analysis were included in the multivariate logistic regression model-building process. Models were built using forward/backward stepwise logistic regression with variables entered into the model and removed at a 0.20 significance level. Probability values < 0.05 were considered statistically significant. The OR and 95% CI were also determined. Commercially available software (JMP 7 for Macintosh, SAS Institute, Inc.) was used for all statistical analysis.

Results

Baseline Characteristics of Patients and Details of Treated Aneurysms

Characteristics of patients and aneurysms are shown in Table 1. We analyzed data from 101 patients (32 men and 69 women) with a mean age of 65.5 ± 14.0 years (range 32–90 years) who underwent endovascular embolization within 72 hours of symptom onset. Among these 101 patients, 62 (61.4%) had a medical history of hypertension, 8 (7.9%) had type 2 diabetes, and 4 (4.0%) had taken oral antiplatelet or anticoagulant agents; 45 (44.6%) were classified in a poor neurological grade (WFNS Grades IV and V), and 85 (84.2%) had aneurysms that were scored as Fisher Grade 3 or 4 on the initial CT scan. The mean duration between symptom onset and embolization was 12.1 ± 14.0 hours, and ultra-early embolization (conducted within 6 hours after onset) was performed in 54 patients (53.5%). The mean durations from onset to the first and second follow-up CT scanning studies were 15.4 ± 16.6 and 61.4 ± 50.0 hours, respectively. The mean aneurysm size was 6.6 ± 3.4 mm; 84 aneurysms (83.2%) were located in the anterior circulation (ICA, anterior cerebral artery, and MCA), and 17 aneurysms (16.8%) were located in the posterior circulation (vertebrobasilar and posterior cerebral arteries).

Results of Embolization and Incidence of Hematoma Growth Unrelated to Aneurysmal Rebleeding

The clinical results of embolization are presented in Table 2. After the procedure, hematoma growth unrelated to aneurysmal rebleeding occurred in 14 patients (13.9%).
Hematoma growth after embolization of ruptured aneurysms

Two representative cases are shown in Figs. 1 and 2. At the end of the procedure, 47 aneurysms (46.5%) were classified as being completely occluded, 44 (43.6%) as having a neck remnant, and 10 (9.9%) as being a residual aneurysm. Procedure-related complications occurred in 10 patients (9.9%), and in 3 (3.0%) the complications were clinically significant (1 vascular perforation and 2 thromboembolic complications). Early rebleeding (within 30 days) from the embolized aneurysm occurred in 3 patients (3.0%). Favorable clinical outcome (mRS Scores 0–2 at 30 days after onset) was obtained in 55 patients (54.4%).

**Risk Factors for Hematoma Growth**

Table 3 shows the results of univariate analysis of risk factors for hematoma growth. All 14 patients who developed hematoma growth unrelated to aneurysmal rebleeding had an anterior circulation aneurysm and Fisher Grade 3 or 4 SAH. Univariate logistic analysis revealed that ultra-early embolization (conducted within 6 hours after onset) (OR 14.6 [95% CI 2.72–271], p < 0.001), female sex (OR 7.20 [95% CI 1.33–134], p = 0.02), history of hypertension (OR 4.44 [95% CI 1.12–29.6], p = 0.03), and poor neurological grade (WFNS Grades IV and V) (OR 3.71 [95% CI 1.14–14.4], p = 0.03) were significant risk factors for hematoma growth. Anterior circulation aneurysms and Fisher Grade 3 or 4 SAH were not suited for the logistic regression model but were found to be significant risk factors using the chi-square test (p = 0.02 for each). Type 2 diabetes, preoperative antiplatelet/anticoagulant use, aneurysm size, and aneurysm occlusion grade after the procedure were not significantly associated with this phenomenon. Multivariate analysis showed that ultra-early embolization (OR 18.0 [95% CI 3.26–338], p < 0.001) and female sex (OR 9.83 [95% CI 1.73–187], p = 0.007) were independent risk factors for this complication (Table 4).

**Clinical Significance of Hematoma Growth**

Among a total of 14 patients who developed hematoma growth, 10 (71.4%) required surgical removal of the hematoma and/or ventriculostomy to control intracranial pressure, and 11 (78.6%) had poor clinical outcome (mRS Scores 3–6 at 30 days after onset). To investigate the relationship between this phenomenon and clinical outcome, we also analyzed the risk factors for poor clinical outcome. In multivariate analysis, age (OR 1.11 [95% CI 1.05–1.18], p < 0.001), poor neurological grade (OR 10.8 [95% CI 3.39–42.0], p < 0.001), and hematoma growth unrelated to aneurysmal rebleeding (OR 11.8 [95% CI 2.31–87.1], p = 0.002) were determined to be independent risk factors for poor clinical outcome (Table 5).

**Discussion**

The present study demonstrated that hematoma growth unrelated to aneurysmal rebleeding was not a rare complication following embolization of a ruptured cerebral aneurysm (14 [13.9%] of 101). The population of the present study differed from that of previous stud-
ies of hemorrhagic complications after embolization of ruptured aneurysms in 2 major ways: the duration from onset to embolization was much shorter (mean 12.1 ± 14.0 hours), and the percentage of patients in a poor neurological grade was higher (44.6%). We hypothesize that these features of our patient group influenced the incidence of hematoma growth.

The major concern for endovascular embolization of ruptured aneurysms is intra- or postoperative aneurysmal rebleeding. Additionally, early cerebral angiography within 6 hours of onset may be linked to aneurysm re-rupture. Partly because of these reasons, most previous reports have described postprocedural hematoma growth as aneurysmal rebleeding. However, it is likely that hematoma growth unrelated to aneurysmal rebleeding occurs after successful endovascular procedures. The reported incidence of early rebleeding after coil embolization of ruptured cerebral aneurysms is 1.4%–3.6%. Initial occlusion grade, small aneurysms, and large aneurysms are considered to be the major relative factors that influence rebleeding from the embolized aneurysm. These risk factors for early aneurysmal rebleeding differ from those for hematoma growth determined in this study. It was also reported that contrast extravasation from aneurysms during initial CT angiography was occasionally observed in patients with hyperacute stages of SAH. However, in the present study, 7 of 14 patients who suffered hematoma growth underwent CT angiography on admission, and none of these 7 patients exhibited clinical signs of aneurysmal rebleeding. Interestingly, the enlarged hematoma was remote from the embolized aneurysm. This patient was treated conservatively, and her mRS score was 4 at 30 days after onset.

Ultra-early single-stage embolization followed by aggressive resuscitation for patients in poor neurological grades is considered a beneficial strategy to prevent aneurysmal rebleeding. In the present study, ultra-early embolization and the presence of dense SAH or ICH were
Hematoma growth after embolization of ruptured aneurysms

identified as risk factors for hematoma growth unrelated to rebleeding. A dense focal hematoma is often observed in patients with a poor-grade SAH. The thick subarachnoid hematoma compresses the pia mater and small vessels, thus disturbing the microcirculation of the pia mater. Pial injury in the cerebral cistern results in subpial extension of the subarachnoid hematoma; this destroys subpial capillary vessels, and minor bleeding from injured subpial vessels continues.18 Furthermore, van Asch et al.21 reported that expansion of ICH from a ruptured aneurysm without the sign of aneurysmal rebleeding is not rare within 48 hours after onset, and the authors speculated that the cause of hematoma expansion was bleeding from damaged vessels surrounding the hematoma. Hence, it is possible that ultra-early endovascular procedures with systemic anticoagulation before the complete hemostasis of injured vessels may promote hematoma growth.

Interestingly, female sex was identified as an independent risk factor for this phenomenon in the present study. Previous studies demonstrated that microvascular endothelial function was markedly influenced by estrogen and was improved by hormone replacement therapy in postmenopausal women.5 Aneurysmal SAH predominantly occurs in women around postmenopausal ages. Postmenopausal estrogen deficiency might be involved in the pathogenesis of vascular complications in women.20 In the present study, regrettably, we could not find a significant association between age and hematoma growth in female patients. The reasons why women are at higher risk for this phenomenon remain unclear. Further investigation would be necessary to answer these questions.

In this study, 10 (71.4%) of 14 patients who developed hematoma growth required surgical intervention, such as external ventricular drainage, decompressive craniectomy, and hematoma removal. Moreover, 11 (78.6%) of these 14 patients had poor clinical outcomes, and the complication was identified as an independent risk factor for a poor clinical outcome. Thus, care should be exercised when attempting ultra-early endovascular embolization in patients at higher risk for hematoma growth. A reduced bolus dose of heparin followed by smaller additional doses may be an alternative strategy for management of anticoagulation in these patients. Potentially, it may be better to refer the patient for direct clipping if appropriate.

Limitations of this study include its retrospective design, the lack of a control group, and the fact that patients were treated at a single institution. In addition, hematoma expansion is an early phenomenon observed in patients with aneurysmal SAH,21 and it may be an artifact of estimated risk factors in the present study. However, this is the first study that investigated the incidence of the phenomenon, and it is not a rare complication following endovascular embolization of ruptured cerebral aneurysms. Further investigation would be necessary to confirm the risk factors and identify causative mechanisms more precisely.

<table>
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<th>Variable (n = 101)</th>
<th>Hematoma Growth (n = 14)*</th>
<th>OR (95% CI)</th>
<th>p Value</th>
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<tr>
<td>mean age (yrs)</td>
<td>62.4 ± 13.4</td>
<td>0.98 (0.94–1.02)</td>
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<td>female sex</td>
<td>13 (92.9)</td>
<td>7.20 (1.33–134)</td>
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<td>hypertension</td>
<td>12 (85.7)</td>
<td>4.44 (1.12–29.6)</td>
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<td>type 2 diabetes</td>
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<td>0.88 (0.05–5.55)</td>
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<td>antiplatelet/anticoagulant use</td>
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<td>0.27†</td>
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<td>poor neurological grade (WFNS IV–V)</td>
<td>10 (71.4)</td>
<td>3.71 (1.14–14.4)</td>
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<tr>
<td>Fisher Grade 3 or 4</td>
<td>14 (100)</td>
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<td>ultra-early embolization</td>
<td>13 (92.9)</td>
<td>14.6 (2.72–271)</td>
<td>&lt;0.001</td>
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<td>mean aneurysm size (mm)</td>
<td>6.7 ± 2.6</td>
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<td>large aneurysm (&gt;12 mm)</td>
<td>1 (7.1)</td>
<td>0.75 (0.39–4.67)</td>
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<td>aneurysm location</td>
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<td>anterior circulation aneurysm</td>
<td>14 (100)</td>
<td>0.02†</td>
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<td>aneurysm occlusion grade</td>
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<td>residual aneurysm</td>
<td>1 (7.1)</td>
<td>0.67 (0.03–4.01)</td>
<td>0.70</td>
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</table>

* Data are presented as the mean ± SD or as the number of patients (%).
† Chi-square test.

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<th>p Value</th>
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<td>hematoma growth</td>
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TABLE 3: Univariate analysis of risk factors for hematoma growth

TABLE 4: Multivariate analysis of risk factors for poor clinical outcome
Conclusions

The results of this study suggest that the endovascular embolization for ruptured aneurysms that undergo systemic anticoagulation in ultra-early stages increases the risk of hematoma growth unrelated to aneurysmal rebleeding. In addition, female patients, those with anterior circulation aneurysms, and those presenting with dense focal SAH or ICH are at higher risk for the complication. Since this complication is not rare and is identified as an independent risk factor for poor prognosis, it is important to recognize the risks and either reduce the amount of heparin or refer the patient for direct clipping if appropriate.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Yoshimura, Egashira. Acquisition of data: Egashira, Enomoto, Ishiguro. Analysis and interpretation of data: Egashira, Enomoto, Asano. Drafting the article: Yoshimura, Egashira. Critically revising the article: all authors. Approved the final version of the manuscript on behalf of all authors: Yoshimura. Statistical analysis: Egashira. Administrative/technical/material support: Enomoto, Ishiguro. Study supervision: Yoshimura, Iwama.

References


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