

Title: Tranexamic Acid - there's new life in the old drug

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Over the last 15 years there has been an explosion in the use of tranexamic acid (TXA) in emergency and surgical care (with publications about TXA increasing from about 50 a year before 2010 to 340 in 2015). With rapidly changing evidence it can be difficult for emergency physicians to judge both 'who' and 'when' to treat, but current use of TXA may be too late to be effective.

Tranexamic acid (TXA) is a rather weak anti-fibrinolytic which prevents the breakdown of clot. It was discovered in the 1950s by the remarkable Japanese husband and wife team of Shosuke and Utako Okamoto[1], however by the late 1990's intravenous TXA was only occasionally used and there was just one manufacturer (forced to continued production under an "orphan drugs" law).

Antifibrinolytics have long been used in cardiac surgery[2]. A 'coffee time' conversation between an emergency physician and an anaesthetist, who had both recently been working in cardiac surgery, led to the question about the use of an antifibrinolytic in trauma. With the involvement of a much larger group of researchers this resulted in the CRASH2 trial, giving definitive evidence in 2010 that trauma patients with, or at risk of, significant bleeding should be given TXA[3]. A large number of trials in other bleeding conditions have subsequently been performed.

There is always difficulty with knowing how far to extrapolate from the clinical trial evidence. Most new drugs go through a cycle of being 'the best thing ever' when first introduced, which is often followed by a 'it is a terrible drug' phase, which is then followed by the matured opinion 'in the right patients at the right time this is a useful treatment'. This cycle is probably caused by clinicians being poor at assessing the 'generalisability' of evidence, as our critical appraisal training is focused on assessing the quality of the evidence rather than the skills involved in deciding how this evidence should affect our practice. There is also a tendency for clinicians to think in black and white terms of a treatment as "good" or "bad" (and to talk to our patients in this language) rather than to accept the psychological discomfort brought on by the uncertainty of the shades of grey which surround the generalizability of evidence to practice.

There is certainly an enthusiasm for TXA at present – a straw poll in the 2015 RCEM Conference showed that about 30% of UK hospitals had TXA included as a routine part of their massive transfusion protocols – therefore recommending its use in all patients with massive haemorrhage whatever the cause of the bleeding. This indication has never been the subject of a clinical trial, and is in fact very different from those that have been tested. The trials in both surgery and trauma have administered TXA at a much earlier stage, before massive haemorrhage has become established. In coagulopathic massive haemorrhage a drug that prevents clot breakdown is unlikely to have much effect if the patient is no longer forming clot. Linking TXA to a massive haemorrhage protocol creates the wrong mindset in clinicians - if you are not giving TXA until the patient fulfills the criteria for massive haemorrhage you will be giving it too late. Universal use of TXA in massive hemorrhage also makes research impossible, as there is no longer equipoise.

The strength of current evidence for TXA use varies between conditions. In some countries the CRASH2 result has been extrapolated to support routine use in the prehospital phase, and many military protocols now recommend TXA for field use. A large enough trial to give definitive evidence for use in prehospital care is unlikely ever to be performed, however the current PATCH (NCT02187120) trial may give some information. A large number of trials in surgery have shown better outcomes in hip, prostatic, vascular, liver and other operations involving large amounts of bleeding[4], but there is not sufficient evidence to recommend it for all types of emergency surgery[5]. In acute subarachnoid haemorrhage there is evidence that there is no benefit from an antifibrinolytic (decreased bleeding, but an increase in cerebral infarcts)[6]. For other types of acute bleeding there is equipoise (we do not know whether there is benefit or not) and there are large ongoing trials; HALT-IT (NCT01658124) in gastro-intestinal bleeding, CRASH3 (NCT01402882) in head injury, WOMAN (NCT00872469) in post-partum haemorrhage and a trial in epistaxis is also in preparation (NO-PAC).

In summary, it seems reasonable to generalize the evidence from major trauma to the prehospital and military situations, and to generalize the evidence from several specific surgical conditions to all surgery where significant bleeding is anticipated. It also seems reasonable to be in equipoise about other acute bleeding conditions – and so fulfill the key ethical requirement for randomisation of these patients into clinical trials. The blanket use of TXA in massive haemorrhage protocols does not seem to be supported by the current evidence as it is too late – in conditions where there is good evidence it should be given earlier, and in conditions where there is equipoise the patients should be randomised into a clinical trial.

References

1. Lancet T. Bringing women to the forefront of science and medicine. The Lancet 2012;**379**(9819):867 doi: 10.1016/S0140-6736(12)60286-4[published Online First: Epub Date]].
2. Ortmann E, Besser M, Klein A. Antifibrinolytic agents in current anaesthetic practice. British Journal of Anaesthesia 2013;**111**(4):549-63
3. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH2). Lancet 2010;**376**:23-32
4. Henry DA, Carless PA, J MA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database of Systematic Reviews 2011(3) doi: 10.1002/14651858.CD001886.pub4 [published Online First: Epub Date]].
5. Perel P, Ker K, Morales UC, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. . Cochrane Database of Systematic Reviews 2013(1) doi: 10.1002/14651858.CD010245.pub2 [published Online First: Epub Date]].
6. Baharoglu MI, Germans MR, Rinkel GJ, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database of Systematic Reviews 2013(8) doi: 10.1002/14651858.CD001245.pub2 [published Online First: Epub Date]].

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