Antiplatelet therapy in aneurysmal subarachnoid hemorrhage: a systematic review

CRD summary
This review assessed antiplatelet treatment in patients with aneurysmal subarachnoid haemorrhage. The authors concluded that antiplatelet therapy can reduce delayed cerebral ischaemia in these patients, but the effects on overall outcome are uncertain. High drop-out rates and differences between the studies mean that the conclusions should be treated as suggestive rather than definitive.

Authors' objectives
To determine the effect of antiplatelet treatment on aneurysmal subarachnoid haemorrhage (SAH).

Searching
MEDLINE (from 1966 to May 2002) and the Cochrane Controlled Trials Register (Issue 1, 2002) were searched; the search terms were stated. The reference lists in identified studies were checked. One identified study that was published in Japanese was subsequently excluded since it did not have an English abstract.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Studies varied with respect to the timing of randomisation relative to surgery. The duration of follow-up ranged from 1 to 6 months.

Specific interventions included in the review
Studies that compared antiplatelet drug with control were eligible for inclusion. The included studies used the following antiplatelet drugs: aspirin, 100-mg suppository per day or 600 mg/day oral or rectal retention enema; OKY-046, 1 microg/kg per minute intravenously, or 80 or 400 mg/day intravenously; or dipyridamole, 100 mg oral or 10 mg intravenously. Studies initiated the treatment pre-operatively (2 trials) or after surgery (3 trials). The duration of treatment ranged from 8 days to 3 months after surgery. Cointerventions varied and included nimodipine, methylprednisolone, tranexamic acid and mannitol if required. Some studies prohibited the use of other platelet drugs, nizofenone and steroids.

Participants included in the review
Studies of patients with aneurysmal SAH were eligible for inclusion. The included studies all treated patients with neurosurgical clipping of the aneurysm. Studies varied in their inclusion criteria for the patients. One study only included patients in good condition, while other studies included patients regardless of their condition.

Outcomes assessed in the review
The inclusion criteria were not specified in terms of outcomes. The primary outcome in the review was poor outcome, defined as death or dependency. The review also assessed delayed cerebral ischaemia (DCI) and symptomatic intracranial haemorrhage. DCI was defined as a decrease in the level of consciousness and/or new focal defect in the absence of other explanations or new hypodensities on computed tomography. Symptomatic intracranial haemorrhage was defined as clinical deterioration explained by an increase in blood on computed tomography. Studies assessed outcomes using the Rankin Scale, the Glasgow Outcome Scale or various self-defined disability scales.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was not assessed using a checklist, but data on the method of randomisation, blinding of treatment and
outcome assessment, definition of outcome measures, and the number of patients excluded or lost to follow-up was recorded. These data were used to determine whether intention-to-treat analysis were possible. Two reviewers assessed validity.

**Data extraction**

Two reviewers extracted the data. The reviewers attempted to extract data on an intention-to-treat basis, but this was not possible for all studies. For each study, the relative risks (RRs) with 95% confidence intervals (CIs) were calculated for each outcome.

**Methods of synthesis**

- **How were the studies combined?**
  The studies were combined in a meta-analysis. Pooled RRs and 95% CIs were calculated using the Mantel-Haenszel method. The number-needed-to-treat (NNT) and 95% CI were calculated for delayed cerebral ischaemia, while the number-needed-to-harm (NNH) and 95% CI were calculated for intracranial haemorrhage.

- **How were differences between studies investigated?**
  Statistical heterogeneity was assessed using the chi-squared statistic. Pre-planned subgroup analyses were undertaken of studies using aspirin and studies that started drug treatment before or after surgery.

**Results of the review**

Five RCTs were included (1,092 patients were randomised but only 699 patients were included in the analysis).

Three studies excluded patients after they had started the study medication. The first RCT excluded patients from the analysis who did not meet the protocol or who had adverse events; the second RCT excluded patient who did not receive surgery, declined to participate, or had poor outcome; the third RCT excluded patients whose aneurysm could not be found or clipped during surgery.

Poor outcome (5 RCTs, 671 patients): the meta-analysis showed no significant difference between antiplatelet therapy and placebo for poor outcome; the RR was 0.87 (95% CI: 0.65, 1.17). No significant statistical heterogeneity was detected (P=0.82). Similar results were found for studies of aspirin (RR 0.78, 95% CI: 0.35, 1.74) and for studies starting treatment pre- or post-operatively (the results were reported).

Delayed cerebral ischaemia (3 RCTs, 258 patients): the meta-analysis showed that antiplatelet therapy significantly reduced DCI compared with placebo; the RR was 0.65 (95% CI: 0.47, 0.89). No significant statistical heterogeneity was detected (P=0.65). The NNT was 7 (95% CI: 4, 40). The results for subgroups were not reported.

Intracranial haemorrhage (4 RCTs, 678 patients): the meta-analysis showed no significant difference between antiplatelet therapy and placebo; the RR was 1.19 (95% CI: 0.76, 1.85). The NNH was 500 (95% CI: 21, infinity). Similar results were found for studies starting treatment post-operatively (the results were reported).

**Authors’ conclusions**

Antiplatelet therapy can reduce delayed cerebral ischaemia in patients with SAH, but the effects on overall outcome are uncertain.

**CRD commentary**

The review question was clear in terms of the participants, study design and intervention. The inclusion criteria were not explicitly specified in terms of outcomes, but the primary outcomes assessed in the review were stated clearly. By limiting the search to two databases the authors might have omitted some relevant studies. Two reviewers independently extracted the data, thus reducing the potential for bias and errors. However, the methods used to select the studies and assess validity were not described in full, so it is not known whether any efforts were made to reduce errors and bias.
Validity was assessed using established criteria and some relevant information on the included studies was tabulated.

The data were combined in a meta-analysis and statistical heterogeneity was assessed. Although there was no statistical heterogeneity, there were important differences between the two trials in the timing and duration of treatment and concomitant medication. Pre-planned subgroup analyses were used to explore the influence on the results of the type of medication and time of starting treatment. The authors discussed some of the limitations of the review: the inability to perform an intention-to-treat meta-analysis; the meta-analysis was based on a small number of patients; and differences between the studies in terms of the time when treatment was started, the drug used and the duration of treatment. About 40% of randomised patients could not be included in the analysis, but the authors did not explore the influence of dropouts on the results. Given the reported limitations of the review and the differences between the studies, any conclusions should be treated as suggestive rather than definitive.

**Implications of the review for practice and research**

**Practice:** The authors stated that routine administration of antiplatelet therapy after SAH cannot be recommended until further research is conducted.

**Research:** The authors stated that adequately powered RCTs are required to assess the effects of antiplatelet therapy after SAH.

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