

COCHRANE REVIEW SUMMARY

Systematic review of antifibrinolytic treatment in aneurysmal subarachnoid haemorrhage

Although in recent years a tendency towards early operative clipping of the aneurysm to prevent rebleeding has emerged, rebleeding is still the major cause of poor outcome, more often than cerebral ischaemia.

Rebleeding is thought to originate from fibrinolysis of the clot at the site of the ruptured aneurysm. Because antifibrinolytic agents inhibit fibrinolytic activity and rapidly cross the blood-brain barrier after subarachnoid haemorrhage, antifibrinolytic therapy may reduce the rate of rebleeds and result in a decrease of morbidity and mortality.

Since the first report, published in 1967, on antifibrinolytic treatment in patients with subarachnoid haemorrhage, over 30 studies on antifibrinolytic therapy in aneurysmal subarachnoid haemorrhage have been published. Unfortunately most are uncontrolled and only a minority of the controlled studies is randomised. The randomised studies are the subject of this systematic review that investigates the effect of antifibrinolytic treatment on clinical outcome in patients with aneurysmal subarachnoid haemorrhage. In addition we analysed the reported rates of rebleeding, cerebral ischaemia, and hydrocephalus.

Methods

This review has drawn on the strategy developed for the Stroke Group of the Cochrane Collaboration as a whole; this implied, among others, electronic searching of the Medline database 1966-97 and the EMBASE-database 1988-97 with the search terms "subarachnoid haemorrhage" combined with "antifibrinolytic therapy" and hand search of the references quoted in the papers found in this way. Included in the review were all truly randomised unconfounded controlled trials in which, after concealed allocation, antifibrinolytic drugs were compared, in an intention to treat analysis, with control treatment (open studies) or placebo (blind studies). The main outcome of interest was poor outcome, defined as death, vegetative state, or severe disability on the Glasgow outcome scale at 3 months follow up. Because most trials did not report dependency but only case fatality, we performed a separate analysis on "death from all causes". In addition, we analysed the reported rates of rebleeding, cerebral ischaemia, and hydrocephalus.

For detailed information about the inclusion criteria ("types of studies", "types of participants", and "types of interventions") and the review techniques used ("data collection and

extraction" and "data analysis"), we refer to the Cochrane electronic version of this review.

Results

Eight trials met the predefined inclusion criteria.¹⁻⁸ These included 937 patients of whom 476 were randomised to receive antifibrinolytic drugs; 364 received placebo treatment and 97 patients received open control treatment.

Two studies recorded dependency in addition to mortality, and were used in the analysis of "poor outcome", our primary outcome of interest.^{2,3} In this analysis antifibrinolytic treatment showed no effect on outcome (relative risk (RR) 1.03, 95% confidence interval (95% CI) 0.86-1.22). There was also no effect of antifibrinolytic treatment in the analysis of the secondary outcome, "death from all causes", which was reported in all eight included studies (RR 0.97, 95% CI 0.81-1.17).

However, the frequency of rebleeding rates, reported in all included studies, was significantly reduced by antifibrinolytic therapy (RR 0.64, 95% CI 0.49-0.85). This was also true in the subgroup analysis of the five double blind, placebo controlled studies (RR 0.55, 95% CI 0.40-0.77).^{1-3,5,8}

The data of the four trials which reported cerebral ischaemia rates showed that antifibrinolytic treatment increased the risk of cerebral ischaemia (RR 1.77, 95% CI 1.30-2.40).^{2,3,6,7} Again, this was also true in the subgroup analysis of the two placebo controlled trials (RR 1.71, 95% CI 1.24-2.35).^{2,3}

Data from the four trials that reported on hydrocephalus showed that antifibrinolytic treatment had no significant effect on the rates of hydrocephalus (RR 1.04, 95% CI 0.77-1.42).^{2-4,7} The subgroup analysis in which only the two placebo controlled trials were included again showed no effect (RR 1.22, 95% CI 0.85-1.74).^{2,3}

Discussion

This systematic review shows that antifibrinolytic treatment reduces the rate of rebleeding by about 45% but does not affect the case fatality rate or overall outcome; the beneficial effect of the reduced rebleeding rate is offset by an increased rate of cerebral ischaemia.

However, the trials presented in this review were all done at least 10 years ago, when prevention or treatment of cerebral ischaemia was not used on a large scale. Since then, calcium antagonists have been shown to reduce the frequency of cerebral ischaemia by about

This review will also be published (and continuously updated) in electronic form by the Stroke Group of the Cochrane Collaboration in the Cochrane Database of Systematic Reviews, available through the BMJ Publishing Group.

33% and of poor outcome by 16%. A similar beneficial effect was also shown by prevention of hypovolaemia, in combination with restriction in the use of antihypertensive drugs. Moreover, several studies described reversal of ischaemia, once it had occurred, by plasma volume expansion. Therefore, antifibrinolytic treatment might nowadays be effective on overall outcome as many cerebral ischaemic complications can now be prevented or reversed. One uncontrolled study supports this hypothesis but a special writing group of the stroke council of the American Heart Association concluded in their *Guidelines for the management of aneurysmal subarachnoid haemorrhage* that, before this combined antifibrinolytic and anti-ischaemic treatment can be recommended, the effectiveness needs to be confirmed in a controlled study. The present reviewers are currently conducting such a randomised trial in which the primary objective is to investigate the effect of antifibrinolytic treatment on outcome.

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- 1 Van Rossum J, Wintzen AR, Endtz LJ, *et al.* Effect of tranexamic acid on rebleeding after subarachnoid hemorrhage: a double-blind controlled clinical trial. *Ann Neurol* 1977;2:238-42.
- 2 Vermeulen M, Lindsay KW, Murray GD, *et al.* Antifibrinolytic treatment in subarachnoid hemorrhage. *N Engl J Med* 1984;311:432-7.
- 3 Tsementzis SA, Hitchcock ER, Meyer CH. Benefits and risks of antifibrinolytic therapy in the management of ruptured intracranial aneurysms. A double-blind placebo-controlled study. *Acta Neurochirurgica* 1990;102:1-10.
- 4 Maurice-Williams RS. Prolonged antifibrinolysis: an effective non-surgical treatment for ruptured intracranial aneurysms? *BMJ* 1978;i:945-7.
- 5 Kaste M, Ramsay M. Tranexamic acid in subarachnoid hemorrhage. A double-blind study. *Stroke* 1979;10:519-22.
- 6 Girvin JP. The use of antifibrinolytic agents in the preoperative treatment of ruptured intracranial aneurysms. *Trans Am Neurol Assoc* 1973;98:150-2.
- 7 Fodstad H, Forssell A, Liliequist B, *et al.* Antifibrinolysis with tranexamic acid in aneurysmal subarachnoid hemorrhage: a consecutive controlled clinical trial. *Neurosurgery* 1981;8:158-65.
- 8 Chandra B. Treatment of subarachnoid hemorrhage from ruptured intracranial aneurysm with tranexamic acid: a double-blind clinical trial. *Ann Neurol* 1978;3:502-4.