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THERAPEUTICS

# Efficacy and safety of tranexamic acid in acute haemorrhage

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**What you need to know**

- Tranexamic acid is a synthetic haemostatic drug that inhibits fibrinolysis
- It is effective in reducing bleeding and mortality, although to different extents in trauma, peripartum, and surgical settings
- It is generally safe and inexpensive with few adverse reactions, although further studies are needed to assess its safety in settings of high thromboembolic risk

*A 33 year old woman in the fourth month of pregnancy is referred to the emergency department because of spontaneous massive antepartum haemorrhage. On admission her haemoglobin level has dropped to 7 g/dL and she is transfused with three packed red blood cell units. Her coagulation parameters are normal but sonography of the fetus reveals a formerly unknown placenta praevia. Bleeding stops immediately after placement into the vagina of a cotton swab soaked with a 1000 mg vial of tranexamic acid. In addition, on-demand oral therapy with tranexamic acid (1000 mg every eight hours) is prescribed at home during minor bleedings for the rest of the pregnancy, enabling successful delivery by caesarean section at week 31.*

## Acute haemorrhage

Haemorrhage is historically defined as the loss of 20% or more of the total blood volume (albeit recent definitions are more focused on haemodynamics[1]), which is associated with an increased risk of morbidity and mortality. The most common causes of severe blood loss include major surgery (especially cardiovascular, liver, and orthopaedic interventions), traumas, and the peripartum period.[2] Postoperative, peripartum, and trauma related bleeding often requires blood transfusions which are lifesaving but have drawbacks, such as scarcity of units, the risk of mismatched transfusion, allergic reactions, transfusion related acute lung injury, and transfusion associated circulatory overload.[2] To minimise the need for transfusions in patients with acute bleeding, several surgical procedures, anaesthetic techniques, and haemostatic medications have been developed. Among the haemostatic medications, tranexamic acid is one of the most commonly used.

## What is tranexamic acid?

Tranexamic acid is a synthetic lysine related anti-fibrinolytic amino acid which binds reversibly to the lysine receptor sites of plasminogen, thereby inhibiting the interaction with formed plasmin and fibrin.[2 3] As a result, fibrin degradation is prevented, and the framework of the fibrin's matrix structure is preserved.[3-5] Tranexamic acid is more commonly used than the other lysine derivative ε-aminocaproic acid (EACA) as it has a 10-fold greater potency.[3]

Because of its ability to inhibit fibrinolysis and clot degradation, tranexamic acid has been used successfully to prevent or reduce blood loss in various clinical conditions characterised by excessive bleeding[6 7] in adults and in children over the age of 1.[8 9] Characteristics of tranexamic acid are presented in table 1.

**Table 1 | Characteristics of tranexamic acid**

| | Tranexamic acid |
|---|---|
| Chemical name | *trans*-4-aminomethylcyclohexanecarboxylic acid |
| Mechanism of action | Anti-fibrinolytic agent. Competitive inhibitor of plasminogen activation |
| Dosage forms | 250-500 mg tablets; 500 mg/5 mL vials; 1000 mg/10 mL vials |
| Route of administration | Oral, topical, or intravenous |
| Dose | 15 mg/kg every 6-8 hours. Dose adjustment in patients with renal failure according to serum creatinine levels. Tranexamic acid is approved in children from 1 year of age. Dosages are calculated based on children's weight |
| Adverse events | Changes to vision (with prolonged treatment). Gastrointestinal symptoms and allergic reactions (skin rash). Concomitant use with oral contraceptives or oestrogens may potentiate a hypercoagulable state. Uncertain risk for venous thromboembolism |

The drug is not a magic bullet, however.[10] Since its enthusiastic reception in the 1960s,[11] researchers have taken a more balanced view of its safety and efficacy.[12 13]

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. To suggest a topic, please email us at practice@bmj.com

## How well does tranexamic acid work in acute haemorrhage?

Trials of tranexamic acid have been conducted in acute trauma, surgery, gastrointestinal bleeding, and peripartum haemorrhage. Key points are presented in the following sections and major trials summarised in table 2. This article primarily focuses on the use of intravenous tranexamic acid in the acute inpatient setting.

Table 2 | Clinical results of the largest randomised controlled trials on the use of tranexamic acid for the treatment of acute bleeding

| Trial | Design | Patients/controls (n) | Results |
|---|---|---|---|
| CRASH-2[21] | Trauma patients randomised to receive tranexamic acid or placebo | 10 096/10 115 | Reduction of all-cause of death (placebo 16% *v* tranexamic acid 14.5%; absolute mortality risk reduction=1.5%; NTT=67; RR 0.91, 95% CI 0.85 to 0.97, P=0.0035) and bleeding-related death (placebo 5.7% *v* tranexamic acid 4.9%; absolute mortality risk reduction=0.8%; NTT=125; RR 0.85, 95% CI 0.76 to 0.96, P=0.0077) |
| CRASH-3[14] | Patients with recent traumatic brain injury randomised to receive tranexamic acid or placebo | 6406/6331 | Reduction of the risk of head injury-related death with tranexamic acid versus placebo in patients treated within 3 hours of injury (placebo 19.8% *v* tranexamic acid 18.5%; absolute mortality risk reduction=1.3%; NTT=77) and in patients with mild-to-moderate head injury (RR 0.78, 95% CI 0.64 to 0.95) |
| WOMAN[15] | Women with postpartum haemorrhage randomised to receive tranexamic acid or placebo | 10 051/10 009 | Death caused by bleeding: placebo 1.9% *v* tranexamic acid 1.5% (RR 0.81; 95% CI 0.65 to 1.00; P=0.045); absolute mortality risk reduction=0.4%; NTT=250, and death if tranexamic acid within 3 hours: placebo 1.7% *v* tranexamic acid 1.2% (RR 0.69; 95% CI 0.52 to 0.91; P=0.008); absolute mortality risk reduction=0.5%; NTT=200, and laparotomy to control bleeding: placebo 1.3% *v* TXA 0.8% (RR 0.64; 95% CI 0.49 to 0.85; P=0.002); absolute mortality risk reduction=0.5%; NTT=200, and no significant differences in composite primary endpoint (death from all causes or hysterectomy): placebo 5.5% *v* tranexamic acid 5.3% or hysterectomy: placebo 3.5% *v* tranexamic acid 3.6%; RR 1.02, 95% CI, 0.88 to 1.07; P=0.84 |
| HALT-IT[16] | Patients with acute gastrointestinal bleeding randomised to receive tranexamic acid or placebo | 5994/6015 | Tranexamic acid did not reduce death from gastrointestinal bleeding (RR 0.99, 95% CI 0.82 to 1.18) |
| PATCH[17] | Trauma patients randomised to receive tranexamic acid or placebo | 661/646 | Tranexamic acid led to reduced mortality at 1 month (RR 0.79) and 6 months (RR 0.83), but no difference in functional outcome at 6 months |
| TRAAP2[18] | Women undergoing caesarean delivery randomised to receive tranexamic acid or placebo | 2086/2067 | Prophylactic tranexamic acid significantly reduced postpartum haemorrhage incidence (adjusted RR 0.84, 95% CI 0.75 to 0.94; P=0.003) compared with placebo |

RR=risk ratio; NNT=number needed to treat

### Trauma

Two randomised controlled trials (RCTs) (n=20 451) have assessed the effect of tranexamic acid in acute trauma. The larger of these (CRASH-2, n=20 211)[15] was conducted in 40 countries and included patients with a variety of trauma; the other (CRASH-3, n=240)[16] was restricted to those with traumatic brain injury. These trials found a lower mortality rate in patients with acute traumatic injury receiving tranexamic acid compared with the placebo group. In CRASH-2 (which, within eight hours of injury, infused 1 g tranexamic acid over 10 minutes followed by 1 g over eight hours[19]), however, 65% of all deaths and 55% of deaths within one hour were not related to bleeding, and the bleeding-related absolute reduction of mortality of 0.8% connotes a number needed to treat of 125. In addition, CRASH-3[20] found a significant reduction in head injury-related death (modified primary endpoint), but not in overall mortality which was the original primary endpoint (only when patients with poorer prognosis were excluded in a sensitivity analysis).[21] The international placebo controlled PATCH RCT which included 1310 adults with major trauma found that pre-hospital administration of 1 g bolus tranexamic acid followed by 1 g infusion over eight hours led to reduced mortality at one month (relative risk, RR, 0.79; 95% CI 0.63 to 0.99) but no difference in favourable functional outcome at six months.[17 22]

A recent systematic review of tranexamic acid use in paediatric trauma found that children treated with tranexamic acid had longer survival despite more severe injuries and worse prognostic

predictors compared with those who did not receive tranexamic acid.[23] The European Medicine Agency's recommended dose of tranexamic acid for children is generally 15 mg/kg of body weight given by intravenous injection every 8-12 hours until bleeding is controlled.[9]

### Surgery

Tranexamic acid has been used successfully to reduce blood loss in several surgical specialties, especially in cardiac and major orthopaedic surgery.[15 16 24 25] It is considered fundamental to blood management programmes in transfusion medicine, which aim to minimise perioperative blood loss and thus exposure to allogeneic blood in elective surgeries.[14 26 27] In the ATACAS RCT that included 4662 patients undergoing cardiac surgery, those randomised to receive tranexamic acid had half the number of major haemorrhages or episodes of cardiac tamponade (1.4% *v* 2.8%, P=0.001) compared with those receiving placebo.[28]

In the POISE-3 RCT, tranexamic acid (1 g intravenously at the start and end of surgery) was compared with placebo in 9535 patients having non-cardiac surgery who were at risk for bleeding and cardiovascular events and were receiving one or more long term antihypertensive medications. The trial found a significantly lower incidence of composite bleeding (life threatening bleeding, major bleeding, or bleeding into a critical organ) at 30 days (9.1% *v* 11.7%, hazard ratio, HR, 0.76, 95% CI 0.67 to 0.87, equivalent to a number needed to treat of 38), but not of cardiovascular events (14.2% *v* 13.9%, HR 1.02, 95% CI 0.92 to 1.14) in the tranexamic acid-treated group than in the placebo group.[29]

### Gastrointestinal and other acute haemorrhages

In the HALT-IT RCT conducted in patients with acute gastrointestinal bleeding, tranexamic acid did not reduce deaths (risk ratio 0.99, 95% CI 0.82 to 1.18)[30] and showed an increased risk of venous thromboembolic events (RR 1.85, 95 CI 1.15 to 2.98) and seizures (RR 1.73, 95% CI 1.03 to 2.93),[31] potentially because of the high tranexamic acid dose (4 g) or late treatment initiation. Similarly, no beneficial effect was seen in patients with haematological malignancy in the A-TREAT study,[32] in patients with intracerebral haemorrhage in the STOP-AUST study,[33] or those with subarachnoid haemorrhage in the ULTRA study.[34] For hyperacute primary intracerebral haemorrhage, the TICH-2 study did not show a better functional outcome after 90 days for tranexamic acid compared with placebo.[35]

### Peripartum haemorrhage

The WOMAN RCT was conducted in women with postpartum haemorrhage (PPH) after vaginal delivery or caesarean section (table 2) and found a marginal but statistically significant effect of 1 g intravenous tranexamic acid (followed by another 1 g if bleeding continued) on reduction of death caused by bleeding (RR 0.81, 95% CI 0.65 to 1.00; P=0.045).[36] This absolute reduction was 0.4% (death caused by bleeding) or 0.5% (death if tranexamic acid was given within three hours of delivery), implying a number needed to treat of 250 and 200, respectively, to prevent one death.[37] In the recent E-MOTIVE RCT recruiting 210 132 women undergoing vaginal deliveries in southern Africa, a holistic multi-component intervention (which included tranexamic acid) reduced major bleeding and maternal mortality following postpartum haemorrhage compared with usual care (1.6% *v* 4.3%, risk ratio, 0.4, 95% CI 0.32 to 0.50, P<0.001).[38] A Cochrane systematic review on three RCTs involving 20 412 women concluded that tranexamic acid administered intravenously reduces mortality caused by bleeding in women with primary postpartum haemorrhage, irrespective of mode of birth, and without increasing the risk of thromboembolic events.[39]

In the TRAAP2 RCT, among 4551 women who underwent caesarean delivery and received prophylactic uterotonic agents, prophylactic administration of tranexamic acid resulted in a statistically significantly lower incidence of calculated estimated blood loss >1000 mL or red cell transfusion by day two than placebo (reduction of blood loss of 107 mL (-63 to -152 mL).[40 41] In contrast, a double blind RCT of 10 995 women undergoing caesarean section found no reduction in red blood cell transfusions but a modest decrease in the use of uterotonics when delivering 1 g intravenous tranexamic acid immediately after cord clamping. Prophylactic intravenous tranexamic acid did not improve blood loss-related outcomes in another RCT on 4079 women with single pregnancy and vaginal delivery.[42] Finally, an overview including 14 systematic reviews of tranexamic acid after caesarean section concluded that prophylactic tranexamic acid may reduce blood transfusion, but rigorous well designed research is still needed due to the limitations of the included studies.[43]

## What are the harms?

### Serious adverse events

The main perceived risk of tranexamic acid is the onset of thrombotic complications owing to its inhibition of fibrinolysis, which is a natural mechanism of defence against thrombus formation. Most publications do not systematically search for thromboembolic complications or even exclude patients at risk, and this between-studies clinical heterogeneity could represent a serious limitation for meta-analyses. Evidence is conflicting and often lacking, but we believe there is an increased risk for those already at high risk of thrombosis. For example, a meta-analysis of 216 clinical trials including 125 550 participants did not find an association between intravenous tranexamic acid treatment and thromboembolic events, and no increased risk of vascular occlusive events in patients with a history of previous thromboembolism.[44] The TRAAP-2 trial, which evaluated the effect of tranexamic acid in preventing blood loss in 4153 caesarean deliveries, found an adjusted risk ratio (aRR) for deep vein thrombosis or pulmonary embolism of 4.01 (95% CI 0.85 to 18.92) three months after delivery and an aRR for arterial embolisation, emergency surgery, or hysterectomy of 1.84 (95% CI 0.73 to 4.62).[40] In trauma, tranexamic acid is a potential adjunctive thromboembolic risk factor,[45] and a recent meta-analysis found an odds ratio (OR) of 2.60 (95% CI 1.7 to 4.1; P<0.001) for the development of thromboembolic events after tranexamic acid administration.[46] Another meta-analysis found a pooled incidence of in-hospital thrombotic events of 5.9% (95% CI 3.3% to 8.5%), about three times higher than that reported in the CRASH-2 trial (2.0%, 95% CI 1.8% to 2.3%).[47] Nevertheless, a recent systematic review and meta-analysis, including 73 RCTs and evaluating the safety of tranexamic acid in the setting of orthopaedic surgery (a procedure carrying an increased thromboembolic risk), found a similar incidence of venous thrombotic events in tranexamic acid -treated patients and controls.[48]

The profound toxicity of inadvertent intrathecal tranexamic acid administration in place of obstetric spinal anaesthesia resulted in a 50% mortality owing to neurotoxicity and seizures across case reports and series.[49]

### Minor adverse events

Other side effects of tranexamic acid use include visual changes or involve the gastrointestinal tract, and are typically dose dependent. Gastrointestinal symptoms, which include nausea, vomiting,

dyspepsia, and diarrhoea, often subside with dose reduction. Hypotension and bradycardia may occur with excessively rapid intravenous infusion. Seizures have been reported with tranexamic acid administration, especially at high doses.[3] Hypersensitivity reactions, such as rash and rarely anaphylaxis, may occur. Tranexamic acid is contraindicated in patients with haematuria because blood from the upper urinary tract can provoke painful clot retention.[3]

## How cost effective is tranexamic acid?

Tranexamic acid is inexpensive and widely available. In addition, its use in patient blood management programmes has shown potential to improve patients' outcomes and thus reduce hospital related costs (in terms of length of stay in hospital and transfusion requirements). Tranexamic acid is about 1000 times cheaper per treatment course than recombinant factor VII activated (rFVIIa), which is shown to be beneficial in preventing obstetric haemorrhage.[50] A head-to-head cost effectiveness analysis between these two agents has not yet been performed, however.

Tranexamic acid at vaginal delivery has a 65-73% probability of saving costs from hospital resources[51] and is likely to be cost effective in countries in sub-Saharan Africa and southern Asia that have a high baseline risk of death from bleeding.[18]

## How does tranexamic acid compare with other treatments?

Tranexamic acid is usually preferred to the other authorised antifibrinolytic agent EACA because it is 10 times more potent and has fewer adverse effects, particularly those involving the gastrointestinal tract. Tranexamic acid can be used in association with the synthetic agent desmopressin to further reduce bleeding.[52] A recent systematic review, assessing the safety and efficacy of the haemostatic agents tranexamic acid, desmopressin, and aprotinin to reduce bleeding and transfusion in major open vascular and endovascular surgery, suggested no effect of tranexamic acid on the risk of thromboembolic events, but did not reach definitive conclusions regarding superiority in terms of efficacy (primary outcomes analysed: all-cause mortality and units of red blood cells transfused) over other agents because of the low certainty of evidence from the RCTs included.[53]

### Education into practice

- How often do you consider tranexamic acid for the management of surgery or trauma related acute haemorrhagic complications?
- How many tranexamic acid related thromboembolic complications have you seen during your practice?

### How patients were involved in the creation of this article

Members of the Italian Association of Anticoagulated Patients (AIPA), section of Mantua (Italy), reviewed this paper and made suggestions regarding content and clarity of the manuscript, in particular on dosages and safety issues.

### Search strategy

On June 1 2023 we searched PubMed (NLM database) and the Cochrane Library using the terms "tranexamic acid", "acute hemorrhage", "trauma", and "obstetrics" for clinical studies and systematic reviews exploring the safety and effectiveness of tranexamic acid in haemorrhage. We used no temporal limits and searched only for papers in English. In addition to this electronic search, we also screened the reference lists of the most relevant reviews and original articles for additional studies not captured in our initial literature search.

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