

What is the role of aminocaproic acid in the management of cerebral bleed post-thrombolytic therapy?

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18 June 2001

## SUMMARY STATEMENT:

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Abdulwadud, O. (2001). What is the role of aminocaproic acid (Amicar) in the management of cerebral bleed post-thrombolytic therapy? [Online]. Available from <http://www.med.monash.edu.au/healthservices/cce>

[Access date]

**Form Version** – B.2001.01.04.1

## REQUEST:

What is the role of aminocaproic acid (Amicar) in the management of cerebral bleed post-thrombolytic therapy?

## REQUESTED BY:

Chris Rasmussen, Manager, Heart Unit, Dandenong Hospital

## METHODOLOGY

### Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

## **Details of Evidence Request**

Patient (subject): Management of cerebral bleeding  
Intervention: The use of Aminocaproic acids post-thrombolytic therapy  
Comparison: Not using aminocaproic acids, placebo, other treatments  
Outcomes: Best management practice, role, benefits, effects, adverse events.

### ***Search terms***

(see Appendix 2 for exact search strategy)

Condition terms: Subarachnoid haemorrhage, cerebral bleeds, cerebral haemorrhage.  
Intervention terms: Aminocaproic acids, Amicar, Epsilon-Aminocaproic acids  
Other terms: Thrombolytic therapy

## **Resources Searched**

We searched the following databases:

Cochrane Library CD-ROM- Issue 2, 2001

EBM Reviews (OVID)- 1<sup>st</sup> Quarter 2001

Medline (OVID)- Mid 1966 to May week 3 2001

CINAHL (OVID) – 1982 to May 2001

PreMedline (OVID)- June 6, 2001

Aggressive Research Intelligence Facility- April 11, 2001

NHS Centre for Reviews and Dissemination

National Guideline Clearinghouse

## **Refinements, Searching & Reporting Constraints:**

Our electronic searching was performed on 7 June 2001. Having identified the 1998 Systematic review by Roos et al from the Cochrane Library, a restriction period of 1999-2001 was applied while searching the other databases. The search was restricted to humans and articles published in English.

## RESULTS:

From our sources we identified 1 relevant systematic review by Roos et al. After examination of the full text, the article was critically appraised.

Table 1. Study designs of articles retrieved by search

Study Design	Number
<b>Systematic reviews or meta-analyses</b>	<b>1</b>
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudorandomised controlled trials	0
Controlled trials, cohort or case-control analytic studies	0

Based on our refinements, searching and reporting constraints we are reasonably confident this article represents the most relevant findings published to date.

## EVIDENCE SUMMARIES

### Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

## REFERENCES

### ARTICLE CRITICALLY APPRAISED

Roos YBWEM, Rinkel GJE, Vermeulen M, Algra A, van Gijn J (2001). Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage (Cochrane Review). In: The Cochrane Library, Issue 2 Oxford: Update Software.

# APPENDIX 1

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## Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
Level II	Evidence obtained from at least one properly designed randomised controlled trial.
Level III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
Level III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with a control group.
Level III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV	Evidence obtained from case series, either post-test or pre-test/post-test.

## APPENDIX 2

### Search strategy

	Search terms for Cochrane Library, EBM Reviews, Medline, CINAHL, PreMedline, ARIF, NHS Centre for Reviews & Dissemination
1	Exp Aminocaproic acids/
2	Aminocaproic acid\$.mp
3	Amicar.tw
4	Exp 6-aminocaproic acid/
5	6-aminocaproic acid.tw
6	Epsilon-aminocaproic acid.mp
7	Cy-116.tw
8	Caprocid.tw
9	Epsamon.tw
10	Epsikapron.tw
11	or/1-10
12	Exp subarachnoid hemorrhage/
13	Subarachnoid hemorrhage.tw
14	Cerebral bleed\$.mp
15	Exp cerebral hemorrhage/
16	Cerebral hemorrhage.tw
17	Or/12-16
18	11 and 17
19	Exp thrombolytic therapy/ or thrombolytic therapy.mp
20	18 and 19
21	Limit 20 to human, English language, 1999-2002

<p style="text-align: center;"><b>Evidence Summary Therapy/Intervention</b></p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p>Role of aminocaproic acid in the management of cerebral bleed post-thrombolytic therapy</p> </div>	<p style="text-align: center;"><b>Study 1</b></p> <p>Roos YBWEM, Rinkel GJE, et al. (2001). Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p style="text-align: center;"><b>Systematic review (Level I)</b></p>
<p><b>DESCRIPTION:</b> Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Patients (subjects):</b> Patients with clinical symptoms and signs of subarachnoid haemorrhage with confirmation of the diagnosis by the presence of subarachnoid blood on CT-scan or on Cerebrospinal Fluid examination.  <b>Intervention:</b> Antifibrinolytic drugs (tranexamic acid or epsilon aminocaproic acid or equivalent drugs), orally or intravenous, versus control treatment (open studies) or placebo treatment (blind studies).  <b>Comparisons:</b> (see above)  <b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• Poor outcome (death, vegetative state or severe disability) on the five point Glasgow Outcome Scale at 3-months follow up ('good outcome' being 'moderate disability' and 'recovered'). 'Deaths from all causes' at at least 3-weeks follow-up.</li> <li>• The effect of antifibrinolytic treatment on the rates of reported and CT-scan or autopsy confirmed (sensitivity analyses) first episodes of rebleeding, cerebral ischaemia and hydrocephalus.</li> </ul> <p><b>Incl &amp; Excl Criteria:</b> Randomised trials comparing oral or intravenous antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid or an equivalent) with control in people with confirmed subarachnoid haemorrhage. Trials were excluded if allocation to treatment or control group was not concealed. Trials were also excluded if an intention to treat analysis was not performed and could not be reconstructed on the basis of published data without a loss of 20% or more of all randomised patients.</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection</p>	<p><b>Search strategy:</b> The Cochrane Stroke Group trials register, reference lists of articles and contacted drug companies for unpublished studies.  <b>Methodological quality:</b></p> <ul style="list-style-type: none"> <li>• The eight studies reviewed were all randomised trials.</li> <li>• Seven of the eight studies used an intention to treat analysis and in one this analysis could be reconstructed.</li> <li>• Five studies used a double blind method (placebo controlled) and three used a control group with standard treatment without placebo.</li> <li>• One study used 'Flip-of-a-coin' randomisation as the method of allocation.</li> </ul> <p><b>Assessed validity:</b> Two reviewers independently selected trials for inclusion and extracted the data. All five reviewers assessed the quality of each trial.</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>Eight trials meet the inclusion criteria. These eight studies included 937 patients (476 patients received antifibrinolytic drugs, 364 placebo treatment and 97 patients control treatment). In one study Epsilon-aminocaproic acid was used (39 patients) and in all other studies tranexamic acid. Only two studies recorded not just mortality, but also dependency. Antifibrinolytic treatment did not provide any evidence of benefit on outcome (OR 1.05, 95% CL. 0.76-1.46). There is neither any evidence of benefit of antifibrinolytic treatment in the analysis on 'deaths from all causes' (OR 0.96, 95% CL. 0.72-1.26). Antifibrinolytic therapy reduces the risk of rebleeding significantly (OR 0.59, 95% CL. 0.42-0.81). This is also true in the sub-analysis on only the five double blind and placebo controlled studies (OR 0.50, 95% CL. 0.34-0.73) as in the sensitivity analysis on the two studies with CT-scan or autopsy confirmed rebleedings (OR 0.35, 95% CL. 0.22-0.57). However, in the four trials, which report cerebral ischaemia rates, antifibrinolytic treatment increases the risk of cerebral ischaemia (OR 2.03 95% CL. 1.40-2.94). Again this is also true in the sub-analysis on the two placebo controlled trials (OR 1.97 95% CL. 1.33-2.92) as in the sensitivity analysis on the two trials with CT-scan or autopsy confirmed cerebral ischaemia (OR 1.82, 95% CL. 1.15-2.90). In four trials hydrocephalus is reported; antifibrinolytic treatment has overall no</p>

	effect on the reported rates of hydrocephalus (OR 1.05, 95% CL. 0.71-1.56). In the sub-analysis on the placebo controlled studies antifibrinolytic treatment results in a non-significant increase of hydrocephalus (OR 1.28, 95% CL. 0.82-1.99), in the trials with control treatment antifibrinolytic therapy shows a trend towards a reduction in the rate of hydrocephalus (OR 0.55, 95% CL. 0.24-1.24).
<b>AUTHOR(S) CONCLUSIONS:</b> Limitations, implications for practice and research	"Antifibrinolytic treatment does not appear to benefit people with aneurysmal subarachnoid haemorrhage. However, the trials were all done more than 10 years ago. New strategies may counteract the ischaemia-inducing potential of antifibrinolytic treatment and lead to improved outcome. A trial of combined antifibrinolytic and anti-ischaemia treatment is underway."
<b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength	<p><b>Potential for bias:</b> Attempted to minimise publication bias by contacting drug companies. Search was not restricted to English language articles. Reviewed only randomised trials with high methodological qualities including those in which intention to treat analysis was performed.</p> <p><b>Weaknesses:</b></p> <ul style="list-style-type: none"> <li>• A substantive amendment to this systematic review was last made on 13 July 1998.</li> <li>• Although the reviewers stated they have conducted a multicenter controlled study of their own and would publish their results in late 1998, we could not locate their study in the databases we have searched.</li> <li>• We aren't sure why the authors didn't search other databases outside the Cochrane Stroke Group trials register.</li> </ul> <p><b>Strength/s:</b></p> <ul style="list-style-type: none"> <li>• Well defined research question</li> <li>• Clear inclusion criteria</li> <li>• Only Randomised trials were included in the review</li> <li>• No language restriction was applied in the search for articles.</li> <li>• Reviewers acknowledged implications of their findings for practice and future research</li> </ul>

## EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

**Level of evidence:** A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

**Intervention:** A therapeutic procedure such as treatment with a pharmaceutical agent, surgery, a dietary supplement, a dietary change or psychotherapy.

**Randomisation:** A process of allocating participants to treatment or control group within a controlled trial by using a random mechanism, such as coin toss, random number table or computer-generated random numbers. Study subjects have an equal chance of being allocated to an intervention or control group; thus, the two groups are comparable. Randomisation ensures that the results are not biased by the selection of particular types of patients to receive a specific therapy.

**Blinding:** Blinding or masking is a process used in epidemiological studies and clinical trials in which the observers and the subjects have no knowledge as to which treatment groups subjects are assigned. It is undertaken in order to minimise bias occurring in patient response and outcome measurement.

**All patients accounted for:** Once patients are randomly allocated to a specific group and withdraw before study conclusion, they have to be accounted for in order to ensure that patients withdrawing from the study are not significantly different from those continuing in the study. The final analysis should be conducted on an intention-to-treat basis, which includes the results of withdrawn patients in the analysis.

**Patients treated equally:** To be able to attribute any difference in the observed outcome to the intervention, study patients need to be treated equally in every way except for the intervention being evaluated.

**Similar groups:** Baseline characteristics of patients that are also likely to affect results should be evenly distributed between the intervention and control groups. Following proper randomisation, patients' attributes would be expected to be equally distributed between groups.

### **Validity:**

Of measurement: an expression of the degree to which a measurement measures what it purports to measure; it includes construct and content validity.

Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

**Potential for bias:** Bias is a systematic deviation of a measurement from the 'true' value leading to either an over (or under) estimation of the treatment effect. Bias can originate from many different sources (including allocation of patients, measurement, interpretation, publication and review of data).