Antiplatelet Therapy in Aneurysmal Subarachnoid Hemorrhage
A Systematic Review

Sanne M. Dorhout Mees, MD; Gabriel J.E. Rinkel, MD, FAHA; Jeannette W. Hop, MD; Ale Algra, MD, FAHA; Jan van Gijn, MD, FRCP, FRCPE

Background and Purpose—Observational studies suggest that platelet inhibitors reduce the risk of delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage and thereby have a beneficial effect on clinical outcome. Robust evidence, however, is lacking. We performed a systematic meta-analysis to determine whether antiplatelet therapy has a beneficial effect after SAH.

Methods—We searched Medline and the Cochrane Library to identify all randomized controlled trials of antiplatelet drugs versus control and calculated relative risks with corresponding 95% confidence intervals (CIs) for poor outcome (dependence or death), the occurrence of DCI, and the occurrence of any intracranial hemorrhage.

Results—We included 5 trials totaling 699 patients. The overall relative risk for poor outcome was 0.87 (95% CI, 0.65 to 1.17); for the occurrence of DCI (reported in 3 of the 5 studies), 0.65 (95% CI, 0.47 to 0.89); and for the occurrence of intracranial hemorrhage, 1.19 (reported in 4 of the 5 studies) (95% CI, 0.76 to 1.85).

Conclusions—Our data indicate that antiplatelet drugs reduce the risk of DCI in patients with subarachnoid hemorrhage. A randomized clinical trial is warranted to assess the effect on overall outcome. (Stroke. 2003;34:2285-2289.)

Key Words: aneurysm ■ antiplatelet therapy ■ subarachnoid hemorrhage

In patients with aneurysmal subarachnoid hemorrhage (SAH), delayed cerebral ischemia (DCI) is an important cause of poor outcome. The pathogenesis of DCI is still poorly understood. Intracranial vasospasm, which results from the release of vasoactive substances, has often been incriminated. Vasospasm is often used as a synonym but is not a sufficient factor because even severe vasospasm does not always lead to secondary ischemia. Platelet aggregation probably plays a role also. Activation of platelet aggregation and the associated release of thromboxane B2 are increased from day 3 after the onset of SAH. This increase is larger in patients who actually develop DCI than in patients without DCI. Data from animal research further support the involvement of platelet aggregation. Both rupture of an artery and the presence of blood at the abluminal side of an intact artery activate platelet aggregation. Moreover, antiplatelet activity of the endothelium is reduced after SAH.

Aspirin (acetylsalicylic acid) is a well-known inhibitor of platelet aggregation. It also inhibits vasoconstriction mediated through oxyhemoglobin, which is released during lysis of erythrocytes. An observational study has indicated that SAH patients who had been using aspirin before the occurrence of SAH had a reduced risk for the development of ischemic complications. These observations suggest that platelet function may be associated with DCI after aneurysmal SAH and that the administration of platelet inhibitors might have a preventive effect on the development of DCI and thereby on outcome after SAH. We performed a systematic literature review to evaluate the results of all randomized clinical trials on antiplatelet therapy in SAH.

Methods

Identification of Studies

We sought to identify all randomized trials on antiplatelet drugs versus control in patients with aneurysmal SAH. To identify the studies, we searched the Medline Database from 1966 until May 2002 and the Cochrane Controlled Trials Register of the Cochrane Library (edition 2002, No. 1). Electronic search terms included subarachnoid, h(a)emorrhage, aneurysm, vasospasm, secondary/delayed cerebral ischemia, (anti)platelets, aspirin, thromboxane, and trial. Reference lists of identified trials were searched for further studies.

Data Extraction

Two articles extracted details of randomization methods, blinding of treatments and outcome assessments, patient’s condition on entry, timing of operation, definition of outcome measures, and number of patients excluded or lost to follow-up from all trials. From these data, we assessed whether intention-to-treat analysis was possible. In addition, we recorded dose and route of drug administration and the duration of follow-up.

The primary outcome measure in this review was poor outcome, defined as dependence or death. Other outcome measures were the...
Main Characteristics of Included Randomized Controlled Trials on the Use of Antiplatelet Drugs in Patients With SAH

<table>
<thead>
<tr>
<th>Study</th>
<th>Included Patients (Treatment/Control), n</th>
<th>Exclusions After Treatment Started (Treatment/Assessment)</th>
<th>Blinding Stated (Treatment/Assessment)</th>
<th>Trial Medication</th>
<th>Route, Dosage</th>
<th>Start of Treatment</th>
<th>Duration of Treatment</th>
<th>Time to Surgery</th>
<th>Follow-Up, mo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hop et al(^{21})</td>
<td>24/26</td>
<td>None</td>
<td>Yes/yes</td>
<td>Aspirin</td>
<td>Supp, 100 mg/d</td>
<td>&lt;12 h after surgery</td>
<td>21 d</td>
<td>&lt;day 5</td>
<td>4</td>
<td>Functional, DCI, ICH</td>
</tr>
<tr>
<td>Tokiyoshi et al(^{22})</td>
<td>13/11</td>
<td>None</td>
<td>No/no</td>
<td>Cataclot*</td>
<td>IV, 1 (\mu g \cdot kg^{-1} \cdot min^{-1})</td>
<td>Postoperatively</td>
<td>8–14 d</td>
<td>&lt;48 h</td>
<td>1</td>
<td>Functional, DCI, IHC</td>
</tr>
<tr>
<td>Suzuki et al(^{21})</td>
<td>170/86</td>
<td>20/9</td>
<td>Yes/yes</td>
<td>OKY-046*</td>
<td>IV, 80 or 400 mg/d</td>
<td>As soon as possible after surgery</td>
<td>10–14 d</td>
<td>&lt;day 4</td>
<td>3</td>
<td>Functional, DCI, ICH</td>
</tr>
<tr>
<td>Shaw et al(^{20})</td>
<td>159/161 (For functional outcome) 179/181 (for ICH outcome)</td>
<td>50/0</td>
<td>No/yes</td>
<td>Dipyridamole</td>
<td>Oral, 100 mg/d or IV, 10 mg/d</td>
<td>Preoperatively</td>
<td>Until 3 mo after surgery</td>
<td>Median, 9.4 days</td>
<td>3</td>
<td>Functional, ICH</td>
</tr>
<tr>
<td>Mendelow et al(^{19})</td>
<td>12/9</td>
<td>15/17</td>
<td>Yes/yes</td>
<td>Aspirin</td>
<td>Oral/rectal retention enema, 600 mg/d</td>
<td>72 h after admission, preoperatively</td>
<td>Until discharge</td>
<td>Not stated</td>
<td>6</td>
<td>Functional</td>
</tr>
</tbody>
</table>

Supp indicates suppository; ICH, intracranial hemorrhage.
*Cataclot and OKY-046 are the same substance.

occurrence of DCI (defined by clinical criteria [decrease in the level of consciousness, new focal deficits, or both] in the absence of other explanations, CT [new hypodensities], or both) and the number of patients with symptomatic intracranial hemorrhage (defined as a clinical deterioration explained by an increase in blood [extradural, subdural, subarachnoid, or intraparenchymal] on CT).

Data Analysis

To obtain an intention-to-treat analysis, we aimed to extract from each trial the outcome data of all patients according to the treatment group to which they were originally allocated. Relative risks (RRs) were calculated per outcome measure per study. An estimate of the treatment effect across trials (RR with a 95% confidence interval [CI]) was calculated by means of the Mantel-Haenszel method. The statistical validity of aggregating the trials was assessed with a \(X^2\) test. We planned beforehand a subgroup analysis of studies with aspirin and of studies starting medication before or after operation.

Results

Description of Trials

We identified 12 trials on antiplatelet drugs in patients with aneurysmal SAH. All identified trials were published between 1981 and 2000. Five trials were excluded because no adequate control group was used.\(^{12–16}\) One study was excluded because the definition of outcome was not clear.\(^{17}\) Another trial was excluded because the article was in Japanese with no English abstract available.\(^{18}\) We included the remaining 5 trials, which were randomized and placebo controlled (Table).\(^{19–23}\) In 1 of these 5 trials, the sponsoring pharmaceutical company performed randomization and statistical analyses.\(^{20}\)

The timing of randomization and start of antiplatelet (or placebo) treatment were not uniform. Two studies randomized the patients preoperatively and started treatment before surgery.\(^{19,20}\) In 1 study, randomization was performed preoperatively, but treatment was started only postoperatively, and actual treatment was left to the discretion of the treating neurosurgeon.\(^{23}\) In 5 randomized patients in this trial, the neurosurgeon decided on the basis of the operative procedure that trial medication could not be started. One study used postoperative randomization and postoperative start of treatment.\(^{22}\) One study started treatment postoperatively but did not state time of randomization.\(^{21}\) In 2 studies, the interval between the SAH and the start of trial medication was not mentioned.\(^{19,20}\) In the other 3 studies, trial medication was begun within 7 days.

One study used 3 groups of patients: those receiving a low or a high dose of study medication and a control group (see the Table).\(^{21}\) One study included only patients in good clinical condition;\(^{21}\) the other studies included patients in any clinical condition. As additional medication, 1 study used nimodipine,\(^{23}\) 1 study used methylprednisolone,\(^{22}\) and 1 study used tranexamic acid in all patients.\(^{19}\) In 1 study, mannitol was used if necessary,\(^{20}\) and in another study, it was explicitly stated that other antiplatelet drugs, nizofenone, or steroids were not used.\(^{21}\) In all studies, the aneurysm was treated by neurosurgical clipping.

In the 5 trials, 1092 patients initially were included, but in 3 studies, patients were excluded after start of the trial medication. In 1 study, 27 of 285 patients (18 treatment group, 9 control group) were excluded at time of analysis because they did not meet the stipulations in the protocol; another 2 (treatment group) were excluded because they had had adverse reactions from the study medication.\(^{21}\) In a second study, 329 patients (163 treatment group, 166 control group) were excluded because they were not operated on, and another 3 were excluded because they declined further participation in the study.\(^{20}\) In this trial, 16% of patients (8% in each group) were excluded from the analysis of poor outcome but not from the analysis of intracranial hemorrhage. The reasons for withdrawal were not stated. In a third study, 32 patients were excluded because an aneurysm was not found or could not be clipped.\(^{19}\) Of the 1092 included patients, in total 699 randomized patients were analyzed, 392 in the treatment group and 307 in the control group.

One study used the modified Rankin Scale as outcome measurement; a second used the Glasgow Outcome Scale.\(^{20}\) The other 3 studies used self-defined disability scales. They included a 4-point scale (excellent, good [combined to good outcome], poor, death [combined to poor outcome]),\(^{22}\) a
9-point scale (0 to 4 [good outcome], 5 to 8 [poor outcome]), and a 3-point scale (A, no neurological deficit [good outcome]; B, neurological deficit [poor outcome]; and C, death [poor outcome]).

**Poor Outcome**
Outcome data were available for 671 patients (378 treatment, 293 control) and are given in Figure 1. Overall, the RR of antiplatelet therapy for poor outcome was 0.87 (95% CI, 0.65 to 1.17). No substantial differences were found in the separate analysis for aspirin studies (RR, 0.78; 95% CI, 0.35 to 1.74) and for studies that started treatment after surgery (RR, 0.84; 95% CI, 0.54 to 1.30) or before surgery (RR, 0.90; 95% CI, 0.61 to 1.33).

**Delayed Cerebral Ischemia**
Data on the occurrence of DCI were available in 3 studies, totaling 258 patients (158 treatment, 100 control) (Figure 2). The risk of antiplatelet therapy on the occurrence of DCI was significantly reduced, with an RR of 0.65 (95% CI, 0.47 to 0.89). To prevent DCI in a single patient, the number needed to treat is 7 patients (95% CI, 4 to 40), which corresponds to an absolute risk reduction of 15% (95% CI, 0.61 to 1.33).

**Intracranial Hemorrhage**
In 4 studies, data were available on the occurrence of intracranial hemorrhage, totaling 678 patients (380 treatment, 298 control) (Figure 3). The overall RR of antiplatelet therapy for intracranial hemorrhage was 1.19 (95% CI, 0.76 to 1.85). The absolute increase in intracranial hemorrhages was 0.2% (95% CI, −0.04 to 0.05), which means that in every 500 treated patients, 1 additional hemorrhage is induced by antithrombotic therapy (number needed to harm, 500; 95% CI, 21 to infinity). In the subgroup analysis for treatment started after surgery, the RR was essentially the same (RR, 1.25; 95% CI, 0.45 to 3.49) as in the overall analysis.

**Discussion**
This meta-analysis indicates that antiplatelet therapy reduces the risk of DCI in patients with SAH. The data also suggest a better overall outcome in patients treated with antiplatelet drugs, but the number of patients included in the review is far too small to draw definitive conclusions. It should not be assumed without proof that prevention of DCI can be equated with improved outcome because, in patients with SAH, avoidance of 1 complication may be offset by another. The results were essentially the same for the subgroup analyses of aspirin studies and of treatment given before or after surgery.

The overall risk of intracranial hemorrhage was not substantially increased by antiplatelet therapy, although a small increase cannot be ruled out. Additionally, in this systematic review, we found no evidence that the risk of intracranial hemorrhage is substantially higher if antiplatelet therapy is started before surgery. We could not find other studies on the bleeding risk of antiplatelet drugs during intracranial surgery. Two randomized, placebo-controlled trials on antiplatelet therapy during carotid surgery found no higher risk of hemorrhagic complications in the antiplatelet-treated group. Data on risk of antiplatelet therapy during coronary artery bypass grafting are conflicting. Some studies found slightly higher rates of postoperative bleeding and blood transfusion, but others did not.

At least 2 factors support the validity of the results. The 5 trials included in this review were comparable with respect to study design and selection of patients, and the treatment and control groups were well balanced with respect to prognostic factors for poor outcome. Moreover, the risks remained unaltered in the subgroups, which further enhances the validity of this review. The meta-analysis, however, has also several drawbacks. In 3 studies, patients were excluded after the start of trial medication. Although the patients were evenly distributed between the treatment and control groups, a strict intention-to-treat analysis could not be performed. There were also differences with respect to the timing of
surgery and start of treatment, the trial medication used, and the duration of treatment. In 2 studies,19,20 the interval between SAH and the start of treatment was not stated. When treatment is started several days after the SAH, the chance of a beneficial effect decreases because DCI usually occurs between 4 and 10 days after the hemorrhage.32 The most important drawback is the small number of patients included in the meta-analysis. Although the effect on DCI was statistically significant, the CIs for poor outcome and intracranial hemorrhage are too wide to confirm or refute an effect of antiplatelet therapy on these outcome measures.

Because every drug used inactivates platelet function, although not in the same way, the fact that different antiplatelet medications were used is unlikely to have influenced the results. Aspirin irreversibly inhibits the cyclooxygenase activity of platelets, which results in a decreased conversion of arachidonate to prostaglandin A2.33 Thromboxane A2 is a potent inducer of platelet aggregation. In addition, aspirin inhibits vasoconstriction mediated by oxyhemoglobin.103 Oxyhemoglobin is released in the cerebrospinal fluid through lysis of erythrocytes, which occurs soon after SAH. OKY-046, the same substance as Cataclot (sodium (E)-3-[1H-imidazol-1-ylmethyl]phenyl]-2-propenoate) acts as selective thromboxane synthetase inhibitor. These drugs inhibit thromboxane formation and thereby platelet aggregation without interfering with the synthesis of prostacyclin in the endothelium, unlike aspirin.34 Dipyridamole inhibits the enzyme phosphodiesterase, which leads to an increase in adenosine monophosphate (AMP) by preventing its intracellular breakdown. AMP acts as a platelet aggregation inhibitor. In this way, dipyridamole is thought to potentiate the effect of adenosine, a potent stimulator of AMP formation.35

We conclude that antiplatelet therapy after SAH can prevent DCI. The effects on the rate of intracranial hemorrhage are modest, and those on overall outcome are uncertain. Before antiplatelet therapy can be routinely recommended, randomized clinical trials with appropriate power are needed.

References


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