Timing of Aneurysm Treatment After Subarachnoid Hemorrhage
Relationship With Delayed Cerebral Ischemia and Poor Outcome

Sanne M. Dorhout Mees, MD; Andrew J. Molyneux, MD, PhD; Richard S. Kerr, MD, PhD; Ale Algra, MD, PhD; Gabriel J.E. Rinkel, MD, PhD

Background and Purpose—The ideal timing of coiling or clipping after aneurysmal subarachnoid hemorrhage is unknown. Within the International Subarachnoid Aneurysm Trial we assessed differences in incidence of delayed cerebral ischemia and clinical outcome between different timings of treatment.

Methods—The treated 2106 patients randomized to coiling or clipping were divided into 4 categories: treatment <2 days, on days 3 to 4, on days 5 to 10, and >10 days after the hemorrhage. ORs with 95% CI were calculated with logistic regression analysis for delayed cerebral ischemia, poor outcome at 2 months, and 1 year for the different timing categories, with treatment <2 days as reference. Analyses were performed for all patients, and for coiled and clipped patients separately, and were adjusted for baseline characteristics.

Results—Adjusted ORs of delayed cerebral ischemia for treatment on days 5 to 10 were 1.18 (95% CI, 0.91–1.53) for all patients, 1.68 (95% CI, 1.17–2.43) after coiling, and 0.79 (95% CI, 0.54–1.16) after clipping. ORs for poor outcome at 2 months were 1.16 (95% CI, 0.89–1.50) for treatment (clipping and coiling combined) at 3 to 4 days, 1.39 (95% CI, 1.08–1.80) for treatment at 5 to 10 days, and 1.84 (95% CI, 1.36–2.51) for treatment >10 days. ORs for coiled and clipped patients separately were in the same range. Results for outcome at 1 year were similar.

Conclusions—Our results support the current practice for early aneurysm treatment in subarachnoid hemorrhage patients. The risk for poor outcome was highest when treatment was performed after day 10; postponing treatment in patients who are eligible for treatment between days 5 to 10 after subarachnoid hemorrhage is not recommended. (Stroke. 2012;43:2126-2129.)

Key Words: subarachnoid hemorrhage • aneurysm

Rebleeding after aneurysmal subarachnoid hemorrhage (SAH) dramatically decreases the chances of good outcome.1,2 To prevent rebleeding, treatment of the ruptured aneurysm was almost exclusively performed by neurosurgical clipping before 1995. Over many years, there has been debate about the most suitable timing of surgery.3-5 In the 1960s and 1970s, most patients were operated on in the late phase 2 or 3 weeks after the hemorrhage. Surgery in the initial 2 weeks was considered too dangerous, because operating on the swollen and vulnerable brain tissue led to high rates of perioperative complications.6-8 This especially applied during the period of maximum vasospasm between days 4 and 10; this was considered a particularly dangerous period to operate, because of the risk of delayed cerebral ischemia (DCI). An observational study performed in the 1980s in patients with aneurysmal SAH admitted within 3 days after the ictus suggested that outcome was worst when patients were operated between 7 and 10 days after the SAH; early surgery was neither more hazardous nor more beneficial than was surgery after day 10.9 A Cochrane review in 2001 identified only 1 randomized clinical trial on timing of surgery after aneurysmal SAH.10 In this trial, patients undergoing early surgery (days 0–3) tended to have the best outcome, and patients with intermediate surgery (days 4–7) the worst.11 A systematic review that included not only this trial, but also 10 observational studies, found that both early (days 0–3) and intermediate (days 4–7) surgical treatment resulted in better outcome than did late surgery.12

In the early 1990s, endovascular aneurysm occlusion by means of detachable coils was introduced; this is now an established method of aneurysm treatment.13 To our knowledge, there are no randomized studies on the optimal timing of coiling. One observational study including 327 coiled
patients did not find any difference with regard to outcome for early, intermediate, or late treatment. Most centers now aim to treat the aneurysm within 2 days after SAH. For patients who are only eligible for treatment later than day 2, it is important to know the optimal timing of aneurysm treatment: as soon as possible or postponed until after the 10th day, and whether the treatment modality influences optimal timing.

Within the International Subarachnoid Aneurysm Trial (ISAT), we assessed differences in occurrence of DCI and clinical outcome between different timings of treatment for coiled and for clipped patients.

Methods

Patients

We analyzed the data of patients who participated in the ISAT trial, a clinical trial that randomized 2143 patients either to endovascular coiling treatment or neurosurgical clipping of the ruptured aneurysm. The methods of this trial have been described previously. In short, patients were included in the trial if they had a definite subarachnoid hemorrhage within the previous 28 days and an aneurysm, which was judged by both the neurosurgeon and the interventional radiologist to be suitable for treatment by either technique, but there was uncertainty which treatment was most appropriate. Informed consent was obtained from the patient or relatives. The majority of included patients were in good clinical condition at admission and had anterior circulation aneurysms. For the current study, we analyzed patients according to the treatment they actually received, and also if treatment crossover occurred (on treatment analysis).

Of the included patients, age, sex, clinical grade on admission by means of the World Federation of Neurosurgeons (WFNS) grading scale, amount of blood on the initial computed tomography according to the Fisher Scale, and the occurrence of DCI were recorded. Age was dichotomized at 55 years. The WFNS scale was dichotomized into good clinical condition (WFNS 1–3) or poor clinical condition (WFNS 4–5). The Fisher scale was dichotomized into small amount of blood on computed tomography scan (Fisher 1–2) or large amount of blood on computed tomography scan (Fisher 3–4). DCI was diagnosed on clinical grounds as delayed ischemic neurological deficit, which was not caused by operative factors or other factors, such as procedural vessel occlusion, hydrocephalus, or aneurysmal rebleeding, and the clinicians judged the deterioration to be caused by vasospasm. Clinical outcome was assessed by self-reported questionnaires with the modified Rankin Scale score at 2 months and at 1 year. Poor outcome was defined as an modified Rankin Scale score of 3 or higher, or death.

Statistical Analyses

First, we analyzed whether there was a relationship between time from SAH until admission and time from admission until randomization with linear regression analysis. Patients were then divided into 4 categories according to the timing of treatment after the SAH: within 2 days, on day 3 or 4, on days 5 to 10, and >10 days. ORs with 95% CI were calculated with logistic regression analysis for DCI, poor outcome at 2 months, and at 1 year for the different timing categories: the first category (treatment within 2 days) was a reference. We performed these analyses for all patients, and separately for coiled and for clipped patients. With subgroups of 450 patients and a risk of poor outcome of 30%, an absolute risk difference of 6% would have a 95% CI of 0.2% to 11.8%. Likewise, with similar subgroups and risk of DCI of 25%, an absolute risk difference of 6% would have a 95% CI of 0.6% to 11.4%. To check for interaction between treatment modality and the timing category, the cross-product of clipping and the particular timing category were entered into the regression analyses. If the probability value of the cross-product was <0.05, we considered there to be an interaction between treatment modality and timing. All analyses were adjusted for age, clinical condition at admission, and amount of blood on initial computed tomography scan.

Results

The time from admission until randomization did not depend on the time from SAH onset until admission (regression coefficient, −0.01; 95% CI, −0.04 to 0.02). Of the 2143 patients randomized in ISAT, 2106 patients received endovascular or neurosurgical treatment. Of these patients, 891 patients were treated on days 0 to 2 after SAH, 482 patients were treated on days 3 to 4, 474 patients between days 5 to 10, and 259 patients on day 11 or later (Table 1). The median day of randomization in patients treated between 5 to 10 days (day 5) and on day 11 or later (day 11) was higher in patients treated on days 0 to 2 (day 1) or 3 to 4 (day 2). Patients treated on days 0 to 2 received treatment on a median of 0.3 day after the randomization day, patients treated on day 3 to 4 or 5 to 10 on a median of 1 day after randomization day, and patients treated after 10 days on a median of 3 days after randomization day. Rebleeding before aneurysm treatment, but after randomization, was more frequent in the group treated after day 10.

Data on DCI were available for 2099 patients (99.7%). The risks of DCI for all treated patients, and for patients after coiling and clipping separately, are given in Table 2. Only between days 5 to 10 was there a statistically significant interaction between treatment modality and timing, with a lower risk of DCI for clipping during this time period than for coiling (P = 0.01).

Data on poor outcome at 2 months and at 1 year are given in Table 3. The risk of poor outcome increased with increasing time lapse of treatment after SAH. There was no inter-

### Table 1. Baseline and Disease Characteristics of the 2106 Included Patients

<table>
<thead>
<tr>
<th>Timing of Treatment, Days After SAH</th>
<th>N</th>
<th>0–2</th>
<th>3–4</th>
<th>5–10</th>
<th>≥11</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2106</td>
<td>891</td>
<td>482</td>
<td>474</td>
<td>259</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>52 (12)</td>
<td>51 (11)</td>
<td>51 (12)</td>
<td>52 (12)</td>
<td>55 (12)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>1321 (63)</td>
<td>562 (63)</td>
<td>300 (62)</td>
<td>285 (60)</td>
<td>174 (67)</td>
</tr>
<tr>
<td>WFNS 1–3 (%)</td>
<td>1990 (95)</td>
<td>815 (92)</td>
<td>469 (97)</td>
<td>460 (97)</td>
<td>246 (95)</td>
</tr>
<tr>
<td>Fisher 1–2 (%)</td>
<td>470 (22)</td>
<td>175 (20)</td>
<td>94 (20)</td>
<td>131 (28)</td>
<td>70 (27)</td>
</tr>
<tr>
<td>Admission day, median (IQR)</td>
<td>1 (1–3)</td>
<td>1 (0–1)</td>
<td>2 (1–2)</td>
<td>3 (1–5)</td>
<td>7 (3–1)</td>
</tr>
<tr>
<td>Randomization day, median (SD)</td>
<td>2 (1–4)</td>
<td>1 (1–1)</td>
<td>2 (2–3)</td>
<td>5 (4–6)</td>
<td>11 (8–1)</td>
</tr>
<tr>
<td>Days between randomization and treat., median (SD)</td>
<td>1 (0–3)</td>
<td>0 (0–1)</td>
<td>1 (1–1)</td>
<td>1 (1–3)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>DCI (%)</td>
<td>511 (24)</td>
<td>218 (25)</td>
<td>118 (25)</td>
<td>123 (26)</td>
<td>52 (20)</td>
</tr>
<tr>
<td>Rebleeding† (%)</td>
<td>28 (1.3)</td>
<td>6 (0.7)</td>
<td>2 (0.4)</td>
<td>5 (1.1)</td>
<td>15 (5.8)</td>
</tr>
</tbody>
</table>

SAH indicates subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons scale; IQR, interquartile range; DCI, delayed cerebral ischemia.

*Measured at randomization.
†Rebleeding after randomization, but before treatment.
Table 2. ORs for DCI for Patients Treated on Days 3–4, Days 5–10, and Days 11 or Later Compared With Patients Treated on Days 0–2, for All Patients and for Coiled and Clipped Patients Separately

<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients</th>
<th>Coiled Patients</th>
<th>Clipped Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)*</td>
</tr>
<tr>
<td>2–4 d</td>
<td>218/886 (25%)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>3–4 d</td>
<td>118/480 (25%)</td>
<td>1.00 (0.77–1.29)</td>
<td>1.04 (0.80–1.36)</td>
</tr>
<tr>
<td>5–10 d</td>
<td>123/474 (26%)</td>
<td>1.07 (0.83–1.39)</td>
<td>1.18 (0.91–1.53)</td>
</tr>
<tr>
<td>11 d</td>
<td>52/259 (20%)</td>
<td>0.77 (0.55–0.88)</td>
<td>0.59 (0.59–1.17)</td>
</tr>
<tr>
<td>Coiled Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 d</td>
<td>58/261 (22%)</td>
<td>1.06 (0.74–1.53)</td>
<td>1.71 (0.77–1.61)</td>
</tr>
<tr>
<td>5–10 d</td>
<td>68/238 (29%)</td>
<td>1.49 (1.04–2.13)</td>
<td>1.68 (1.17–2.43)</td>
</tr>
<tr>
<td>11 d</td>
<td>22/109 (20%)</td>
<td>0.94 (0.56–1.58)</td>
<td>1.01 (0.60–1.72)</td>
</tr>
<tr>
<td>Clipped Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4 d</td>
<td>116/404 (29%)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>3–4 d</td>
<td>60/219 (27%)</td>
<td>0.94 (0.65–1.35)</td>
<td>0.97 (0.67–1.41)</td>
</tr>
<tr>
<td>5–10 d</td>
<td>55/236 (23%)</td>
<td>0.75 (0.52–1.09)</td>
<td>0.79 (0.54–1.15)</td>
</tr>
<tr>
<td>11 d</td>
<td>30/150 (20%)</td>
<td>0.62 (0.39–0.98)</td>
<td>0.64 (0.41–1.02)</td>
</tr>
</tbody>
</table>

DCI indicates delayed cerebral ischemia.

*Adjusted for age, clinical condition at admission, and amount of blood on the initial computed tomography scan.

Discussion

Our study shows that clinical outcome is worse when aneurysm occlusion is performed later after SAH, after differences in baseline characteristics have been taken into account. In patients who were coiled between 5 to 10 days after the SAH, the risk for DCI was higher than in other treatment periods, but this increased risk did not result in worse outcome either at 2 months or at 1 year compared with treatment within 2 days. Clipped patients had no higher risk of DCI when treated between 5 to 10 days.

Patients who were randomized and treated after day 10 had worse outcome than did patients treated earlier. It is important to realize that patients were not randomized for the timing of treatment, and the worse outcome in this group is probably related to the reasons for postponing treatment, such as poor clinical condition on admission, early rebleeding, or early deterioration from other causes. This assumption is supported by the fact that patients in this group were randomized on a median of 11 days after the SAH, which suggests that these patients were only eligible for treatment from day 11 onwards.

The time from admission until randomization did not depend on the time of admission since SAH. As soon as patients were considered eligible for treatment, they could be randomized, and treatment was not postponed because of randomization. Although the clinical condition (WFNS) did not differ between the groups, the grade was measured at time of randomization and not at time of presentation at the hospital. Patients treated after day 10 may have been at a worse clinical condition at admission and improved by the time of randomization. The occurrence of DCI does not seem to be the cause of poor outcome, as it was not increased in this patient group. As might be expected, rebleeding did occur more often in patients treated after day 10, and this is an important reason for poor clinical outcome.

Because these are observational data, no direct causal effect between timing and clinical outcome can be concluded. Also, 92% of patients were in a good clinical condition at the time of randomization. This means that we cannot extrapolate our results to patients who present with poor clinical condition. Patients were only randomized when both the neurosurgeon and the interventional neuroradiologist considered the aneurysm suitable for treatment, which also limits generaliz-
ability. DCI was diagnosed on clinical grounds, and transcranial Doppler or radiographic studies were not used in the definition. The strengths of this study are the large sample size in each timing category, and the fact that patients were randomized for coiling or clipping, giving us the opportunity to look for differences between these 2 treatment modalities. Based on our sample size considerations, an absolute risk difference of 6% between timing subgroups for poor outcome or DCI would have sufficient precision. This means that smaller differences could not be detected precisely enough. Historically, clipping between days 5 to 10 is considered the worst period for neurosurgery.9,11 Interestingly, in our study, the risk for DCI was low in patients clipped during this time, and outcome was not worse when compared with treatment after day 10. On the basis of the current evidence, there seems no reason to postpone treatment in patients who are eligible for treatment at day 5. Ideally, given all the methodological concerns mentioned above, a new randomized trial would be needed to give definite answers to the ideal timing of aneurysm treatment after SAH; however, such a trial is not likely to be performed given the observational evidence for benefit of early treatment. If a randomized trial on timing of treatment were conducted, we think it should address the question of when patients who present to the hospital in poor clinical condition should be treated or about those who present for treatment later than day 4 after the hemorrhage. An alternative strategy to study optimal timing would be to use a Markov decision model.

Conclusion
In conclusion, our results show that aneurysm treatment after day 10 is associated with worse outcome, regardless of treatment modality. The results are in line with the latest literature that advocates treatment of the aneurysm as early as possible after SAH.10,12,14 Interestingly, clipping between days 5 to 10 did not lead to a higher chance of DCI, whereas coiling between days 5 to 10 did increase the chance of DCI, but not poor outcome. Based on these results, we do not recommend postponing clipping until day 10 or later in patients who are candidates for aneurysm treatment between 5 and 10 days after hemorrhage.

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Disclosures
None.

References
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