Intravenous Administration of Acetylsalicylic Acid During Endovascular Treatment of Cerebral Aneurysms Reduces the Rate of Thromboembolic Events

Thorsten Ries, MD; Jan-Hendrik Buhk, MD; Thomas Kucinski, MD; Einar Goebell, MD; Ulrich Grzyska, MD; Hermann Zeumer, MD; Jens Fiehler, MD

Background and Purpose—The purpose of this study is to analyze the effect of a modified intraoperative anticoagulation strategy including acetylsalicylic acid (ASA) on complication rates during endovascular coil embolization.

Methods—Two hundred and sixty-one cerebral aneurysms were treated in 247 patients by endovascular coil embolization from January 2001 to September 2004. Additional intravenous administration of 250 mg ASA was applied since January 2003. Patients treated before (−ASA; n=102 aneurysms) and after that date (+ASA; n=159 aneurysms) were compared. End points were rates of thromboembolism and severity of hemorrhages after intraoperative aneurysm rupture.

Results—Thromboembolic events during the procedure were observed more often in the −ASA group (18/102 aneurysms, 17.6%) in comparison with the +ASA group (14/159 aneurysms, 8.8%; P=0.028; Fisher exact test). Aneurysm perforation events occurring during or immediately after the procedure were observed equally often in the −ASA group (7/102 aneurysms, 6.9%) in comparison with the +ASA group (10/159 aneurysms, 6.3%).

Conclusion—Intravenous application of ASA is feasible and safe during interventional aneurysm embolization. ASA seems to be associated with a significant reduction in the rate of thromboembolic events without increase in the rate or severity of intraoperative bleedings. (Stroke. 2006;37:1816-1821.)

Key Words: anticoagulants ■ aspirin ■ cerebral aneurysm ■ embolism ■ rupture ■ subarachnoid hemorrhage
TABLE 1. Initial Anticoagulation Strategy Until January 2003 (−ASA)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ruptured</th>
<th>Unruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premedication</td>
<td>Acute Treatment</td>
</tr>
<tr>
<td>Low-molecular-</td>
<td>40 mg SC on day before intervention</td>
<td>40 mg SC on day of intervention</td>
</tr>
<tr>
<td>weight heparin</td>
<td>20 mg SC on day of intervention</td>
<td>20 mg SC on day of intervention</td>
</tr>
<tr>
<td>Heparin</td>
<td>ACT 250–300 s before guiding-catheter</td>
<td>ACT 250–300 s before guiding-catheter</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time.

was not applied. Patients were categorized in all cases based on treatment date before or after January 2003 as −ASA and +ASA on an intention-to-treat basis. The initial and modified anticoagulation strategies are specified in Tables 1 and 2.

Definition of Clotting and Perforation

A thromboembolic event was angiographically defined as any event with complete or partial occlusion of arteries in any vascular territory. Aneurysm perforation was assumed in case of any amount of contrast agent extravasation with or without any clinical impact.

Data Analysis

The patients treated with intraoperative ASA administration (+ASA, n=159) and without intraoperative ASA administration (−ASA, n=102) were compared with regard to thromboembolic and perforation events. Furthermore, we analyzed clinical presentation, morphological findings, and clinical outcome. Statistical analysis was performed using SPSS10.07. Fischer exact test was used for comparison of the rate of incidents. The significance level was defined as P<0.05.

Results

Two hundred and sixty-one aneurysms were treated with Guglielmi detachable coils in 247 patients (195 women, 52 men). The median age of the patients was 52 (20 to 80) years. We observed clotting in 67/77 (7.7%) of the patients with unruptured aneurysms and in 26/184 (13.3%) in patients with subarachnoid hemorrhage (SAH). Intraprocedural aneurysm perforation occurred in 2/77 (2.6%) of the patients with unruptured aneurysms and in 15/184 (8.2%) in patients with SAH.

Before modification of anticoagulation regimen, we treated 102 aneurysms (−ASA group) and after introduction of ASA 159 aneurysms (+ASA group). The rate of unruptured aneurysms was 27/102 patients (26.5%) in the −ASA group and 50/159 (31.4%) patients in the +ASA group. Among SAH patients there was no significant difference in the rate of poor initial Hunt & Hess grades (4 and 5) between the groups: 48.6% (−ASA group) versus 40.5% (+ASA group).

There were also no significant differences between −ASA and +ASA regarding the aneurysm sizes and localizations. We treated 41%/49% (−ASA+/ASA) aneurysms <6 mm, 53%/45% aneurysms 6 to 15 mm, and 6%/5% aneurysms 15 to 25 mm. Aneurysm localizations were internal carotid artery 17%/26% (−ASA+/ASA), middle cerebral artery 6%/5%, anterior cerebral artery 34%/38%, posterior communicating artery 12%/10%, posterior cerebral artery (P2) 1%/0%, basilar artery 19%/13%, basilar tip 7%/4%, vertebral artery 2%/1%, and posterior inferior cerebellar artery 3%/3%.

Thromboembolic Events

Thromboembolic events occurring during or immediately after the procedure were observed more often in the −ASA group (18/102 patients, 17.6%) in comparison with the +ASA group (14/159 patients, 8.8%; P=0.028). In a separate analysis of patients with ruptured aneurysms we found fewer (P=0.047) thromboembolic events in the +ASA group (11/109 patients, 10.1%) in comparison with the −ASA group (15/75 patients, 20.0%). In patients with unruptured aneurysms we observed an unequivocal trend (not significant) toward fewer patients with thromboembolism in the +ASA group (3/50 patients, 6.0%) in comparison with the −ASA group (2/27 patients, 11.1%). For illustrations and numbers see the Figure.

After occurrence of embolism we intra-arterially applied GPIIb/IIIa antagonists (ReoPro) in 10 patients and tissue plasminogen activator (tPA) in 4 patients (Actilyse). No thrombolytic therapy was applied in cases of incomplete vessel narrowing, spontaneously resolving thrombi, good collateralization, and very peripheral location of the embolus and in cases of concomitant hemorrhage (Table 3). An infarct in the corresponding vascular territory was found on follow-up CT in 17/32 (47.2%) of the patients. In 1 case no follow-up CT was performed. There was no difference in outcome in case of a thromboembolism between both groups. Good outcome (Glasgow Outcome Scale 4 or 5) was observed in 10/18 (56%) of the patients in the −ASA group and 8/14 (57%) of the patients in the +ASA group.

Aneurysm Perforation

Intraprocedural aneurysm perforation events were observed equally often in both groups: 7/102 patients in the −ASA group (6.9%) versus 10/159 patients in the +ASA group (6.3%). A perforation was recorded before or during the first coil in 7/71 patients (41%) and, therefore, without intraoperative application of ASA even in the +ASA group (Table 4).
Two of these 7 patients had unruptured aneurysms (+ASA group) and had received clopidogrel preoperatively (Table 2).

There were no differences in outcome after perforation between the −ASA and the +ASA group. Good outcome was observed in 3/7 of the patients in the −ASA group and 5/10 of patients in the +ASA group. The mortality rate after intraoperative aneurysm perforation was 2/7 in the −ASA group and 4/10 of the patients in the +ASA group. Among surviving patients, there was no difference in outcome after intraoperative aneurysm perforation between both groups (Table 4).

Discussion

We found a decrease in the rate of thromboembolic events without an increase of the intraoperative bleeding rate after introduction of intraoperative ASA application. In cases of parent vessel or aneurysm perforation, we found no evidence for a different outcome after ASA application.

Current Standards in Anticoagulation/Antiplatelet Strategy

Because of the absence of evidence-based data, the guidelines of several neuroradiological and neurointerventional societies state that anticoagulant therapy for patients with cerebral aneurysms should be at the discretion of the endovascular therapist.10 There seems to be fundamental agreement among institutions about the usage of heparin during aneurysm embolization because reported anticoagulation strategies are similar.11,12,8,13 This is somewhat supported by a review comparing observational series with and without administration of heparin or ASA after the procedure which showed a lower rate of thromboembolic complications when heparin or ASA was used.14 Furthermore, a meta-analysis did not confirm an increase in morbidity and mortality rates after intraprocedural perforation in heparinized patients in comparison to patients without heparin.15

Pathophysiology of Thromboembolism and ASA

Thromboembolism during endovascular embolization of cerebral aneurysms may result from acute clotting originating from arterial catheters, contrast agents, implanted devices such as coils and stents and mobilization of thrombus from within the aneurysm which may lead to distal embolism. Intraoperative thrombosis of the parent artery probably primarily develops at the interface of coils attributable to platelet aggregation. Anticoagulation using heparin has primarily antithrombotic effects through its activity on several coagulation factors and shows minor platelet effects, whereas ASA shows strong and irreversible blocking of the platelet aggregation. As compared with conventional anticoagulant therapy, combined antiplatelet therapy after the placement of coronary-artery stents reduces the incidence of cardiac events and vascular complications.16 The different action of ASA might have an additive effect on coagulation to heparin alone in endovascular therapy. Our data support this hypothesis: administration of ASA in addition to heparin seems to reduce the rate of thromboembolic events.

SAH patients who had salicylates on admission revealed a reduced risk of cerebral infarction compared with those without salicylates.17 Patients who had already used ASA before SAH and continued these medication after SAH revealed an increased risk for rebleeding.17 It has been suggested by a recent meta-analysis that ASA can prevent delayed cerebral ischemia after SAH with only modest effects on the rate of intracranial hemorrhage.18

Frequency of Thromboembolism

Using the highly sensitive diffusion-weighted MRI, predominantly silent embolism was detected in up to 61% of the patients.19,20 The intraoperative rate of symptomatic thromboembolic events is reported to be 2.4% to 5.2% of the endovascularly treated aneurysm patients.1,4,7

Using angiography, we found 6.0% to 20% thromboembolic events dependent on the presence of SAH and application of ASA. This is well within the range found in the
literature of 2.4% to 28% of patients. A major finding of our analysis is the significant decrease in the rate of thromboembolic events from 20.0% to 10.1% in SAH patients after intravenous application of ASA during the procedure. Because of heterogeneity in the patients we did not attempt to find a difference in the clinical outcome.

Treatment and Clinical Relevance of Thromboembolism

An infarct in the corresponding vascular territory was found in 47.2% of patients with angiographically confirmed thromboembolism. Treatment options in case of thromboembolism include local application of tPA, urokinase or GPIIb/IIIa antagonists. Red thrombi (low-flow-thrombus; rich in fibrin and trapped erythrocytes, thought to be caused by guiding catheter) can be treated by tPA, whereas white thrombi (high-flow-thrombus; mainly platelet aggregation, thought to be coil-related) do much better respond to GPIIb/IIIa antagonists. The local treatment of thromboembolic events may have disastrous consequences. Coil-related platelet aggregation is unlikely to respond to fibrinolytics but has a high risk of hemorrhage. In the International Subarachnoid Aneurysm Trial (ISAT), all 5 patients who had received thrombolytic therapy with tPA to treat a thromboembolic complication after endovascular treatment rebled and all of these patients died. In our series, 2/4 patients treated by tPA died (1 by a space-occupying hemorrhage and 1 by a sepsis later on).

**TABLE 3. Patients With Clotting Events**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Sex</th>
<th>Hunt &amp; Hess Grade</th>
<th>GOS</th>
<th>Location of Aneurysm</th>
<th>Size, mm</th>
<th>Location of Thrombus</th>
<th>Acute Therapy</th>
<th>Infarct on CT/ Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+ASA F II 5 ACom 4 MCA</td>
<td>ReoPro</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+ASA M 0 UC ICAo 8 MCA</td>
<td>ReoPro</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+ASA F 0 I ACom 9 MCA</td>
<td>ReoPro</td>
<td>No/MSOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+ASA F V 1 ACom 5 ICA</td>
<td>ReoPro</td>
<td>Yes/CDICP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>+ASA F I 5 ACom 3 MCA</td>
<td>ReoPro</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+ASA F II 5 ACom 7 ACA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+ASA F II 4 BA tip 14 PCA</td>
<td>...</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+ASA F V 3 ICA 2 ACA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+ASA F IV 4 BA tip 2 PCA</td>
<td>ReoPro</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+ASA M I 5 ACA 8 MCA</td>
<td>ReoPro</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>+ASA F III 3 ICAo 11 MCA</td>
<td>ReoPro</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>+ASA F 0 UC PCom 7 MCA</td>
<td>rtPA</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>+ASA F III 3 BA tip 6 PCA</td>
<td>ReoPro</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>+ASA F IV 5 ACom 9 ACA</td>
<td>ReoPro</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>-ASA F V 5 ICA 14 ICA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>-ASA F 0 UC PCom 10 PCA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>-ASA M I 5 ACom 3 MCA</td>
<td>...</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>-ASA F III 4 PCom 10 MCA</td>
<td>rtPA</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>-ASA F II 5 BA tip 8 PCA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>-ASA F V 1 BA tip 11 PCA</td>
<td>...</td>
<td>No/CDICP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>-ASA F 0 UC ICAo 4 ICA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>-ASA F I 5 ACA 6 ACA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>-ASA F V 1 ACA 10 MCA</td>
<td>...</td>
<td>Yes/MSOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-ASA M V 1 ACom 12 MCA</td>
<td>rtPA</td>
<td>Yes/sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>-ASA F V 1 ACom 5 ACA</td>
<td>...</td>
<td>Yes/CDICP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>-ASA F II 1 MCA 18 MCA</td>
<td>rtPA</td>
<td>Yes/hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>-ASA M V 5 ACA 8 ACA</td>
<td>...</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>-ASA F 0 UC PCom 8 PCA</td>
<td>...</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>-ASA M IV 2 ACom 4 MCA</td>
<td>...</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>-ASA F II 5 ICAo 15 ICA</td>
<td>...</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>-ASA F V 1 ACom 7 ACA</td>
<td>...</td>
<td>Yes/MSOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>-ASA F V 1 ACom 9 ICA/MCA</td>
<td>...</td>
<td>No CT/MSOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GOS indicates Glasgow Outcome Scale; UC, outcome unchanged; ACA, anterior cerebral artery; ACom, anterior communicating artery; BA tip, basilar tip; ICA, internal carotid artery; ICAo, internal carotid artery, ophthalmic artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCom, posterior communicating artery; PICA, posterior inferior cerebellar artery; CDICP, cerebral deregulation, intracranial pressure increase; MSOI, multiple space occupying infarcts, intracranial pressure increase.
Recently, GPIIIb/IIIa antagonists are considered the main progress for the treatment of procedure-related thromboembolism.23–25 We found a mortality rate in 2/10 patients treated with GPIIIb/IIIa antagonists (abciximab). Both patients died from secondary complications of SAH, not from a procedure-related hemorrhage. This supports the view that abciximab does not resolve slow flow thrombi within the aneurysm but the white thrombus related embolism. However, numbers are too low to allow sound conclusions.

Perforation and Aneurysm Perforation
One of the main risks of endovascular treatment is the perforation of the parent vessel or aneurysm. Reported rates are 0.5% to 2.4% of the patients with unruptured aneurysms15,26 and 2.3% to 4.3% of the SAH patients.1,2,4,15,27 However, unrecognized perforations almost certainly occur in an uncertain number of more patients.2

An adverse event after application of ASA could be a larger hematoma in case of intraprocedural aneurysm perforation while the perforation risk itself should not be increased. In our series, first catheterization of the aneurysm sac with its inherently increased perforation risk attributable to the manipulation with guide wire and microcatheter was done without ASA because it was applied intravenously after placement of the first coil. It is uncertain in the literature whether the perforation risk is higher during administration of the first coil or during later filling of the sac.27–30 Our strategy to apply ASA after placement of the first coil allows confirmation of the correct placement of the microcatheter, thereby enabling quick progress of the procedure in case of perforation and bleeding. Probably based on similar reasoning Bendok et al describe that the second half of the heparin dose is administered after the first coil has been securely placed in the aneurysm.31 We found perforation in 7/17 (41%) of the cases before or during the deployment of the first coil and thus without ASA application. Six of these patients were treated after January 2003 and were categorized as + ASA on an intention-to-treat basis. There was no unequivocal difference in outcome after perforation between patients who truly received ASA (n=4) compared with patients who did not receive ASA (n=13; Table 4).

Conclusion
Intravenous application of ASA is feasible and safe during interventional aneurysm treatment both in unruptured aneurysms and after SAH. The presented data suggest that intraoperative ASA application is associated with a significant reduction in the rate of thromboembolic events without increasing in the rate or severity of intraoperative bleedings. Before ASA can be routinely recommended during endovascular aneurysm therapy, a randomized clinical trial would be desirable.

Acknowledgments
We thank Dr Matthew Wing of Hamburg for his advice on language.

Disclosures
None.

References
Ries et al. ASIA During Endovascular Aneurysms Treatment 1821


Intravenous Administration of Acetylsalicylic Acid During Endovascular Treatment of Cerebral Aneurysms Reduces the Rate of Thromboembolic Events
Thorsten Ries, Jan-Hendrik Buhk, Thomas Kucinski, Einar Goebell, Ulrich Grzyska, Hermann Zeumer and Jens Fiehler

*Stroke*. 2006;37:1816-1821; originally published online June 15, 2006;
doi: 10.1161/01.STR.0000226933.44962.a6

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/37/7/1816

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/