Systematic review of antifibrinolytic treatment in aneurysmal subarachnoid haemorrhage
Roos, Y.B.W.E.M.; Vermeulen, M.; Rinkel, G.J.E.; Algra, A.; van Gijn, J.

Published in:
Journal of Neurology, Neurosurgery and Psychiatry

DOI:
10.1136/jnnp.65.6.942

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Systematic review of antifibrinolytic treatment in aneurysmal subarachnoid haemorrhage

Y B W E M ROOS, M VERMEULEN, G J E RINKEL, A ALGRA, J VAN GIJN and A ALGRA


Updated information and services can be found at:
http://jnnp.bmjournals.com/cgi/content/full/65/6/942

These include:

References
This article cites 8 articles, 2 of which can be accessed free at:
http://jnnp.bmjournals.com/cgi/content/full/65/6/942#BIBL

3 online articles that cite this article can be accessed at:
http://jnnp.bmjournals.com/cgi/content/full/65/6/942#otherarticles

Rapid responses
You can respond to this article at:
http://jnnp.bmjournals.com/cgi/eletter-submit/65/6/942

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

Sociology (341 articles)
Other Neurology (3636 articles)

Notes

To order reprints of this article go to:
http://www.bmjournals.com/cgi/reprintform

To subscribe to Journal of Neurology, Neurosurgery, and Psychiatry go to:
http://www.bmjournals.com/subscriptions/
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. 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. 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). 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). Again, this was also true in the subgroup analysis of the two placebo controlled trials (RR 1.71, 95% CI 1.30–2.40).

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). 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).

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...
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.

YR is funded by a research grant from the Dutch Heart Association (Nederlandse Hartstichting). GR is partially funded by a clinical investigator grant from the University Hospital Utrecht.

Y B W E M ROOS
M VERMEULEN

Department of Neurology, Academic Medical Centre, University of Amsterdam, The Netherlands

G J E RINKEL
A ALGRA
J VAN GIJN

Department of Neurology

Julius Centre for Patient Oriented Research, Clinical Epidemiology Unit, Academic Hospital Utrecht, The Netherlands

Correspondence to: Dr Yvo Roos, Department of Neurology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam-zuidoost, The Netherlands. Telephone 0031 20 5663647; fax 0031 20 6971438; email Y.R.ROOS@AMC.UVA.NL