The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials

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CRD summary
This review found that thrombotic events in adults with spontaneous bleeding, treated with antifibrinolytic drugs, were rare, except cerebral infarction after a subarachnoid haemorrhage. The limitations of the review process and the evidence mean that these findings should be interpreted with caution.

Authors' objectives
To assess the frequency of thrombotic events in adults with spontaneous bleeding, treated with antifibrinolytic drugs.

Searching
MEDLINE (from 1966), EMBASE (from 1980) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in October 2009. It was not clear whether any language restrictions were applied. The search strategies were reported. Bibliographies of identified studies and review articles were searched. Where the full-text article was not available, attempts were made to contact the authors.

Study selection
Studies of patients over 16 years old, that evaluated an antifibrinolytic agent for spontaneous bleeding unrelated to haemophilia, trauma, surgery or an iatrogenic cause, were eligible for inclusion. Studies had to include more than 20 patients and report an explicit qualitative or quantitative statement on the occurrence of thrombotic events. Eligible designs were observational studies, case series, and non-randomised or randomised controlled trials (RCTs). Studies of any antifibrinolytic agent (tranexamic acid, epsilon-aminocaproic acid or aprotinin), given orally or intravenously, were eligible.

In the included studies, the most common drug was tranexamic acid, ranging in dose from 0.5g to 12g per day. Treatment lasted from one dose to 84 days. Epsilon-aminocaproic acid dose ranged from 4g to 48g per day, with treatment lasting from one to 216 days. Both drugs were given orally, intravenously, or intravenously then orally. The most common indication for treatment was subarachnoid haemorrhage; other indications were: acute promyelocytic leukaemia, acute myeloid leukaemia, upper gastrointestinal bleeding, ulcerative colitis, intracerebral haemorrhage, post-partum haemorrhage, menorrhagia, urinary tract bleeding, cirrhosis, thrombocytopaenic bleeding, placental abruption, and epistaxis. Where reported, the median age was 49 years (range 38 to 68). Comorbidities were described in about a third of studies. Most studies that reported it excluded patients with a history of thrombotic disease, but many studies did not report it. Outcomes were deep vein thrombosis or pulmonary embolism, cerebral infarction, peripheral ischaemia and myocardial infarction.

One reviewer selected studies; uncertainties were discussed with the other reviewer.

Assessment of study quality
Studies were assessed for selective outcome reporting and incomplete outcome data. Cochrane reviewers’ assessments of the quality of the RCTs included in the review, were considered.

The authors did not state how many reviewers assessed quality.

Data extraction
The proportion of patients with thrombotic events was extracted from observational studies, and from the intervention arms of controlled trials. The data were extracted by one reviewer.

Methods of synthesis
The study data were combined using a random-effects meta-analysis, based on DerSimonian and Laird's method, to
estimate the pooled frequencies of adverse events, with 95% confidence intervals. Heterogeneity between studies was assessed using $I^2$. Analyses were planned for the following subgroups: indication for treatment, age, presence of comorbidities, total dose, duration and route of therapy.

**Results of the review**

Fifty-seven studies (5,049 patients) were included in the review, including 30 RCTs, nine controlled studies and 18 observational case series. Sample sizes ranged from 12 to 1,114 patients. The completeness of reporting of the review's primary outcomes ranged from 77% to 91%.

In patients treated with tranexamic acid (3,414 patients), the frequency of deep vein thrombosis or pulmonary embolism was 1.9% (95% CI 1.1 to 2.9; 39 studies; $I^2=63$%), the frequencies of peripheral ischaemia and myocardial infarction were each under 0.5% (34 studies; $I^2=0$). The overall risk of cerebral infarction was 5.1% (95% CI 2.0 to 9.5; 37 studies; $I^2=95$%), but this varied by indication; the frequency was 9.7% (95% CI 5.5 to 14.8; 14 studies) for patients with subarachnoid haemorrhage, and zero (95% CI zero to 0.5%; 23 studies) for patients with other indications.

In patients treated with epsilon-aminocaproic acid (1,635 patients), the frequency of deep vein thrombosis or pulmonary embolism was 3.0% (95% CI 1.8 to 4.6; 16 studies; $I^2=46$%), the frequencies of peripheral ischaemia (13 studies) and myocardial infarction (12 studies) were each under 1%. The overall risk of cerebral infarction was 6.0% (95% CI 1.1 to 14.3; 12 studies; $I^2=92$%), but this varied by indication; the frequency was 7.7% (95% CI 1.8 to 17.4; seven studies) for patients with subarachnoid haemorrhage, and zero (95% CI zero to 2.1%; five studies) for patients with other indications.

**Authors' conclusions**

Thrombotic events following antifibrinolytic therapy were infrequent, except cerebral infarction after a subarachnoid haemorrhage.

**CRD commentary**

The review question was clear. The eligibility criteria were well defined and appropriate. The search was in several databases and was likely to have identified most of the relevant published studies. Publication bias was not assessed. The authors noted that the exclusion of identified studies that could not be accessed in full was unlikely to have affected their results. As no language criteria were stated, it is not clear whether the results could have been affected by language bias. One reviewer selected the studies, extracted the data and assessed quality, meaning that errors and bias were possible. It was not clear whether the outcome definitions were similar, and hence comparable, across studies. The duration of follow-up in the included studies was not stated.

The validity assessment was brief, and insufficient for the observational studies, so the quality of the included studies was unclear. It was unclear whether the meta-analysis was appropriate; the trials varied in their drug dose and treatment regimens, so it is unclear how clinically relevant it was to pool the data. Attempts were made to investigate heterogeneity in subgroup analyses, and the authors acknowledged that poor reporting of the included studies meant that they could not investigate this further.

The limitations of the review process and the evidence mean that the findings should be interpreted with caution.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that RCTs of the efficacy and safety of antifibrinolytic drugs in the treatment of spontaneous bleeding were warranted, in particular Phase II RCTs of tranexamic acid for intracerebral haemorrhage. They recommend that studies should stratify their results by age and comorbidities, and report the neurological outcomes, such as seizures. They stated that a RCT of tranexamic acid in intracerebral haemorrhage was underway in the UK (details given in the review).

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