Antifibrinolytic Therapy for Aneurysmal Subarachnoid Hemorrhage
A Major Update of a Cochrane Review

Yvo Roos, MD, PhD; Gabriel Rinkel, MD, FAHA; Marinus Vermeulen, MD, PhD; Ale Algra, MD, FAHA; Jan van Gijn, MD, FRCP(Edin)

Background
Rebleeding is an important cause of death and disability in aneurysmal subarachnoid hemorrhage. Rebleeding is probably caused by dissolution of the clot by activation of the fibrinolytic system.

Objectives
The objective of this review was to assess the effect of antifibrinolytic treatment in patients with aneurysmal subarachnoid hemorrhage.

Search Strategy
We searched the Cochrane Stroke Group Trials Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE (last search September 2002), and reference lists of articles. We also contacted drug companies.

Selection Criteria
Randomized trials comparing oral or intravenous antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid, or an equivalent) with control in patients with confirmed subarachnoid hemorrhage were selected.

Data Collection and Analysis
Two reviewers independently selected trials for inclusion and extracted the data. All 5 reviewers assessed trial quality.

Main Results
Nine trials involving 1399 patients were included. Three trials, involving 1041 patients, assessed outcome in terms of not only case fatality but also degree of dependence. In these 3 trials, antifibrinolytic treatment had no beneficial effect on poor outcome (death, vegetative state, or severe disability) with an odds ratio (OR) of 1.12, 95% CI 0.88 to 1.43 (Figure, A). Death from all causes was not significantly influenced by treatment across all 9 trials (OR 0.99, 95% CI 0.79 to 1.24). Figure, B shows that antifibrinolytic treatment reduced the risk of rebleeding at the end of follow-up (reported in all trials), with some heterogeneity between trials (OR 0.55, 95% CI 0.42 to 0.71). Treatment increased the risk of cerebral ischemia in 5 trials (OR 1.39, 95% CI 1.07 to 1.82) with considerable heterogeneity between the most recent study, in which specific measures to prevent cerebral ischemia were taken, and the 4 earlier studies (Figure, C). Antifibrinolytic treatment had no effect on the reported rate of hydrocephalus in 5 trials (OR 1.14, 95% CI 0.86 to 1.51).

Implications for Practice
In current clinical practice, surgery or endovascular treatment is often delayed for clinical or logistic reasons. In the meantime, these patients are at risk for rebleeding. Antifibrinolytics seem an attractive possibility for weathering this period, but this systematic review shows that although rebleeding is reduced by approximately 40%, clinical outcome does not improve because in these patients cerebral ischemia or at least impaired recovery from it is impeded by treatment with antifibrinolytics.

Implications for Research
The effects of antifibrinolytic treatment on cerebral ischemia after subarachnoid hemorrhage merit further investigation. We could not yet include a new trial from Sweden, in which 505 patients were admitted within 48 hours of the ictus and scheduled for aneurysm occlusion within 24 hours. Despite a reduction of the rebleeding rate with antifibrinolytics, the overall outcome after 6 months was not significantly better; details on the rate of ischemia are not yet available. It would be hard to justify further randomized trials of antifibrinolytic agents versus control in patients with subarachnoid hemorrhage until the ischemic complications are better understood and can be avoided or counteracted.

Reviewers’ Conclusions
Treatment with antifibrinolytics does not improve overall outcome because the reduction in the rate of rebleeding is
offset by an increase in poor outcome caused by cerebral ischemia. These findings do not support the routine use of antifibrinolytic drugs in the treatment of patients with aneurysmal subarachnoid hemorrhage.


Systematic review of trials comparing antifibrinolytic treatment with control treatment with or without placebo in patients with aneurysmal subarachnoid hemorrhage (SAH). Results expressed as Peto odds ratio (OR) with a fixed-effects model. OR < 1 suggest antifibrinolytic treatment superior to placebo or control treatment. A, no effect on poor outcome (death or severe disability on the Glasgow Outcome Scale) at 3 months follow-up, although antifibrinolytic treatment causes a significant reduction in the occurrence of rebleeding as shown in B. Apparently, the beneficial effect on rebleeding is largely counterbalanced by an increase in cerebral ischemia in patients with antifibrinolytic treatment as shown in C (Figures 1, 2, and 3. Roos YBWEM, Rinkel GJE, Vermeulen M, Algra A, van Gijn J. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. © Cochrane Library. Reproduced with permission from John Wiley & Sons Ltd.)

Reference
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