Uses of tranexamic acid

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Revalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 1A02, 2A06, 3A10

Key points

- Fibrinolysis is an important component of the coagulopathy associated with bleeding in medical, surgical, and trauma patients.
- Tranexamic acid is a synthetic lysine analogue which inhibits fibrinolysis, promotes clot stability, and may reduce inflammation.
- When administered to medical, elective, and emergency surgical patients, tranexamic acid can reduce bleeding and transfusion requirements.
- Current evidence suggests no increase in thromboembolic complications associated with tranexamic acid use.
- Studies suggest that tranexamic acid reduces bleeding and mortality associated with trauma.

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Tranexamic acid is an antifibrinolytic drug used in the prevention and treatment of excessive bleeding both in primary and secondary care. First described in the 1960s, recent years have seen a resurgence of interest in its use in the management of bleeding[1,2] and particularly in the context of severe trauma.[3]

Fibrinolysis

Fibrinolysis is a key component of the haemostatic processes that maintain patency of the vascular system. Circulating plasminogen is converted to the serine protease plasmin by the enzyme tissue plasminogen activator (tPA), causing the breakdown of fibrin to fibrin degradation products (FDPs). Fibrinolysis is regulated by a complex series of interactions and feedback mechanisms.

Fibrinolysis has been implicated in the pathogenesis of coagulopathy after severe tissue damage, or trauma. It is postulated that hypoperfusion, hypoxia, and up-regulation of tPA contribute to drive the balance of haemostasis towards 'hyperfibrinolysis' and subsequent coagulopathy.

Plasmin also activates monocytes, neutrophils, and the complement pathway, leading to the development of inflammation and is not simply involved in fibrinolytic systems. This highlights the close interaction between coagulation, inflammation, and immunological processes as part of the host defence mechanism.

Fibrinolysis can be monitored via changes in blood markers (e.g. D-dimer, FDPs, Plasminogen activator inhibitor-1), by measuring the euglobulin lysis time, or by viscoelastic tests (e.g. thromboelastometry, thromboelastography).

Pharmacology

Chemical

Tranexamic acid is a *trans*-stereoisomer of 4-(aminomethyl)cyclohexane-carboxylic acid) and has a molecular weight of 157.

Mode of action

Tranexamic acid is a synthetic derivative of the amino acid lysine and binds the 5 lysine binding sites on plasminogen. This inhibits plasmin formation and displaces plasminogen from the fibrin surface. It may also directly inhibit plasmin and partially inhibit fibrinogenolysis at higher concentrations. Tranexamic acid is also thought to exert an anti-inflammatory effect (by inhibiting plasmin-mediated activation of complement, monocytes, and neutrophils) and may improve platelet function in certain circumstances (Fig. 1).

Dose

The oral dose is 1–1.5 g (15–25 mg kg^{-1}) 2–3 times per day. I.V. dosage is typically 0.5–1 g by slow injection three times per day. Alternatively, the initial dose can be followed by an infusion of 25–50 mg kg^{-1} over 24 h. Dosing should be reduced to 5–10 mg kg^{-1} i.v. in patients with renal failure.

Side-effects/toxicity

Tranexamic acid is generally well tolerated. The risk of thromboembolic phenomena associated with tranexamic acid use has traditionally led to caution in its use, particularly in those with other risk factors (e.g. previous thrombotic events, hormonal contraceptive use), but recent studies have suggested that such concerns may not necessarily be justified (discussed in more detail below). Seizure activity after tranexamic acid use has also been described, although the mechanism for this is yet to be confirmed.

Indications: medical

Hereditary angioneurotic oedema

Patients with angioneurotic oedema can experience abdominal symptoms, subcutaneous swelling, and life-threatening laryngeal oedema in the perioperative period. This is precipitated by plasmin generation inducing complement. Tranexamic acid has been used for long-term

doi:10.1093/bjaceaccp/mku009 Advance Access publication 30 May, 2014

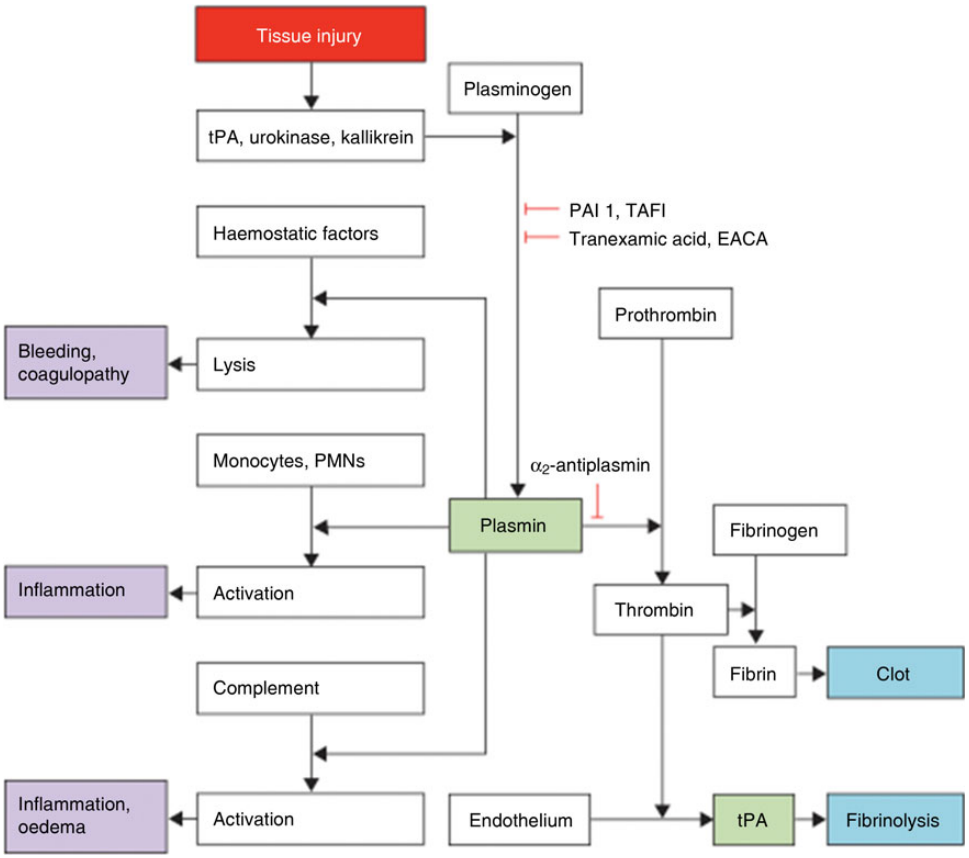

Fig 1 Tranexamic acid and its relationship with tissue injury, fibrinolysis, and inflammation. Reproduced from The Lancet, Levy (2010)[4], with permission from Elsevier, © 2010.

prophylaxis of hereditary angioneurotic oedema, although more recent guidelines no longer recommend its routine use.

Upper gastrointestinal bleeding

A Cochrane review in 2012 showed a mortality benefit of using tranexamic acid *vs* placebo in the treatment of upper gastrointestinal bleeding. Lack of data regarding other outcome measures and its efficacy *vs* other interventions mean that it cannot be recommended for routine use in this context.

Reversal of drug-induced bleeding

Cases of tranexamic acid being used to successfully treat bleeding related to tPA treatment have been reported and its use in this context has been included in recent guidelines. Tranexamic acid may improve platelet function and it has successfully lowered blood loss attributed to anti-platelet drugs in cardiac surgery. Tranexamic acid may be of use in treating bleeding caused by new antithrombotic drugs such as dagibatran, rivaroxaban, and fondaparinux.

Indications: elective surgery

A meta-analysis involving more than 10 000 patients undergoing a range of procedures confirmed that tranexamic acid use is associated with a 37% reduction in blood transfusion. Effects on thromboembolic events and mortality remained uncertain.[1]

Oral surgery

Tranexamic acid has an established role in the prevention of postoperative bleeding after oral surgery in patients with inherited and drug-related disorders of coagulation. This is largely thought to result from inhibition of fibrinolytic enzymes present in saliva and is effective when administered i.v. or as a mouthwash.

Obstetrics/gynaecology

Oral tranexamic acid has an established role as an effective treatment of menorrhagia and current guidelines recommend tranexamic acid as a second-line agent when hormonal treatments are not suitable. While tranexamic use in the management of acute post-partum

haemorrhage has also been described, it is hoped that an ongoing large international study will clarify its role in this context.

Cardiac

Tranexamic acid use reduces blood loss in cardiac surgery without an increased risk of thromboembolic complications.[5] Tranexamic acid may also have a role in reducing the postoperative inflammatory response that often follows cardiopulmonary bypass. Evidence suggests a plateau effect of dosages >10 mg kg^{-1} in cardiac surgery. Studies involving high-risk, open cardiac procedures have suggested that a dose-related increased risk of postoperative seizures and mortality may exist at doses above this.[6] Suggested mechanisms for this are that tranexamic acid may act as a competitive inhibitor of the central nervous system neurotransmitter GABA and it may also cause cerebral vasoconstriction and ischaemia.

Orthopaedics

Major joint arthroplasty and spinal surgery is associated with the potential for significant blood loss. It is postulated that increased fibrinolysis may contribute to bleeding, in orthopaedic surgery, and particularly where tourniquet use is prevalent. Meta-analyses of total hip and knee arthroplasty surgery concluded that tranexamic acid reduces both blood loss and transfusion requirements and is not associated with an increase in thromboembolic events.[7] Tranexamic acid appears to show a similar benefit in adult and paediatric patients undergoing spinal surgery. There is also evidence that both oral (e.g. 1.5 g 8-hourly before operation) and intra-articular (e.g. 50 mg kg^{-1} at the end of procedure) administration may confer a benefit.

Liver

Liver surgery is associated with significant mortality (1–5%) and blood loss, with hyperfibrinolysis as a recognized feature. This is likely to be due to the pivotal role the liver plays in haemostasis (where many of the constituents, of the fibrinolytic pathway are manufactured) but also hyperfibrinolysis can be precipitated by PAI-1 down-regulation during the anhepatic phase, followed by tPA up-regulation during the reperfusion phase. Tranexamic acid appears to reduce transfusion requirements in liver surgery, but recent Cochrane reviews of 1913 patients in 33 trials concluded that more evidence is required before recommending routine tranexamic acid use in liver resection or transplant surgery.[8]

ENT/maxillo-facial

A recent review suggested that tranexamic acid reduces total blood loss in tonsillectomy patients and in children undergoing adenoidectomy. Tranexamic acid has been used to treat epistaxis; however, no conclusive benefit has been shown and a Cochrane review on the subject is yet to be published. There is currently no evidence that tranexamic acid reduces bleeding in functional endoscopic sinus surgery.

Neurosurgery

Tranexamic acid reduces the rate of re-bleeding in subarachnoid haemorrhage; this is offset by a significant rate of delayed cerebral ischaemia (possibly caused by microthrombus formation in the cerebral circulation) and recent European guidelines do not recommend its routine use.[9] Tranexamic acid is also not recommended for the routine treatment of intracerebral haemorrhage and a 2009 Cochrane review concluded that more research is required before it can be recommended in this context. Hyperfibrinolysis has been described in a small proportion of traumatic brain injury (TBI) patients, and is associated with high mortality. Subgroup analysis from the CRASH-2 trial showed that tranexamic acid may improve outcome after TBI, but clearer guidance may result from findings of the ongoing CRASH-3 trial.

Urology

Urological procedures are associated with a significant bleeding risk due to the vascular nature of the tissues and their high levels of fibrinolytic enzymes in the tissues and urine. Tranexamic acid can be safely used to reduce blood loss in TURP, percutaneous nephrolithotomy, and serious haematuria of other causes. There is no evidence of a significant rate of thromboembolic complications, although concerns remain regarding the possibility of increased rates of urinary clot retention. For this reason, its routine use in urological surgery is not recommended, but it should be considered when bleeding becomes problematic.

Chest/pulmonary

Pulmonary endothelium demonstrates tPA activity and tranexamic acid can be safely used in the management of major haemoptysis of various causes. A recent Cochrane review however suggests that tranexamic acid cannot currently be recommended for routine use until more evidence is available. In thoracic surgery, one study suggested that intrapleural tranexamic acid can be used to reduce transfusion requirements and blood loss.

Indications: emergency surgery

There is surprisingly little evidence regarding the use of tranexamic acid in emergency surgery. A recent review identified three studies, involving 260 patients and demonstrated a 30% reduction in the probability of requiring a transfusion. No clear conclusions could be drawn on effects on morbidity or mortality.[2]

Indications: trauma

Up to 25% of trauma patients are coagulopathic on arrival at hospital and this can account for a five-fold increase in mortality. Fibrinolysis is a recognized early feature of severe trauma and is associated with increased transfusion requirements and mortality

rates. An increased use of tranexamic acid in elective surgical patients has prompted calls for its use in trauma.

Civilian trauma: CRASH-2

The landmark CRASH-2 study published in 2010 examined 20 211 trauma patients presenting within 8 h of injury, with, or at risk of significant haemorrhage, and randomized them to receive either tranexamic acid (an initial 1 g loading dose followed by 1 g over 8 h) or placebo. Patients were excluded if there was either a clear indication or contraindication to tranexamic acid use.

The tranexamic acid group demonstrated a statistically significant absolute decrease in mortality of 1.5%.[3] Subgroup analysis confirmed that this was attributed to a reduction in bleeding and that the greatest benefits were in those treated within the first 3 h after injury (Fig. 2). An unexplained increase in mortality from bleeding in those treated after 8 h was identified, suggesting a more careful risk assessment be undertaken in this population before treatment.

A subgroup analysis of UK patients showed a significant reduction in fatal and non-fatal thrombotic events[10] (Table 1). This may result from an anti-inflammatory drug-related effect.

Military trauma: MATTERs

Tranexamic acid has been incorporated into military trauma management algorithms since 2009. The MATTERs study[11] examined 896 casualties admitted to a military hospital in Afghanistan. Casualties receiving tranexamic acid exhibited in-hospital mortality rates 6.5% lower overall and 13.7% lower in those who received a massive transfusion, where tranexamic acid was an independent predictor of survival. The outcome benefit was greatest in those with the more severe injuries and the tranexamic acid group was less coagulopathic after operation. There was a higher rate of thromboembolic complications in the tranexamic acid group, but there was no independent association between the drug and complication. Because the mortality benefit of tranexamic acid was delayed until after 24 h, some benefit may result from non-haemostatic mechanisms such as attenuation of the inflammatory response.

The MATTERs II study also showed tranexamic acid to be an independent predictor of survival in military trauma casualties and demonstrated a possible synergistic action with the administration of cryoprecipitate (presumably to restore fibrinogen levels consumed during coagulopathy).

Tranexamic acid appears to be a reliable, safe, and cost-effective treatment for traumatic bleeding. While its greatest effect is on the most severely injured, it appears to reduce bleeding in patients of all injury severities and when considering populations, it is the less severely injured who overall gain the most benefit from treatment. If the administration of tranexamic acid within 1 h of injury was introduced worldwide, it is estimated that 128 000 lives could be saved every year.[10]

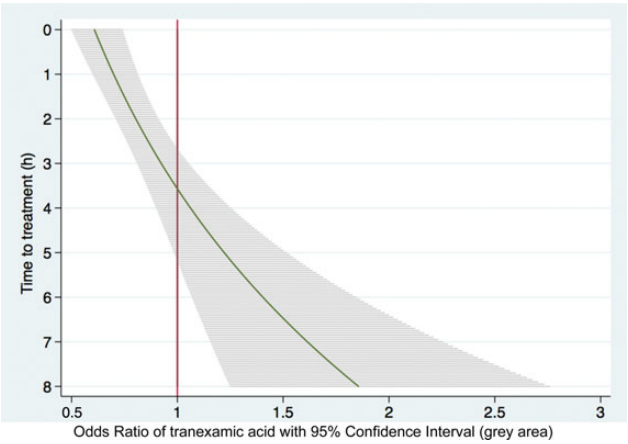

Fig 2 CRASH-2: effect of tranexamic acid on death due to bleeding by time to treatment. Reproduced from The Lancet, Roberts (2012)[12], with permission from Elsevier, © 2011.

Current concerns and future developments

Evidence that tranexamic acid reduces bleeding and transfusion requirements in both elective and emergency surgery remains patchy (Table 2). Where its use has become more commonplace (e.g. cardiac surgery), there remain some concerns over the risk of complications.[1]

Thromboembolic phenomena

The evidence for thromboembolic complications related to tranexamic use is not strong,[3] but many studies did not measure the incidence of these phenomena, while others excluded patients judged at an increased risk. As a result, the risk to the general population, particularly those with existing risk factors (e.g. MI, DVT, PE) remains unclear. It is also unknown how readily the findings of studies such as CRASH-2 can be translated to surgical patients, where the

Table 1 CRASH-2: effect of tranexamic acid on fatal and non-fatal thrombotic events. OR, odds ratio; TXA, tranexamic acid

Thrombotic events	TXA (n=6684)	Placebo (n=6589)	OR (95% CI)	P-value
Any event	98 (1·5%)	140 (2·1%)	0·69 (0·53–0·89)	0·005
Any arterial event	47 (0·7%)	80 (1·2%)	0·58 (0·40–0·83)	0·003
Myocardial infarction	23 (0·3%)	46 (0·7%)	0·49 (0·30–0·81)	0·005
Stroke	28 (0·4%)	40 (0·6%)	0·69 (0·43–1·11)	0·128
Any venous event	60 (0·9%)	71 (1·1%)	0·83 (0·59–1·17)	0·295
Pulmonary embolism	42 (0·6%)	47 (0·7%)	0·88 (0·58–1·33)	0·548
Deep vein thrombosis	25 (0·4%)	28 (0·4%)	0·88 (0·52–1·50)	0·641

Table 2 A summary of the evidence base for uses of tranexamic acid. ENT, ear, nose and throat; GI, gastrointestinal; HAO, hereditary angioneurotic oedema

Application	Known benefits	Identified risks	Routine use supported?
Medicine			
HAO	Reduces symptom frequency/intensity	No	No
Upper GI bleeding	Reduced mortality	No	No
Drug-induced bleeding	Reduced blood loss	No	No
Emergency surgery			
Overall	Reduced blood transfusion	Uncertain	No
Trauma	Reduced bleeding, reduced mortality	Increased mortality if given after 8 h	Yes
Elective surgery			
Overall	Reduced blood transfusion	Uncertain	No
Oral	Reduced bleeding	No	Yes
Obs/gynae	Reduced bleeding	No	In chronic heavy menstrual bleeding
Cardiac	Reduced bleeding, reduced inflammation	Increased seizure rates and mortality (high dose, open chamber surgery)	Yes
Ortho	Reduced blood loss/transfusion requirements	No	Hip and knee arthroplasty, spinal surgery
Liver	?transfusion requirements	No	No
Maxillofacial/ENT	reduced blood loss in tonsillectomy/adenoidectomy	No	No
Neuro	Reduced re-bleeding in subarachnoid haemorrhage	Delayed cerebral ischaemia	No
Urology	Reduced blood loss in TURP, percutaneous lithotomy, haematuria	Clot retention	No
Chest	Reduced blood loss and transfusion requirements in chest surgery/haemoptysis	No	No

haemostatic picture may be very different. Tranexamic acid should be used to reduce blood loss in elective surgical and medical patients (where the evidence supports its use) and in bleeding trauma patients, without significant existing risk factors for thromboembolic complications. The threshold for use may decrease in patients where intraoperative bleeding becomes significant or life-threatening.

Seizures

The evidence for tranexamic acid causing seizures remains largely confined to those undergoing high-risk open cardiac surgery exposed to very high doses of tranexamic acid.[6] The risk to the wider population is unknown, although it would be prudent to avoid its routine use in neurosurgical patients and those with epilepsy.

Defining the coagulopathy

Acute traumatic coagulopathy has become better defined since its initial description in 2003 and includes fibrinolysis. The coagulopathy affecting surgical patients is less well defined and the effect tranexamic acid would have on the wider haemostatic picture is uncertain. Further research will clarify how reliably results of studies such as CRASH-2 can be extrapolated to guide treatment of surgical patients.

Diagnosing coagulopathy

Rapid, early diagnosis of hyperfibrinolysis offers the potential to target the administration of tranexamic acid to those most likely to benefit from it. Viscoelastic techniques can diagnose fibrinolysis at the bedside, but currently there are no validated parameters indicating when to commence treatment. One recent study suggested that thromboelastometry was unable to detect 'moderate' fibrinolysis in 57% of 303 patients.

Optimum dosing

While some studies from cardiac surgery suggest benefits plateau above doses of 10 mg kg^{-1}, there is little consensus on the optimum dose in other contexts and in trauma. Further studies to clarify this may enable tranexamic acid to be administered with the optimum balance of benefit and risk.

Summary

There are many historical uses for tranexamic acid; however, there is a lack of research and therefore evidence to support these uses. Increasingly, concerns over the potential risk of thrombus formation have led to guidelines 'not recommending the use of tranaexamic acid.' Recent interest in the use of tranexamic acid in bleeding trauma patients has identified a mortality benefit without an apparent increased risk of thromboembolic events. It has been speculated that this survival benefit may be attributable to an anti-inflammatory rather than an antifibrinolytic effect.

It is the authors' view that in the presence of bleeding prompting transfusion, tranexamic acid should be used. Its use as a prophylaxis to prevent potential bleeding is more controversial; however, in the absence of strong risk factors for thromboembolic disease, its use should be considered.

Declaration of interest

None declared.

References

1. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *Br Med J* 2012; **344**: e3054
2. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database Syst Rev* 2013; **1**: CD010245
3. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376**: 23–32
4. Levy JH. Antifibrinolytic therapy: new data and concepts. *Lancet* 2010; **376**: 3–4
5. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *Can Med Assoc J* 2009; **180**: 183–93
6. Koster A, Borgermann J, Zittermann A, Lueth JU, Gillis-Januszewski T, Schirmer U. Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: incidence and clinical outcome. *Br J Anaesth* 2013; **110**: 34–40
7. Blake P, Gillette MD, Lori J *et al.* Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. *Clin Orthop Relat Res* 2013; **471**: 150–4
8. Gurusamy KS, Li J, Sharma D, Davidson BR. Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection. *Cochrane Database Syst Rev* 2009; **4**: CD008085
9. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; **35**: 93–112
10. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. *BMC Emerg Med* 2012; **12**: 3
11. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg* 2012; **147**: 113–9
12. Roberts I. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; **377**: 1096–101

Please see multiple choice questions 21–24.