British Journal of Anaesthesia, 126 (1): 12–17 (2021)
doi: 10.1016/j.bja.2020.09.014
Advance Access Publication Date: 14 October 2020

Tranexamic acid and trauma coagulopathy: where are we now?

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Keywords: bleeding; tranexamic acid; trauma; trauma induced coagulopathy; transfusion

Uncontrolled haemorrhage remains the leading cause of early mortality in major trauma accounting for 30–40% of all trauma deaths. Approximately 50% of trauma deaths that are attributed to severe haemorrhage occur in the pre-hospital period.[1] Trauma-associated haemorrhagic deaths occur from the combined effect of uncontrolled bleeding and trauma-induced coagulopathy. The routine use of the anti-fibrinolytic drug tranexamic acid (TXA) is based on the results of several key trauma trials. Tranexamic acid is widely available, simple to administer, and relatively inexpensive, creating a highly feasible life-saving and blood conservation technique for all countries worldwide. With massive expansion of science in this research area, we aimed to critically explore key features of trauma coagulopathy, use of TXA to improve outcomes for trauma victims, and the growing role of pre-hospital TXA use.

Complex and dynamic nature of trauma coagulopathy

The underlying mechanisms of acute traumatic coagulopathy (ATC) are highly complex and remain poorly delineated with a lack of consensus on its definition. There are three broadly defined phases of ATC with multiple overlapping mechanisms and phenotypes. First, immediately after injury, there appears to be an initial endogenous adaptive response hallmarked by dysregulation and hyper-activation of the thrombomodulin-activated protein C pathway. Increased activated protein C activity promotes anticoagulation and hyper-fibrinolysis through increased release of tissue plasminogen activator (t-PA) and reduction of plasmin activator inhibitor-1 (PAI-1).[2] The severity of this response correlates with the degree of injury and sustained hypoperfusion, and is an independent risk factor for increasing mortality. Urokinase (u-PA), another plasminogen activator, is released later (>3 h) in trauma, peaking around 8 h after injury. The second phase of coagulopathy occurs with resuscitation using fluids and blood products without coagulation factors, and is associated with the lethal triad of hypothermia, coagulopathy, and acidosis. Hypothermia, in particular, impairs fibrinogen synthesis.[3] The final and late post-resuscitation phase is often a pro-coagulable phenotype with increased risk of thromboembolic complications.[4] However, severely injured patients may present acutely with this phenotype, recently termed 'fibrinolytic shutdown', owing to rapidly evolving temporal changes in fibrinolytic and protein C activity, thrombin generation, and endothelial glycocalyx shedding.[5] Recent evidence suggests that 70% of those who present with fibrinolytic shutdown remain in this state for up to 120 h post-injury with associated prothrombotic risk and increased late mortality.[6]

Severe hyper-fibrinolysis develops in up to 20% of trauma patients and confers the highest early mortality of the fibrinolytic phenotypes.[6,7] Fibrinolytic shutdown, where TXA administration has been hypothesised to be potentially harmful, occurs in up to 64%.[6] The transition to hypo-fibrinolysis, fibrinolytic resistance, and fibrinolytic shutdown is believed to occur rapidly within the first 3 h after injury, which is consistent with the evidence that TXA administration after 3 h is not beneficial. However, this fibrinolytic spectrum theory is controversial.[8] The 'anti-fibrinolytic gap' theory offers an alternative explanation. Coats and Morsy[9] demonstrated that the initial injury triggers a differential peak in t-PA and PAI-1 release. This creates a significant gap of unopposed t-PA action, possibly because of a timing imbalance between pro-fibrinolytic and anti-fibrinolytic signalling. This theory reinforces the mechanistic basis for early pre-hospital anti-fibrinolytic therapy.[9]

Coagulopathy in isolated traumatic brain injury (TBI) affects up to 60% of patients and plays a major role in the development of secondary brain injury by promoting new or progressive intracranial haemorrhage (ICH), cerebral oedema, and subsequent cerebral ischaemia. Unlike extra-cranial trauma, the general absence of severe bleeding and sustained hypoperfusion in isolated TBI moderates the role of activated protein C. The underlying mechanism is primarily driven by an overwhelming surge of endogenous plasminogen activator resulting in hyper-fibrinolysis, in addition to increased activation of brain tissue factor, platelet, and endothelial dysfunction. Hyper-fibrinolysis is a strong independent predictor of ICH progression and mortality.[10] Hyper-

fibrinolysis mediated by t-PA provides a mechanistic basis for the use of early TXA in TBI. Given the current lack of concrete evidence regarding benefit on mortality and functional outcomes in cerebral haemorrhage overall, the individual risk–benefit profile must be seriously considered given the potential risk of adverse events.[11]

Role of TXA in trauma coagulopathy

TXA is a lysine analogue with anti-fibrinolytic properties. It competitively binds to the lysine sites of plasminogen and plasmin, resulting in inhibition of the binding of plasmin to fibrin and subsequent fibrinolysis. There is some evidence that TXA also improves platelet function and inhibits plasmin-induced platelet activation, which facilitates clot stabilisation rather than thrombogenesis. Importantly, TXA can have differential effects on t-PA- and u-PA-mediated plasminogen activation. Although TXA is usually anti-fibrinolytic, it can potentiate u-PA fibrinolysis, which may be particularly relevant in delayed ICH progression.[12] Beyond fibrinolysis, plasminogen and plasmin are pro-inflammatory mediators that play a key role in activating the cellular and complement inflammatory responses to injury. Through inhibition of plasminogen and plasmin-mediated inflammation, TXA may attenuate the intense inflammatory response seen during trauma that contributes to coagulopathy. It may also preserve the integrity of the glycocalyx.[13] However, to date, the evidence for this has been limited primarily to animal studies.[14] Attenuation of hyperfibrinolysis is a clinically important effect of the *early* administration of TXA, which has been shown to reduce bleeding outcomes and mortality in trauma, including TBI.[15–17]

Efficacy of TXA in trauma clinical trials: where are we now?

To date, the large clinical trials exploring TXA and trauma have mainly focused on polytrauma and have been conducted in the in-hospital setting. The landmark Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, which recruited more than 20 000 adult trauma patients from 247 predominantly low-to middle-income countries has underpinned major guidelines recommending TXA use for civilian trauma.[15,18] This pivotal trial demonstrated the success of the implementation and acceptance of a pragmatic treatment protocol worldwide with no significant concerns of thromboembolic adverse effects. Compared with no anti-fibrinolytic treatment, i.v. TXA showed a significant reduction in all-cause 28 day mortality (absolute risk reduction: 1.5%; relative risk [RR]: 0.91; 95% confidence interval [CI]: 0.85–0.97; P=0.0035), but without any significant reduction in red cell transfusion requirements. When analysed more closely, the effect on all-cause mortality was greatest in those with haemorrhagic shock (30.6% *vs* 35.1%; RR: 0.87; 95% CI: 0.76–0.99) and was only significant in the subgroup analysis evaluating death attributed to bleeding (4.9% *vs* 5.7%; RR: 0.85; 95% CI: 0.76–0.96; P=0.0077). Use of TXA within 1 h of injury was associated with the greatest mortality benefit, but administration beyond 3 h after trauma actually showed higher mortality secondary to bleeding (4.4% *vs* 3.1%; RR: 1.44; 95% CI: 1.12–1.84; P=0.004), although no difference in all-cause mortality.[19]

The large retrospective Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS) also showed a survival benefit for TXA (bolus 1 g *vs* no TXA), which was greatest in those most severely injured, penetrating trauma, and patients requiring more than 10 units of red cell transfusion (mortality 14.4% *vs* 28.1%; P=0.004).[20] The MATTERS-2 study identified that the addition of cryoprecipitate to TXA was associated with a greater survival benefit than TXA alone (odds ratio: 0.34; 95% CI: 0.20–0.58; P=0.001).[21] There is limited detail on timing of TXA administration, which may have underestimated the true effect of TXA therapy in MATTERS.

The use of in-hospital TXA in patients with TBI has been evaluated in several small studies and more recently in the CRASH-3 trial.[16,22–24] The CRASH-3 trial studied TXA administration predominantly within 3 h of injury in more than 12 000 patients with TBI using the same dosing protocol as CRASH-2.[17] Patients with a Glasgow Coma Scale (GCS) of 3 or unreactive pupils were excluded. The major findings were a trend towards a reduction in 28 day in-hospital head-injury-related mortality in those who received TXA within 3 h of injury (18.5% *vs* 19.8%; RR: 0.94; 95% CI: 0.86–1.02). This reduction in head-injury-associated mortality was identified in patients with mild-to-moderate TBI (5.8% *vs* 7.5%; RR: 0.78; 95% CI: 0.64–0.95), but not severe TBI. Mild-to-moderate TBI showed larger survival benefits the earlier TXA was used.

These in-hospital studies should be interpreted with several caveats in mind. The considerable international differences in trauma systems, pre-hospital care infrastructure and intervention, rapid access to blood products, damage control surgery, angiography, and advanced critical care resources likely influence the reproducibility and applicability of the CRASH trial results in modern trauma care settings. There are concerns regarding study methodology and design. Like its predecessors and successors, CRASH-3 altered its original protocol to only include patients within 3 h of injury rather than 8 h secondary to lack of efficacy and possible harm of late TXA administration. There was no data regarding the effect of pre-hospital interventions, no formal stratification of severity of injury, and not all patients were severely injured. In CRASH-2, only 50% were transfused blood or required damage control resuscitation surgery, and most patients in CRASH-3 had mild-to-moderate TBI. In addition, the CRASH studies lack assessment of fibrinolysis or coagulation. There are also issues with the analysis and interpretation of results.

Earlier is better: pre-hospital trials of TXA use

Most bleeding-related trauma deaths occur in the pre-hospital setting, which is likely attributed to the rapid development of hyper-fibrinolysis within minutes after injury. The pre-hospital period represents a crucial period for damage control resuscitation that may influence patient survival and neurological and functional outcomes. Trauma scene analyses show many victims spend the ‘golden hour’, and frequently longer, in the pre-hospital environment.[25] According to the UK trauma database, 80% of patients receive TXA within the first 3 h, but only 30% actually receive it within the golden hour, and it is often co-administered as part of a massive transfusion protocol (MTP).[26] Although there have been some data to suggest a mortality benefit and improved coagulopathy in extra-cranial trauma, there remains a paucity of definitive evidence to inform whether pre-hospital TXA improves trauma outcomes overall. Despite this, both European and North American guidelines recommend its use.[18,27]

The recently published Resuscitation Outcomes Consortium-Tranexamic Acid for Traumatic Brain Injury

(ROC-TXA) is arguably the most important pre-hospital TXA study to date.[28] In this multicentre randomised trial, 1063 patients with moderate-to-severe TBI were randomised to one of three arms within 2 h of injury: TXA bolus 2 g pre-hospital and placebo infusion *vs* TXA bolus 1 g and infusion 1 g pre-hospital *vs* placebo bolus and placebo infusion. There was no difference in 6 month functional outcomes and 28 day absolute mortality across treatment regimens. In patients diagnosed with a subsequent in-hospital ICH, 28 day mortality for TXA bolus, TXA bolus/infusion, and placebo were 18%, 26%, and 27%, respectively (bolus maintenance *vs* placebo [adjusted difference: −0.8%; 95% CI: −7.0 to 8.7%]; P=0.84; bolus only *vs* placebo [adjusted difference: −8.2%; 95% CI: −16.6 to −0.8%]; P=0.03; bolus only *vs* bolus maintenance [adjusted difference: −9.0%; 95% CI: −16.1 to −1.8%]; P=0.01). However, TXA did not significantly reduce ICH progression overall. There was no significant difference in the incidence of thrombosis, but interestingly a higher incidence of seizures in the bolus 2 g group, which is discussed further as follows.

This study has important limitations. It focused on a high-risk moderate-to-severe isolated TBI group who may be less likely to benefit from TXA. The use of GCS to stratify the severity of TBI lacks discrimination and may have resulted in inclusion of patients with non-TBI causes of neurological impairment (e.g. intoxication). This may account for administration of TXA to a large proportion of patients with minimal TBI or ICH, where benefit was also unlikely. The mortality benefit of the 2 g bolus was based on a small underpowered subgroup finding. This should be interpreted with caution, and calls for more pre-hospital clinical trials of TXA in this setting. The study raises questions about randomisation to an intervention when a diagnosis has not been radiologically confirmed, and administration of an intervention in those with irrecoverable injury. It also does not address the role of TXA in those with polytrauma involving major bleeding and TBI. We await further data from ongoing trials, including the Study of Tranexamic Acid During Air and Ground Medical Prehospital Transport (STAMMP, NCT02086500) and Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage study (PATCH, NCT02187120).

Using TXA as part of a multimodal trauma coagulation strategy

Pre-hospital use of other clotting factors with TXA appears an attractive option for further improving patient outcomes. Early fibrinogen supplementation, including pre-hospital replacement, results in improved coagulation, a reduction in haemorrhage and transfusion requirements, and lower mortality.[18] Fibrinogen concentrate (20 g L^{-1} in a reduced volume) requires no ABO matching or thawing, and is virally inactivated, providing a more reliable and practical treatment for the pre- or in-hospital setting compared with plasma or cryoprecipitate. Results from the Fibrinogen Early in Severe Trauma Study (FEISTY, NCT02745041), the Pilot Randomised Trial of Fibrinogen in Trauma Haemorrhage (ProoF-iTH, NCT02344069), and the Early Cryoprecipitate for Severe Bleeding after Trauma Trial (CRYOSTAT-2, ISRCTN 4998314) are keenly awaited.

Clotting factor deficiency is seen within 3 h of injury in more than 20% of patients with severe trauma before commencement of fluids or blood products, and correlates with impaired thrombin generation.[29] Early and aggressive clotting factor transfusion using fresh frozen plasma is logistically problematic for pre-hospital replacement in civilian trauma, with conflicting clinical evidence. The Control of Major Bleeding After Trauma (COMBAT) trial, an individual patient randomised trial, found a 5% higher mortality in the plasma group, although this was not statistically significant. However, the PreHospital Air Medical Plasma (PAMPer) study, a cluster randomised trial, demonstrated a 30% reduction in mortality when administered to patients at risk for haemorrhagic shock.[30,31] A *post hoc* analysis of the harmonised results demonstrated a survival benefit for plasma compared with standard care if the pre-hospital transport time was greater than 20 min, which is consistent with previous observational data.[32] Although not a pre-hospital study, MATTERS-2 demonstrated that the addition of cryoprecipitate to TXA was independently associated with increased survival and reduced blood product transfusion.[21] Lyophilised plasma may provide a solution to the logistical concerns, in addition to supplementation of coagulation factors and fibrinogen, and mitigation of trauma endotheliopathy. The Resuscitation with Pre-Hospital Blood Products trial (RePHILL, ISRCTN 62326938) is in progress and may provide further clarity.

Administration of adjunctive coagulation factor concentrates, such as prothrombin complex, may improve survival and reduce transfusion requirements in severe trauma.[33] Routine use remains controversial due to the mechanistic increase in thrombin and theoretical concern for an increase in thrombosis risk. However, it may be appropriate in carefully selected patients with TBI not only to reduce ICH expansion, but also to decrease the time interval to craniotomy and reduce blood product transfusion.[34] Further research is needed to investigate the *combined* effect of TXA with fibrinogen supplementation and clotting factor therapy in the context of an MTP for major trauma.

Refining TXA treatment: many unanswered questions

With many large-scale trauma trials showing the efficacy of TXA, we arguably no longer need to repeat the same trial in different care settings, but do need to answer several questions necessary to optimise its clinical application.

The main question is: which trauma patients should receive TXA? Although there are increasing numbers of publications advocating more liberal use in trauma, the guidelines only recommend it for excessive haemorrhage, or in a patient who is at risk of severe haemorrhage that is attributable to or suspected to be caused by hyper-fibrinolysis.[35] This is interesting, given that the majority of deaths caused by bleeding in trauma seem to occur in lower-haemorrhagic-risk patients.[36] Given the evidence regarding the dynamic nature of trauma coagulopathy and potential harm if the fibrinolytic phenotype and timing of TXA administration are suboptimal, it is prudent to consider that in some cases we may be causing harm.

Is it safe? The CRASH trials have been criticised for their low incidence of thrombosis and that prospective thrombosis screening with leg Dopplers was not routinely performed. To date, most of the data implicating TXA and increased thrombotic risk has been retrospective and observational. In military trauma, TXA was found to be an independent risk factor associated with deep venous thrombosis. Unlike the CRASH

trials, MATTERS reported a nine-fold increase (0.3% *vs* 2.7%) in pulmonary embolism and a 12-fold increase (0.2% *vs* 2.4%) in deep vein thrombosis in those who received TXA, although this was not significant when adjusted for the severity of injury. Significant variability in dosing regimens, timing of administration, and confounders (e.g. blood product transfusion) may contribute to differences in reported rates. In addition, there are marked differences between military and civilian trauma in terms of baseline patient characteristics, mechanism and severity of injury, and the level of prehospital intervention. Patients in military trauma TXA studies tend to be more severely injured. The most common fibrinolytic phenotype in severe trauma, particularly those with higher injury severity scores, is fibrinolytic shutdown, where untimely anti-fibrinolytic use could potentially increase the risk of thrombosis.[6] Certainly, given the clear mortality benefit of early TXA in severe trauma, considerate use of TXA should not be withheld because of concerns regarding a theoretical increase in thromboembolic complications at a later point in their trauma care. However, further clarification is warranted, given that indiscriminate use of TXA could result in increased thrombotic complications, eclipsing its benefits, particularly when administered with other prothrombotic products.[13,37]

The risk of TXA-associated seizures has not been adequately addressed in trauma. Seizures are a well described dose-related complication, particularly in cardiac surgery with doses in the 80–100 mg kg^{-1} range. The ROC-TXA study demonstrated a seizure incidence of 5% in the TXA 2 g bolus group compared with the other two arms (bolus maintenance *vs* placebo [adjusted difference: −0.6; 95% CI: −2.8 to 1.6]; bolus only *vs* placebo [adjusted difference: 2.8; 95% CI: −0.1 to 5.6]; bolus only *vs* bolus maintenance [adjusted difference: 3.4; 95% CI: 0.7–6.1]). The mechanism is possibly attributable to central inhibition of glycine and gamma-aminobutyric acid type A ($GABA_A$) receptors, which may be exaggerated in those with renal impairment. Some anaesthetic agents may mitigate seizure activity by modulating glycine receptor function (e.g. propofol) and increasing $GABA_A$ receptor activity (e.g. lorazepam).[38,39] It is possible that the true incidence of TXA-associated seizures may be underestimated in the trauma population and is unmasked once these agents are withdrawn. It may also be reasonable to suspect that trauma patients who receive TXA, albeit at lower doses compared with cardiac surgery, may have a reduced threshold for seizure incidence, especially in TBI due to disruption of the blood–brain barrier, the severity of intracranial bleeding, inflammation, and cerebral oedema. Whether TXA-associated seizures translate into poorer neurological and other outcomes in trauma patients also needs to be further investigated.

What is the optimal TXA dose in trauma? To date, this has been understudied. Dosing appears empirical with no adjustment for patient-specific pharmacokinetic and dynamic factors, such as weight, renal function, and haemorrhage volume, or guided by viscoelastic haemostatic assays.[39,40] The CRASH dosing regimen used a 1 g bolus followed by a 1 g infusion over 8 h. This regimen was based on the best evidence at the time, which was a 2007 Cochrane review of anti-fibrinolytic use in surgery.[41] The review included a heterogeneous surgical population with many undergoing cardiopulmonary bypass surgery, where mechanisms for bleeding will differ and dosing regimens are predominantly not supported by patient or drug factors. This 1 g bolus and 1 g infusion approach is a safe regimen that is below doses that may precipitate seizure, but raises important questions of whether this dosing regimen is appropriate for all types of trauma in all types of patient, outside the setting of a clinical trial. A bolus followed by slow infusion regimen is not practical during chaotic trauma resuscitations with patients transitioning rapidly from the trauma room to CT to interventional radiology, and then to the operating theatre.

How do we monitor and guide therapy? Measuring plasma levels of TXA could be used; however, the plasminogen activator subtype and degree of drug elimination as a result of haemorrhage need to be taken into consideration. *In vitro* studies have shown that a minimum plasma concentration of ≈20 μg ml^{-1} is required to inhibit t-PA-induced fibrinolysis, whilst higher ranges may be needed to counter u-PA-mediated fibrinolysis. Higher plasma concentrations of TXA are often achieved in cardiac surgery (≈120–150 μg ml^{-1}), which possibly contributes to less bleeding and transfusion, but increases the risk of seizures. A pharmacokinetic study using blood samples from trauma patients who received TXA 1 g at the scene within 1 h of injury has suggested that this dosing regimen is suboptimal with concentrations below 20 μg ml^{-1} in 20% of patients.[42] Measuring plasma TXA levels can be performed using rapid bench-to-bedside testing with new technology, although this is not widely available.[43]

Whether patient selection and quantity of TXA therapy should be guided by routine use of viscoelastic haemostatic assays (VHAs) i.e. thromboelastography (TEG®; Haemonetics Corporation, Braintree, MA, USA); Haemonetics Corporation, Braintree, MA) and thromboelastometry (ROTEM®; Instrumentation Laboratory, Bedford, MA, USA) and laboratory coagulation profile remains controversial. Coagulopathy in trauma is a dynamic and rapidly evolving process, and any diagnosed abnormalities change rapidly within the first hour of injury. The main limitations of this approach include level of sensitivity to identify a maladaptive coagulation–fibrinolysis response and relative utility of the result in a rapidly changing haemostatic response. VHAs are routinely used in only 9% of North American trauma centres as part of MTPs.[44] ROTEM® and TEG®, although better and faster at assessing global coagulation, are not interchangeable, which makes interpretation difficult, and although highly specific for fibrinolysis, they are not sensitive and occult hyper-fibrinolysis will be missed.[45] Of note, in a ROC-TXA substudy, TEG® was unable to detect post-TXA fibrinolytic inhibition compared with biochemical markers (D-dimers, and plasmin–antiplasmin complexes).[46]

Identification of ideal endpoints for TXA clinical trials requires further discussion with most trials using all-cause mortality, blood loss, transfusion rates, and disease-specific outcomes (such as bleeding and head injury). These clinical outcomes suffer from several important limitations. All-cause mortality provides an objective endpoint, but improving this outcome using TXA alone may be a biological stretch and not always generalisable, given non-haemorrhagic deaths will be affected by local health system resource availability and delivery, and use of other blood products. Defining a disease-specific mortality can be complex and subjective. Within the CRASH-2 trial, 55% of deaths in the first hour were attributable to causes other than uncontrolled bleeding. Measurement of blood loss as an outcome is also notoriously difficult to measure and highly subjective. The CRASH trials failed to identify a significant reduction in blood product transfusion, and the survival benefit is possibly attributable to the mechanistic effects on reducing bleeding, inflammation, and possibly

secondary complications. This can be seen in isolated TBI, where TXA inhibits not only fibrinolysis to reduce haemorrhage expansion, but may reduce perilesional cerebral oedema through its inhibition of t-PA.[23]

Conclusion

The haemostatic management of trauma resuscitation is a time-critical problem with most deaths attributed to haemorrhage. TXA offers a simple and efficacious treatment that should ideally be administered to all trauma victims within the pre-hospital period. Hyper-fibrinolysis is the target of therapy. A single bolus appears a pragmatic regimen that will be easier to apply in clinical practice, but further research is needed on dose optimisation and the impact of co-infusion of coagulation factor concentrates with TXA.

Authors' contributions

All authors contributed to the concept, content, writing, and review of final paper.

Declarations of interest

The authors declare that they have no conflicts of interest.

References

1. Callcut RA, Kornblith LZ, Conroy AS, et al. The why and how our trauma patients die: a prospective multicenter Western Trauma Association study. *J Trauma Acute Care Surg* 2019; **86**: 864–70
2. Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. *Br J Anaesth* 2016; **117**. iii31–43
3. Martini WZ. The effects of hypothermia on fibrinogen metabolism and coagulation function in swine. *Metabolism* 2007; **56**: 214–21
4. Cap A, Hunt B. Acute traumatic coagulopathy. *Curr Opin Crit Care* 2014; **20**: 638–45
5. Chang R, Cardenas JC, Wade CE, Holcomb JB. Advances in the understanding of trauma-induced coagulopathy. *Blood* 2016; **128**: 1043–9
6. Roberts DJ, Kalkwarf KJ, Moore HB, et al. Time course and outcomes associated with transient versus persistent fibrinolytic phenotypes after injury: a nested, prospective, multicenter cohort study. *J Trauma Acute Care Surg* 2019; **86**: 206–13
7. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost* 2013; **11**: 307–14
8. Moore HB, Moore EE, Liras IN, et al. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. *J Am Coll Surg* 2016; **222**: 347–55
9. Coats TJ, Morsy M. Biological mechanisms and individual variation in fibrinolysis after major trauma. *Emerg Med J* 2020; **37**: 135–40
10. Maegele M. Coagulopathy after traumatic brain injury: incidence, pathogenesis, and treatment options. *Transfusion* 2013; **53**: 28S–37S
11. Hu W, Xin Y, Chen X, Song Z, He Z, Zhao Y. Tranexamic acid in cerebral hemorrhage: a meta-analysis and systematic review. *CNS Drugs* 2019; **33**: 327–36
12. Hijazi N, Abu Fanne R, Abramovitch R, et al. Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice. *Blood* 2015; **125**: 2558–67
13. Lier H, Maegele M, Shander A. Tranexamic acid for acute hemorrhage: a narrative review of landmark studies and a critical reappraisal of its use over the last decade. *Anesth Analg* 2019; **129**: 1574–84
14. July J, Pranata R. Tranexamic acid is associated with reduced mortality, hemorrhagic expansion, and vascular occlusive events in traumatic brain injury—meta-analysis of randomized controlled trials. *BMC Neurol* 2020; **20**: 119
15. CRASH-2 Trial Collaborators, Shakur H, Roberts I, Bautista R, et al. 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
16. Crash-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ* 2011; **343**: d3795
17. CRASH-3 Trial Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet* 2019; **394**: 1713–23
18. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* 2019; **23**: 98
19. CRASH-2 Collaborators, Roberts I, Shakur H, Afolabi A, et al. 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. 101.e1–2
20. 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
21. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II study. *JAMA Surg* 2013; **148**: 218–25
22. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med* 2013; **13**: 20
23. Zehtabchi S, Abdel Baki SG, Falzon L, Nishijima DK. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. *Am J Emerg Med* 2014; **32**: 1503–9
24. Weng S, Wang W, Wei Q, Lan H, Su J, Xu Y. Effect of tranexamic acid in patients with traumatic brain injury: a systematic review and meta-analysis. *World Neurosurg* 2019; **123**: 128–35
25. Lockey DJ, Weaver AE, Davies GE. Practical translation of hemorrhage control techniques to the civilian trauma scene. *Transfusion* 2013; **53**(Suppl 1): 17S–22S
26. Coats TJ, Fragoso-Iniguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a

longitudinal and cross-sectional study. *Emerg Med J* 2019; **36**: 78–81
27. Fischer PE, Bulger EM, Perina DG, et al. Guidance document for the prehospital use of tranexamic acid in injured patients. *Prehosp Emerg Care* 2016; **20**: 557–9
28. Rowell SE, Meier EN, McKnight B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA* 2020; **324**: 961–74
29. Rizoli SB, Scarpelini S, Callum J, et al. Clotting factor deficiency in early trauma-associated coagulopathy. *J Trauma* 2011; **71**: S427–34
30. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med* 2018; **379**: 315–26
31. Moore HB, Moore EE, Chapman MP, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet* 2018; **392**: 283–91
32. Pusateri AE, Moore EE, Moore HB, et al. Association of prehospital plasma transfusion with survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials. *JAMA Surg* 2020; **155**, e195085
33. Erdoes G, Koster A, Ortmann E, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. *Anaesthesia* 2020. https://doi.org/10.1111/anae.15181. Advance Access published on July 17, 2020
34. Joseph B, Pandit V, Khalil M, et al. Use of prothrombin complex concentrate as an adjunct to fresh frozen plasma shortens time to craniotomy in traumatic brain injury patients. *Neurosurgery* 2015; **76**: 601–7. discussion 7
35. Lier H, Shander A. Tranexamic acid: the king is dead, long live the king! *Br J Anaesth* 2020; **124**: 659–62
36. Ageron FX, Gayet-Ageron A, Ker K, et al. Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. *Br J Anaesth* 2020; **124**: 676–83
37. Benipal S, Santamarina JL, Vo L, Nishijima DK. Mortality and thrombosis in injured adults receiving tranexamic acid in the post-CRASH-2 era. *West J Emerg Med* 2019; **20**: 443–53
38. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol* 2016; **79**: 18–26
39. Jerath A, Yang QJ, Pang KS, et al. Tranexamic acid dosing for cardiac surgical patients with chronic renal dysfunction: a new dosing regimen. *Anesth Analg* 2018; **127**: 1323–32
40. Yang QJ, Jerath A, Bies RR, Wasowicz M, Pang KS. Pharmacokinetic modeling of tranexamic acid for patients undergoing cardiac surgery with normal renal function and model simulations for patients with renal impairment. *Biopharm Drug Dispos* 2015; **36**: 294–307
41. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007; **4**: CD001886
42. Grassin-Delyle S, Theusinger OM, Albrecht R, et al. Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis. *Anaesthesia* 2018; **73**: 719–29
43. Wasowicz M, Jerath A, Bojko B, Sharma V, Pawliszyn J, McCluskey S. Use of a novel technique, solid phase microextraction, to measure tranexamic acid in patients undergoing cardiac surgery. *Can J Anaesth* 2012; **59**: 14–20
44. Etchill E, Sperry J, Zuckerbraun B, et al. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. *Transfusion* 2016; **56**: 2478–86
45. Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg* 2013; **74**: 1575–86
46. Dixon AL, McCully BH, Rick EA, et al. TXA administration in the field does not affect admission TEG after traumatic brain injury. *J Trauma Acute Care Surg* 2020. https://doi.org/10.1097/TA.0000000000002932. Advance Access published on August 28, 2020

British Journal of Anaesthesia, 126 (1): 17–20 (2021)
doi: 10.1016/j.bja.2020.10.003
Advance Access Publication Date: 24 October 2020

Intramuscular tranexamic acid: a real-world application of pharmacokinetics

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DOI of original article: 10.1016/j.bja.2020.07.058.