Tranexamic acid: a review of its use in surgery and other indications  
Dunn C J, Goa K L

Authors' objectives  
This review examines the status of tranexamic acid (TRA) in the management of surgical and other conditions in which antifibrinolytic therapy is appropriate.

Searching  
Medical literature published in any language since 1966 on tranexamic acid, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), MEDLINE and EMBASE. Searches were last updated 30 April 1999. Additional references were identified from the reference lists of published articles. Bibliographic information, including contributory unpublished data, was also requested from the company developing the drug.

Study selection  
Study designs of evaluations included in the review  
Most studies were randomised, double-blind placebo controlled studies, but non-randomised trials were also included as were studies without the use of placebo in the control group.

Specific interventions included in the review  
1. Use of TRA in cardiac surgery with cardiopulmonary bypass (CPB): 2.5 to 40 mg/kg before or after CPB (sometimes followed by 0.25-4 mg/kg/h for 5-12h or during surgery) or 10-15g TRA (either without anything or followed by placebo infusion during surgery or infused over 20min after anaesthesia induction or after heparinisation) versus placebo or eta-aminocaproic acid (EACA) or desmopressin (DES) or TRA + DES or aprotinin + kallikrein inhibitor units or no antifibrinolytic therapy or dipyridamole.

2. Use of TRA in acute upper gastrointestinal bleeding:
1-2g TRA (6-3 times a day during 2-7 days, orally or intravenously) versus placebo or cimetidine.

3. Use of TRA in oral surgery:
4.8-5% TRA w/v for 2 min (4 times daily) for 7 days after surgery versus placebo.

4. Use of TRA in orthopaedic surgery:
10-15mg/kg intravenous infusion before release of tourniquet and after 3h versus placebo.

Participants included in the review  
1704 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB); 1471 patients suffering from bleeding from gastrointestinal lesions; 158 patients undergoing oral surgery; 145 patients undergoing orthopaedic surgery; 148 gynaecology patients and patients undergoing other types of surgery or suffering from ocular trauma, hereditary angioneurotic oedema and subarachnoid haemorrhage (no numbers reported).

Outcomes assessed in the review  
The most important outcome of the use of TRA in cardiac surgery with cardiopulmonary bypass (CPB) is reduction in use of allogeneic blood products. Intermediate outcomes are postoperative bleeding, coagulation profiles and platelet counts.

Primary outcomes of TRA in upper gastrointestinal bleeding are deaths, number of patients with rebleeding and number of patients needing surgery.
The primary outcome of TRA in oral surgery is the percentage of patients with postoperative bleeding complications.

Primary outcomes of TRA in other types of surgery are reduction of perioperative blood loss and transfusion requirements.

Primary outcomes of TRA use in gynaecology are mean menstrual blood loss, mean duration of menses and number of sanitary towels used.

How were decisions on the relevance of primary studies made?
Studies in patients undergoing surgery and those with haemorrhagic disorders who received tranexamic acid were selected. Inclusion of studies was based mainly on the methods sections of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data were also included. It was not reported how many reviewers were involved in the data extraction.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
Studies were described in a narrative manner according to indication.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
There were 16 studies evaluating the use of TRA in cardiac surgery, 6 trials in upper gastrotestinal bleeding, 3 trials in oral surgery, 2 trials in orthopaedic surgery trials in gynaecology and several other trials evaluating the use of TRA in other indications were included.

Intravenously administered TRA caused reductions relative to placebo of 29-54% in postoperative blood losses in patients undergoing cardiac surgery with CPB, with statistically significant reductions in transfusion requirements in some studies. TRA had similar efficacy to aprotinin 2 \times 10^{-6} (ten to the power of 6) kallikrein inhibitory units and was superior to dipyridamole in the reduction of postoperative blood losses. Transfusion requirements were reduced significantly by 43% with TRA and by 60% with aprotinin in 1 study. TRA was associated with reductions relative to placebo in mortality of 5-54% in patients with upper gastrointestinal bleeding.

Reductions of 34-57.9% versus placebo or control in mean menstrual blood loss occurred during TRA therapy in women with menorrhagia; the drug has also been used to good effect in placental bleeding, postpartum haemorrhage and connisation of the cervix. TRA significantly reduced mean blood losses after oral surgery in patients with haemophilia and was effective as a mouthwash in dental patients receiving oral anticoagulants.

Reductions in blood loss were also obtained with the use of the drug in patients undergoing orthotopic liver transplantation or transurethral prostatic surgery, and rates of rebleeding were reduced in patients with traumatic hyphaema. Clinical benefit has also been reported with TRA in patients with hereditary angioneurotic oedema. TRA is well tolerated, nausea and diarrhoea are the most common adverse events. Increased risk of thrombosis with the drug has not been demonstrated in clinical trials.
Cost information
The authors state that, although no cost-analysis of patients receiving TRA specifically has been carried out, several authors have pointed out that the acquisition cost of the drug is considerably lower than that of aprotinin, and that its use circumvents any risk of allergic reactions and sensitations.

Authors’ conclusions
Tranexamic acid is useful in a wide range of haemorrhagic conditions. The drug reduces postoperative blood losses and transfusion requirements in a number of types of surgery, with potential cost and tolerability advantages over aprotinin, and appears to reduce rates of mortality and urgent surgery in patients with upper gastrointestinal haemorrhage. Tranexamic acid reduces menstrual blood loss and it is a possible alternative to surgery in menorrhagia, and has been used successfully to control bleeding in pregnancy.

CRD commentary
The review question was clear and the inclusion criteria seem well chosen. The databases searched and search strategy seem complete and appropriate. Authors did not report the way how decisions on inclusion or exclusion of studies were taken and how data extraction was done. There is no information on the quality of studies included.

The authors did not attempt to generate a summary estimate of effect across studies. Instead they described the results of primary studies in a narrative way, which seems appropriate given the heterogeneity of interventions. The conclusions of the review author seem to follow from the evidence presented although, due to the limitations mentioned above, they should be treated with caution.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.