Rebleeding risk after treatment of ruptured intracranial aneurysms

Clinical article


Department of Surgery, Division of Neurosurgery, University of Alabama, Birmingham, Alabama; Department of Neurosurgery, University of Florida, Gainesville, Florida; Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, Tennessee; and Department of Neurosurgery, University of Texas Southwestern Medical Center, Dallas, Texas

Object. Postprocedural rebleeding is a significant source of morbidity following endovascular treatment of ruptured intracranial aneurysms. Previous large-scale reports include the Cerebral Aneurysm Rerupture After Treatment trial, the International Subarachnoid Aneurysm Trial, and the study on Early Rebleeding after Coiling of Ruptured Cerebral Aneurysms, which reported nonprocedural rebleeding rates within 30 days of treatment of 2.7%, 1.9%, and 1.4%, respectively. However, coiling of intracranial aneurysms is in a state of continual change due to advancing device design and evolving techniques. These studies included only patients initially treated prior to 2004. In the present study the authors assess the most recent short-term results with endovascular treatment of ruptured aneurysms.

Methods. A multicenter retrospective chart review was conducted of patients undergoing endovascular treatment for ruptured intracranial aneurysms between July 2004 and October 2009. The technique used, including the use of stent or balloon assistance, was evaluated. Demographic and clinical factors, such as sex, age, initial clinical presentation, aneurysm size, aneurysm location, and modified Raymond Classification following initial treatment, were also evaluated and compared between the groups in which rebleeding did and did not occur.

Results. A total of 469 patients underwent endovascular treatment for a ruptured aneurysm; nonprocedural rehemorrhage occurred within 30 days of the initial coiling in 4 cases (0.9%). Two patients (50%) died after rehemorrhage. Stent-assisted coiling was used during the original treatment in 1 (25%) of the 4 patients with a rerupture. However, no technical, clinical, or demographic factors were found to be statistically significant in association with rebleeding.

Conclusions. Recent data suggest that the periprocedural rebleeding rate may be improving over time. (DOI: 10.3171/2011.1.JNS101232)

Key Words • coil embolization • intracranial aneurysm • subarachnoid hemorrhage • rerupture

Recurrent hemorrhage is an uncommon but significant threat after endovascular treatment of ruptured intracranial aneurysms. Several studies have evaluated postprocedural rebleeding in the acute phase. These studies only included patients treated prior to 2004. However, the endovascular treatment of aneurysms is in a state of continual change, with the development of new techniques and improved technology. The purpose of the present study was to assess the most recent short-term risk of rebleeding associated with endovascular treatment of ruptured intracranial aneurysms in light of more recently developed technology.

Abbreviations used in this paper: ACoA = anterior communicating artery; CARAT = Cerebral Aneurysm Rerupture After Treatment; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; SAH = subarachnoid hemorrhage.
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left a cohort of 469 patients for analysis. Devices included bare platinum coils and polymer-treated coils (Micrus Endovascular; Cordis; Boston Scientific; ev3, Inc.; and MicroVention, Inc.), liquid embolic agents (Onyx, ev3 Inc.), the Neuroform stent (Boston Scientific), and the Enterprise Vascular Reconstruction Device (Cordis). Stent-assisted and balloon-assisted techniques were used when they were deemed necessary by the treating physician.

The goal of the procedure was to achieve as complete an obliteration of the target aneurysm as possible while preserving flow through the parent artery. The degree of occlusion was determined by the operating neurointerventionalist at each of the institutions according to the modified Raymond Classification. Prior to initiating the study, our inclusion criteria defined rebleeding from a treated aneurysm as deterioration in clinical status within 30 days after treatment along with a CT scan that showed a new hemorrhage at the aneurysm site. There were no instances identified in which rebleeding occurred without clinical deterioration and no instances in which rebleeding occurred at a site remote from the aneurysm.

For statistical analysis, means, proportions, variances, and ranges were calculated for all variables. Two-sample t-tests were used to test for mean difference between participants on the continuous variables. To test for association between characteristics of those patients with repeated hemorrhage compared with none, chi-square tests were used on all nominal and ordinal variables, and the Fisher exact test was used when expected cell sizes were fewer than 5 data points. Multiple linear regression models were used to evaluate the impact of factors on rebleeding. All variables that were identified with p values less than or equal to 0.05 in the previous simple linear regression models were used to evaluate the impact of factors on rebleeding. All variables that were identified with p values less than or equal to 0.05 in the previous simple linear regression models were used to determine the conditional probability, but time/date variables were not captured in our dataset, and therefore logistic regression was performed to determine the likelihood of having a rerupture. Data analysis was conducted using SAS statistical software 9.2.

Results

The patient population consisted of 319 women (67%) and 150 men (32%) whose mean age was 51 years. At the time of treatment, the Hunt and Hess grade distribution was as follows: Grade I, 98 patients (21%); II, 94 (20%); III, 169 (36%); IV, 89 (19%); and V, 19 (4%). Aneurysm size was divided into 3 categories: 0–5 mm in 169 patients (36%); greater than 5–10 mm in 220 patients (47%); and greater than 10 mm in 80 patients (17%). Treated aneurysms were located in the following areas: vertebrobasilar region, 151 patients (32%); ACoA, 122 patients (26%); posterior communicating artery, 98 patients (21%); ICA, 61 patients (13%); MCA, 23 patients (5%); anterior cerebral artery, 9 patients (2%); and PCA, 5 patients (1%).

After initial treatment, 291 patients (62%) had complete occlusion of the target aneurysm, 136 (29%) had a residual neck, and 42 (9%) had aneurysm filling according to the modified Raymond Classification. Overall, 418 patients (89%) were treated primarily, without the use of balloons or stents; 28 (6%) were treated with stent assistance; and 23 (5%) were treated with balloon assistance. The incidence of early rebleeding of ruptured aneurysms was 0.9% (4 of 469 patients). Two (50%) of the 4 patients died. The characteristics of the patients with rebleeding are listed in Table 1. Analysis revealed that the likelihood of a rerupture given the technique and controlling for all covariates in the model was $p = 0.938$ (CI 0.174–5.028).

Case 1

One (25%) of the 4 patients in whom an early rerupture occurred, Case 1, underwent stent-assisted coiling. This patient was a 37-year-old woman with 2 lesions: a right MCA aneurysm measuring 4.5 mm in greatest dimension and a right ICA aneurysm (Fig. 1). She presented with a Hunt and Hess Grade IV SAH 2 days postictus. A CT scan showed a 2.5-cm right perisylvian intraparenchymal hemorrhage, and it was surmised that the MCA aneurysm had ruptured. Complete occlusion of both aneurysms was achieved, the MCA aneurysm requiring stent-assisted coiling. This patient suffered another rebleeding event 1 day after treatment, with an increase in the perisylvian hemorrhage to 4 cm. She subsequently underwent craniotomy and clipping of both aneurysms. She survived. This patient received dual antiplatelet therapy with aspirin and clopidogrel during and after the original procedure.

Case 2

This male patient presented with a bilobed aneurysm; only one of the lobes was coiled during the initial treatment. This 35-year-old man with a 12-mm ACoA aneurysm (Fig. 2) presented with a Hunt and Hess Grade V SAH 8 days postictus. He underwent coiling of a snowman-shaped aneurysm on the day he presented. Only the larger distal lobe could be coiled, and rebleeding occurred 21 days later. The patient was taken back for aneurysm recoiling, and he was found to have aneurysm recanalization, as well as a new pseudoaneurysm. This time the aneurysm was nearly completely coiled. Ten days following recoiling, rerupture occurred. A repeat angiogram showed superior migration of the existing coil mass with recanalization of the aneurysm. No further attempts at recoiling were made and the patient died that same day.

Case 3

This 65-year-old woman presented with a Hunt and Hess Grade IV SAH due to a 12-mm right MCA trifurcation aneurysm (Fig. 3). The initial CT scan showed SAH without an intraparenchymal clot. The patient was treated the same day as her ictal event, and at the completion of the coil therapy, she still harbored a residual aneurysm neck. Furthermore, she required a heparin drip overnight due to thromboembolic complications during the procedure. Rehemorrhage occurred the following day and the patient died.

Case 4

This 67-year-old woman presented with a Hunt and Hess Grade II SAH due to a 5 mm right P1–P2 junction
PCA aneurysm (Fig. 4). Initial CT scan revealed an SAH without an intraparenchymal clot. The aneurysm was coiled the day after the ictal event, and a residual aneurysm neck remained at the conclusion of the procedure. On postcoiling Day 17, the patient experienced a sudden worsening of her mental status, prompting a CT scan that showed a rehemorrhage. A repeated cerebral angiogram demonstrated that the lesion had expanded and was now approximately 12 mm in greatest dimension. The patient underwent endovascular sacrifice of the right PCA. A follow-up guide catheter–based angiogram showed no further filling of the aneurysm. The patient survived her rebleeding event.

**Discussion**

Previous studies have reported incidences of early rebleeding (within 30 days) ranging from 1.4% to 2.7%
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There has been a gradual downward trend in the early rebleeding rate over time. The rate of 0.9% found in the present study compares favorably with previous reports.

The results may be due to several factors. First, the devices used in the endovascular treatment of aneurysms are evolving continually. Since the introduction in 1991 of Guglielmi Detachable Coils for the treatment of intracra-
nial aneurysms, one has seen rapid advancement in this technology. In the former studies, only bare platinum detachable coils were used to treat ruptured aneurysms. In the present day, newer coil product lines include a wider array of sizes, shapes, and degrees of softness, which may translate into better initial coil-related results. In addition to these advancements, other strategies have been implemented to improve aneurysm sac fibrosis and decrease recanalization. In the present study, these included Cerecyte coils (containing a polymer coating that maintains initial packing volume and resists stretching), Matrix coils (containing a polymer coating that resists stretching), Hydrocoils (containing a polymer coating that promotes expansion after placement), and Onyx (liquid embolic agent).

A second potential reason for the decreased rerupture rate in our study is that the operating physicians may have become more experienced. There has been an evolution in treatment method selection favoring endovascular techniques over surgery for intracranial aneurysms since 2002. This affords more opportunities to practice the craft. In a study of complication rates associated with endovascular treatment of aneurysms, the rate of complications diminished significantly with operator experience.

Other studies have sought to identify risk factors for rebleeding after endovascular aneurysm treatment. In one study of 431 patients, independent risk factors for early rebleeding included aneurysm size less than 6 mm and adjacent hematoma on admission CT scan. In this report, all rebleeding events occurred within 16 days of initial treatment. In another study of early rebleeding, post-treatment aneurysm growth was most common in cases of sidewall aneurysms, and compaction occurred most frequently in bifurcation and termination types.

The CARAT study found that the degree of aneurysm occlusion after initial coiling is a strong predictor of the risk of subsequent rupture in patients presenting with SAH. In another study, the best long-term angiographic results were obtained for aneurysms with a narrow neck (< 4 mm), when the acutely ruptured aneurysm was treated within 15 days of ictus, and with ACoA and basilar tip aneurysms.

In the present study, a number of variables were evaluated to identify factors associated with early rerupture, and none was found to be significantly related to rerupture.

Stent therapy would be considered an advancement in endovascular aneurysm coiling because it allows the treatment of wide-necked aneurysms; 1 (25%) of the 4 patients with a rerupture underwent stent-assisted coiling. Only 6% of the total number of patients received this treatment. The patient survived the rerupture episode.

### Table 2: Comparison of rebleeding rates and cohort size in studies evaluating rebleeding of ruptured intracranial aneurysms after endovascular treatment within 30 days of treatment

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Study Enrollment Period</th>
<th>Rerupture Rate (%) within 30 Days of Initial Coiling</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARAT*</td>
<td>1996–1998</td>
<td>2.7</td>
<td>299</td>
</tr>
<tr>
<td>ISAT†</td>
<td>1994–2002</td>
<td>1.9</td>
<td>1073</td>
</tr>
<tr>
<td>Early Rebleeding Study‡</td>
<td>1994–2003</td>
<td>1.4</td>
<td>431</td>
</tr>
<tr>
<td>present study</td>
<td>2004–2009</td>
<td>0.9</td>
<td>469</td>
</tr>
</tbody>
</table>

* Reported by the CARAT Investigators, 2006.
† Reported by Molyneux et al., 2002.
‡ Reported by Sluzewski and van Rooij, 2005.
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treatment. Stent-assisted coiling of ruptured aneurysms, which requires dual antiplatelet therapy and thus poses greater anatomical and procedural complexity, may in fact increase the risk of rebleeding, although this finding did not reach statistical significance. Were the power of this study greater, stent-assisted coiling might have been a statistically significant risk factor for rebleeding.

Increased risk with stent-assisted coiling has been demonstrated in other studies. In a recent study by Piotin and colleagues, evaluating stent-assisted coiling in both ruptured and unruptured aneurysms, they found stent assistance to decrease the number of angiographic recurrences of aneurysms but increase the overall risk of lethal complications. They go on to note that the stent-treated aneurysms required more guidewire-exchange maneuvers compared with those not requiring a stent, which would allow greater opportunity for error.

Dual-antiplatelet therapy, necessary in cases of stent-assisted coiling, may contribute to rebleeding risk. In the present study, all patients treated with stent-assisted coiling were given aspirin and clopidogrel (Bristol-Myers Squibb/Sanofi Pharmaceuticals) during and after treatment. This regimen has been shown in prior studies to place the patient at greater risk of hemorrhagic complications from subsequent procedures.

In the present study, the distribution of aneurysms was based on size similar to that in the CARAT study. The authors of the CARAT study found the following distribution: aneurysms 0–5 mm, 38.3% of cases; greater than 5–10 mm, 46.8%; and greater than 10 mm, 14.9%. A similar distribution did not exist in the ISAT (51%, 41%, and 8%, respectively). These size categories were not used in the Early Rebleeding after Coiling of Ruptured Cerebral Aneurysms study and therefore could not be compared.

Infectious and dissecting aneurysms were excluded from the present study. There were 3 patients with SAH (1 with an infectious aneurysm and 2 with a dissecting aneurysm) who were not included for this reason. Infectious aneurysms are distinct from spontaneous aneurysms and are more friable. Dissecting aneurysms were excluded because they too are at higher risk of rerupture and are often not saccular; coil embolization is therefore frequently not feasible. For these reasons, dissecting aneurysms are often treated by endovascular sacrifice of the parent vessel. In comparison, the CARAT study excluded dissecting aneurysms. Neither the ISAT nor the study on Early Rebleeding After Coiling of Ruptured Cerebral Aneurysms specifically mentioned their treatment of dissecting or infectious aneurysms. However, the ISAT does mention that the aneurysms included in their study had to be judged by both the neurosurgeon and interventional neuroradiologist treating them to be suitable for either clipping or coiling based on angiographically demonstrated anatomy. This would have likely excluded both infectious and dissecting aneurysms from the study.

The morphology of some of the aneurysms in this series appears more favorable for initial clipping than coiling (for example, the patients in Cases 1 and 3 who had MCA aneurysms); however, embolization was chosen in Cases 1 and 3 because of the patients’ poor clinical status.

The limitations of this study are as follows. Although the data were culled from multiple institutions, the study is a retrospective chart review. This makes the comparison with prospective studies weaker. By nature of being a retrospective chart review, data were missing in some cases, limiting us to the variables analyzed in the study. A more comprehensive review would have included evaluation cases involving adjacent hematomas and comorbidities.

Rebleeding was defined as clinical deterioration in combination with a head CT scan that showed bleeding from the aneurysm site. It is possible that some patients may have experienced rebleeding, but this was not detected because it was not accompanied by a neurological change. This could have potentially increased the rerupture rate in the study.

In a similar manner, the patients removed from the study due to death from causes other than aneurysm re-rupture could have potentially gone on to rerupture within 30 days if they survived. Applying the same rate of rerupture as that found in this study, one could expect one additional rerupture in 111 patients. Therefore, if any one of these patients experienced a rerupture, the hemorrhage would significantly increase the rerupture rate found in this study, making it similar to or worse than the results of prior studies (1 additional rerupture in this study would raise the rate of rerupture to 1.1%).

Conclusions

The overall short-term rebleeding rate found in this study is consistent with previous reports. There is evidence to suggest a downward trend in early rerupture rates over the last decade and a half. Stent-assisted coiling may be associated with a higher rate of rerupture.

Disclosure

Dr. Hoh received an honorarium from Actelin Pharmaceuticals. Dr. Pride is a clinical proctor for Codman Neurovascular and ev3 Neurovascular. Dr. Purdy is a patent holder with Codman (Johnson & Johnson).

Author contributions to the study and manuscript preparation include the following. Conception and design: Fleming. Acquisition of data: Fleming, Hoh, Simon, Welch, Mericle, Fargen, Pride, Purdy. Analysis and interpretation of data: Fleming. Drafting the article: Fleming. Critically revising the article: Fleming, Hoh, Simon, Welch, Mericle. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Fleming, Shannon. Administrative/technical/material support: Fleming. Study supervision: Harrigan.

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Address correspondence to: Mark R. Harrigan, M.D., 1530 3rd Avenue South, Birmingham, Alabama 35294-3410. email: mharrigan@uabmc.edu.