Rescue Treatment of Thromboembolic Complications During Endovascular Treatment of Cerebral Aneurysms

Waleed Brinjikji, MD; Jennifer S. McDonald, PhD; David F. Kallmes, MD; Harry J. Cloft, MD, PhD

Background and Purpose—Acute intraprocedural thrombus formation complicating endovascular cerebral aneurysm treatment is often treated with intra-arterial or intravenous administration of thrombolytic agents or glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors. We sought to evaluate the morbidity and mortality associated with such treatments using a large multihospital database.

Methods—Using the Premier Perspective Database, we examined outcomes for patients receiving endovascular coiling for ruptured and unruptured aneurysms requiring rescue therapy, defined as treatment with GpIIb/IIIa inhibitors and fibrinolytics. We compared discharge status, length of stay, and complication rates across 3 groups: (1) patients receiving GpIIb/IIIa inhibitors only, (2) patients receiving fibrinolytic therapy only, and (3) patients receiving both GpIIb/IIIa inhibitors and fibrinolytics. Student t test was used to compare continuous variables, and Fisher exact test was used to compare categorical variables.

Results—Seven-percent (254/3627) of patients treated for unruptured aneurysms received rescue therapy. When compared with patients receiving GpIIb/IIIa inhibitors alone, patients receiving only fibrinolytics had significantly higher rates of discharge to institutions other than home (37.5% [9/24] versus 7.4% [15/201]; P<0.0001). Eight-percent of patients (338/4204) treated for ruptured aneurysms received rescue therapy. When compared with patients receiving GpIIb/IIIa inhibitors alone, patients receiving only fibrinolytics had significantly higher rates of mortality (26.0% [18/69] versus 14.5% [35/241]; P=0.02) and discharge to institutions other than home (59.4% [41/69] versus 36.5% [88/241]; P<0.0001).

Conclusions—Pharmacological rescue therapy occurred in 7% to 8% of endovascular coiling patients with unruptured and ruptured intracranial aneurysms. Rescue therapy with thrombolytic agents resulted in significantly more morbidity and mortality than rescue therapy with GpIIb/IIIa inhibitors. (Stroke. 2013;44:1343-1347.)

Key Words: endovascular treatment ■ interventional neuroradiology ■ outcomes ■ subarachnoid hemorrhage

Periprocedural thromboembolic complications from endovascular treatment of intracranial aneurysms are estimated to occur in ≈2% to 15% of patients.1 Aggressive treatment of acute intraprocedural thrombus formation with intra-arterial or intravenous administration of fibrinolytics or glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors has become a standard treatment for these complications. Recanalization of the treated artery is usually essential to avoid permanent neurological deficit. Many studies have demonstrated benefit from the intraprocedural administration of GpIIb/IIIa inhibitors and thrombolytic agents during endovascular treatment of intracranial aneurysms. However, the real-world outcomes of patients requiring such treatments are not well known. Using a large multihospital database, we sought to determine the periprocedural morbidity and mortality of patients requiring rescue therapy (ie, intraprocedural administration of GpIIb/IIIa inhibitors or thrombolytic agents) during endovascular treatment of intracranial aneurysms.

Methods

Study Population and Data Retrieval

The Premier Perspective database is a voluntary, fee-supported collection of data developed by Premier, Inc. to assess quality and resource use. As of 2011, the Perspective database consisted of ≈15% of hospitalizations nationwide and represented >600 US hospitals. Detailed information of a patient’s hospitalization, including patient demographics, hospital information, diagnoses, procedures, discharge status, and all billed items are recorded. Patients who presented with a ruptured aneurysm (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM] diagnostic code 430) or unruptured aneurysm (ICD-9-CM code 437.3 without concurrent diagnostic code 430) from November 2005 through December 2011 were identified. Patients were included if they underwent aneurysmal coiling (ICD-9 procedural codes 39.52 [other repair of aneurysm], 39.72 [endovascular repair of occlusion of head and neck vessels], 39.75 [endovascular embolization or occlusion of vessel(s) of head or neck using bare coils], 39.76 [endovascular embolization or occlusion of vessel(s) of head or neck using bioactive coils], or 39.79 [other endovascular repair (of aneurysm) of other vessels]) during hospitalization. Patients who received a stent during the coiling procedure were similarly identified using billing information.

Received December 27, 2012; accepted February 20, 2013.

From the Department of Radiology (W.B., J.S.McD., D.F.K., H.J.C.) and Department of Neurosurgery (D.F.K., H.J.C.), Mayo Clinic, Rochester, MN.

Correspondence to Waleed Brinjikji, MD, Mayo Clinic Department of Radiology, 200 SW First St, Rochester, MN 55905. E-mail brinjikji.waleed@mayo.edu

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.000628
Patients with ruptured and unruptured aneurysm who received rescue therapy were identified using billing records. GpIIb/IIIa therapy or fibrinolytic rescue therapy was included only if they were administered on the day of or the day after the coiling procedure. Antiplatelet rescue therapy was defined as administration of Abciximab (ReoPro), Eptifibatide (Integrillin), or Tirofiban (Aggrastat). Fibrinolytic rescue therapy was defined as administration of Alteplase (Activase), Reteplase (Retavase), Tenecteplase (Tnkase), or Urokinase (Abbokinase).

We compared demographics and outcomes from patients with unruptured aneurysm and patients with subarachnoid hemorrhage separately. For each patient population, we compared outcomes across 3 groups: (1) patients receiving GpIIb/IIIa inhibitors only, (2) patients receiving fibrinolytic therapy only, and (3) patients receiving both GpIIb/IIIa inhibitors and fibrinolytics. The following demographic variables were compared: (1) age, (2) sex, (3) hospital location (urban versus rural), (4) hospital teaching status, and (5) stent-assisted coiling rates. The following outcomes were compared: (1) discharge status (mortality, discharge to institution other than home, discharge to home/home care); (2) length of stay; and rates of (3) aphasia, (4) hemiparesis, (5) postoperative neurological complications, and (6) ventriculostomy. Discharge to institutions other than home was used as an indicator of morbidity. Hemorrhage rates were compared for the unruptured aneurysm group only.

Statistics

Data were extracted from the Perspective database using SAS (SAS, version 9.3; SAS Institute, Cary, NC) and analyzed using JMP (version 9, SAS Institute, Cary, NC). Continuous results are presented as mean (SD). Categorical results are presented as percentage. Comparison of continuous results was performed using the Student t test. Comparison of categorical results was performed using Fisher exact test. The group of patients receiving GpIIb/IIIa inhibitors only was the reference for statistical analysis.

Results

Unruptured Aneurysm Group

A total of 3627 patients in the Premier Perspective database received endovascular therapy for treatment of unruptured aneurysm. Of which, 254 patients (7.0%) received rescue therapy with GpIIb/IIIa inhibitor and thrombolytic agents; 202 patients (5.6%) received GpIIb/IIIa inhibitor rescue therapy; 24 patients (0.7%) received fibrinolytic therapy; and 28 patients (0.8%) received both fibrinolytic and GpIIb/IIIa inhibitor rescue therapy. The demographic characteristics of these patients are summarized in Table 1.

Patients receiving GpIIb/IIIa inhibitors had significantly better outcomes compared with the fibrinolytic group. GpIIb/IIIa inhibitor patients had significantly higher rates of discharge to home/home care compared with patients receiving fibrinolytic therapy (90.6%, 183/202 versus 58.3%, 14/24, respectively; \(P<0.0001\)). There was a trend for GpIIb/IIIa inhibitor patients to have higher rates of discharge to home/home care facilities compared with the combination therapy group (90.6%, 183/202 versus 78.6%, 22/28, respectively; \(P=0.06\)). GpIIb/IIIa inhibitor patients had decreased rates of aphasia compared with the fibrinolytic therapy group (1.5%, 3/202 versus 8.3%, 2/24, respectively; \(P=0.03\)). Compared with patients receiving combination therapy, patients receiving GpIIb/IIIa inhibitors had decreased rates of hemorrhage (2.0%, 4/202 versus 10.7%, 3/28, respectively; \(P=0.01\)). These data are summarized in Table 2.
Table 3. Demographics of Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>GpIIb/IIIa Inhibitors Only</th>
<th>Fibrinolytic Only</th>
<th>P Value</th>
<th>Both</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>241 (5.7)</td>
<td>69 (1.6)</td>
<td>…</td>
<td>28 (0.7)</td>
<td>…</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>54.2 (11.5)</td>
<td>56.7 (11.8)</td>
<td>0.12</td>
<td>54.3 (13.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>178 (73.9)</td>
<td>45 (65.2)</td>
<td>0.16</td>
<td>16 (57.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Urban hospital, N (%)</td>
<td>240 (99.6)</td>
<td>68 (98.6)</td>
<td>0.34</td>
<td>27 (96.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Teaching hospital, N (%)</td>
<td>121 (50.2)</td>
<td>26 (37.7)</td>
<td>0.07</td>
<td>12 (42.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Stenting, N (%)</td>
<td>7 (2.9)</td>
<td>0 (0.0)</td>
<td>0.15</td>
<td>0 (0.0)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

GpIIb/IIIa indicates glycoprotein IIb/IIIa.

Ruptured Aneurysm Group

A total of 4204 patients received endovascular therapy for treatment of ruptured intracranial aneurysm. Of which, 338 patients (8.0%) received GpIIb/IIIa inhibitor and thrombolytic rescue therapy; 241 patients (5.7%) received GpIIb/IIIa inhibitor therapy only; 69 patients (1.6%) received fibrinolytic therapy only; and 28 patients (0.7%) received a combination of GpIIb/IIIa inhibitor and fibrinolytic therapy. The demographic characteristics of these patients are summarized in Table 3.

Patients receiving GpIIb/IIIa inhibitors had significantly better outcomes compared with the fibrinolytic group. GpIIb/IIIa inhibitor patients had significantly higher rates of discharge to home/home care (49.0%, 118/241 versus 14.5%, 10/69, respectively; \(P<0.0001\)) and significantly lower rates of discharge to institutions other than home (36.5%, 88/241 versus 59.4%, 41/69, respectively; \(P<0.001\)) and mortality (14.5%, 35/241 versus 26.0%, 18/69, respectively; \(P=0.03\)). GpIIb/IIIa inhibitor patients had significantly higher rates of discharge to home/home care compared with the combination therapy group (49.0%, 118/241 versus 25.0%, 7/28, respectively; \(P=0.02\)). They also had significantly lower rates of aphasia (8.3%, 20/241 versus 25.0%, 7/28, respectively; \(P=0.005\)). These data are summarized in Table 4.

Discussion

Using a large administrative database, we demonstrated that \(\approx7%\) to 8% of patients who underwent endovascular treatment of unruptured or ruptured intracranial aneurysms received rescue therapy with intraprocedural administration of either GpIIb/IIIa inhibitor agents or thrombolytic agents. GpIIb/IIIa inhibitors were used at much higher rates than thrombolytics. Notably, outcomes for patients with both unruptured and ruptured aneurysms, on the basis of numerous outcomes, including discharge status, aphasia, and other complications, were significantly better for patients receiving GpIIb/IIIa inhibitors than those treated with fibrinolytic agents. These data should prompt practitioners to avoid fibrinolytics in place of GpIIb/IIIa agents for rescue therapy during coil embolization of both ruptured and unruptured aneurysms.

In most case series, the rate of rescue therapy for thromboembolic complications ranges between 5% and 10%.1–14 The infarction rate among patients receiving rescue therapy ranges between 10% and 40% with higher rates generally seen in studies with postoperative MR imaging.1–14 In a series of 477 patients with 515 intracranial aneurysms, Ries et al1 reported that 48 patients (10%) had thromboembolic events; 42 of these patients received rescue therapy with GpIIb/IIIa inhibitors, and 1 patient received rescue therapy with recombinant tissue plasminogen activator. Of the patients who did not receive rescue therapy, 3/5 had infarcts, whereas 31% of patients receiving GpIIb/IIIa inhibitor rescue therapy had infarction on computed tomography. Linfante et al10 demonstrated that \(\approx10%\) of patients undergoing endovascular embolization of intracranial aneurysms required intra-arterial GpIIb/IIIa inhibitor rescue therapy with an infarct and hemorrhage rate of 0%. Many previous studies that have demonstrated high-infarct rates on postoperative imaging also highlight the fact that many of these infarcts are clinically silent.1,2,9 We cannot evaluate infarct rates or success of recanalization with thrombolytic agents versus GpIIb/IIIa inhibitors in this study, but better outcomes suggest that GpIIb/IIIa inhibitors are a better option for rescue therapy.15,16

Table 4. Outcomes of Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>GpIIb/IIIa Inhibitors Only</th>
<th>Fibrinolytic Only</th>
<th>P Value</th>
<th>Both</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>35 (14.5)</td>
<td>18 (26.0)</td>
<td>0.02</td>
<td>7 (25.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Discharge home/home care</td>
<td>118 (49.0)</td>
<td>10 (14.5)</td>
<td>&lt;0.0001</td>
<td>7 (25.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Discharge to institution other than home</td>
<td>88 (36.5)</td>
<td>41 (59.4)</td>
<td>0.0007</td>
<td>14 (50.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean (SD) length of stay in days</td>
<td>15.4 (13.9)</td>
<td>22.9 (15.9)</td>
<td>0.0006</td>
<td>14.4 (8.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Aphasia</td>
<td>20 (8.3)</td>
<td>10 (14.5)</td>
<td>0.12</td>
<td>7 (25.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>43 (17.8)</td>
<td>15 (21.7)</td>
<td>0.46</td>
<td>5 (17.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Postoperative neurological complications</td>
<td>23 (9.5)</td>
<td>3 (4.4)</td>
<td>0.17</td>
<td>6 (21.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ventriculostomy</td>
<td>74 (30.7)</td>
<td>44 (63.8)</td>
<td>&lt;0.0001</td>
<td>10 (35.7)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

GpIIb/IIIa indicates glycoprotein IIb/IIIa.
The use of GpIIb/IIIa inhibitors in patients with ruptured aneurysms has been reported to be relatively safe with most series reporting intracranial hemorrhage rates of <10%.1–3,7–10,12 Aviv et al3 reported 13 patients with ruptured aneurysm treated with abciximab rescue therapy and only 1 hemorrhagic complication. Aggour et al2 included 11 patients with ruptured aneurysm in their abciximab rescue series without hemorrhagic complication. Park et al12 reported hemorrhagic complications in 3 of 16 patients with ruptured cerebral aneurysms treated with abciximab rescue therapy. On the other hand, the literature has shown that rescue therapy with thrombolytic agents in patients with ruptured aneurysms is associated with a very high mortality. In a series reported by Cronqvist et al17 of 19 patients undergoing rescue therapy with urokinase, 3 had intracranial bleeding complications. In the International Subarachnoid Aneurysm Trial (ISAT), 5 patients had thromboembolic complications treated with thrombolytic agents, and all 5 died from rebleeding of their ruptured aneurysms.18 Catastrophic hemorrhage has also been reported with rescue using thrombolytic agents in setting of unruptured aneurysm.19 There are few reports on rescue therapy with thrombolytic agents,15–19 perhaps because their use has been largely replaced by GpIIbIIIa inhibitors. Despite these past reports, our study shows that thrombolytic agents continue to be used. Our data confirm the higher risk of morbidity and mortality of thrombolytic agents relative to GpIIbIIIa inhibitors, and might help to discourage continued use of thrombolytic agents for rescue therapy, especially in the setting of subarachnoid hemorrhage.

Limitations

Our study has limitations. Using this database, we are unable to determine whether some patients had intraprocedural thrombus formation and did not receive rescue therapy. Thus, we are unable to compare outcomes between treatment and nontreatment groups. Furthermore, we are unable to determine whether patients with subarachnoid hemorrhage had further bleeding as a result of rescue therapy. Thus, the bleeding rate can only be obtained for patients presenting with unruptured aneurysm. This database does not offer any data on presenting condition and aneurysm geometric features (aspect and dome-to-neck ratio), size, or location. Thus, we are unable to correlate our outcomes with the anatomic features of the treated aneurysm. We are unable to assess whether the rescue agent was given by intra-arterial or intravenous route. Some patients may have received GpIIbIIIa inhibitors for prophylaxis of thromboembolism, but this should be relatively uncommon, as it is not standard practice and would be contraindicated with subarachnoid hemorrhage. Coding inaccuracies can affect the accuracy of any administrative database, including the Premier Perspective database.

Conclusions

Using a large administrative database, we demonstrated an intraprocedural rescue therapy rate of ≈7% to 8% for endovascular coiling patients with unruptured and ruptured intracranial aneurysms. Rescue therapy with thrombolytic agents resulted in significantly more morbidity and mortality than rescue therapy with GpIIbIIIa inhibitors.
Disclosures
Dr Cloft is the Site PI at enrolling site for Stenting and Angioplasty with Protection in Patients and High Risk for Endarctectomy registry sponsored by Cordis Endovascular. Dr Kallmes has received grant and ev3-funding for clinical trials and preclinical research, and has received grants and has grants pending from Penumbra, MicroVention, Micrus, Cordis. The other authors have no conflicts to report.

References
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Stroke. 2013;44:1343-1347; originally published online April 18, 2013;
doi: 10.1161/STROKEAHA.111.000628

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