Tactical Field Care

Tranexamic Acid (TXA)

27 July 2020

TXA in the TCCC Guidelines:
* New wording in red text

TACTICAL FIELD CARE

c. Tranexamic Acid (TXA)
   - If a casualty will likely need a blood transfusion (for example: presents with hemorrhagic shock, elevated lactate, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)
   or
   - If the casualty has signs or symptoms of significant TBI or has altered mental status associated with blast injury or blunt trauma:

   - Administer 2 gm of tranexamic acid via slow IV or IO push as soon as possible but NOT later than 3 hours after injury.

Case Study:
The Setting
   - A small unit is moving outside of a village
   - There is a single shot from somewhere in the village
   - No other hostile fire

The Casualty
   - Single gunshot wound to abdomen (see Figure 1 below)
   - The casualty is alert and in moderate pain
   - There is no life-threatening external hemorrhage
   - There is a normal radial pulse 2 minutes after the wound was sustained

Figure 1: Gunshot Wound to the Abdomen
Casualty Status
- AVPU Alert
- Airway Patent
- Breathing RR 18 and unlabored
- Radial Pulse Strong
- O2 Saturation 97%

Question: What is the NEXT action you should take?
1. Start an IV and administer TXA immediately
2. Start an IV and administer a unit of freeze-dried plasma
3. Administer 50 mg of ketamine IM
4. Administer an 800ug fentanyl lozenge

Answer: See the answer at the end of the Discussion Section below

Discussion:

TXA and Hemorrhage

Hemorrhage is the leading cause of preventable death in combat casualties. (Kelly 2008, Holcomb 2007, Eastridge 2012) The widespread use of commercially-manufactured limb tourniquets in the US military has almost eliminated death from isolated extremity hemorrhage and hemostatic dressings have helped to control bleeding from anatomic sites not amenable to extremity tourniquets. (Butler 2015) Junctional hemorrhage can now be effectively addressed with CoTCCC-recommended hemostatic dressings or junctional tourniquets. (Kotwal 2017, Kotwal 2013) Non-compressible hemorrhage is now the cause of 67% of hemorrhagic deaths on the battlefield. (Eastridge 2012)

Tranexamic acid (TXA) is a lysine analogue that binds to the lysine receptor sites in plasminogen, preventing its transformation into plasmin and thereby inhibiting the breakdown of clots in the fibrinolytic process. TXA does not promote the formation of new clots: it stabilizes clots that have already formed which may be of benefit in establishing hemostasis in bleeding casualties. TXA has other properties in addition to its anti-fibrinolytic activity. It has been shown to reduce inflammation and to stabilize the vascular endothelium. (Diebel 2017) Both of these properties may be of benefit in bleeding trauma patients. TXA is not approved by the FDA for use in trauma despite the findings outlined below, so its use in this setting is off-label. (CRASH-2 Early Treatment - 2011)

The CRASH-2 study examined the effect of TXA as an intervention to reduce death from hemorrhage in 20,211 trauma patients. (CRASH-2, 2010) In that study, a small but statistically significant benefit from TXA use was found. There was no difference in the rate of vascular occlusive events between the two arms of the study, and no unexpected adverse events from TXA use were reported. Subsequent subgroup analysis of the CRASH-2 data examining the impact of the timing of TXA administration on the 1,063 deaths from bleeding in the CRASH-2 study found that the risk of death due to bleeding was significantly reduced (5.3% vs 7.7%) if TXA was given within 1 hour of injury. (CRASH-2 Early Treatment, 2011) When TXA was given 1-3 hours after injury, the decrease in mortality was smaller but remained significant (4.8 vs 6.1%). TXA administered more than 3 hours after injury, however, was associated with increased mortality as compared to controls.

The findings of the CRASH-2 study were compelling, but their applicability to the care of combat casualties was uncertain. Different mechanisms of wounding, differences in injury patterns, longer delays to evacuation, and differences in trauma systems made it less than obvious that TXA would provide similar benefits to individuals wounded in combat. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERs) was performed to address this question. It was carried out at a
Role 3 facility in Afghanistan. (Morrison 2012) In this case series of 896 combat casualties who received a blood transfusion, mortality in those casualties who received TXA was reduced compared to those who did not (17.4% vs 23.9%; P=0.03), despite the fact that those receiving TXA were more severely injured (ISS 25.2 vs 22.5.) In the subgroup of casualties who received massive transfusions, however, mortality was markedly lower in the TXA group (14.4%) as compared to the no-TXA group (28.1%; p=0.004.)

In the MATTERS study, both deep venous thrombosis (DVT) and pulmonary embolism (PE) were increased in the TXA group, (PE in the massive transfusion TXA group was 3.2% vs 0% in the no-TXA massive transfusion group), but no fatalities from PE were reported in this study. The CRASH-2 and MATTERS findings support the use of TXA in combat casualties who are in hemorrhagic shock or at significant risk for that condition. Accordingly, TXA (Figure 2) was added to the TCCC Guidelines in 2011. (Dickey 2011)

**Figure 2. Tranexamic Acid**

In his 2011 review of the literature on TXA (Cap 2011), Colonel Andre Cap concluded that: “This inexpensive and safe drug should be incorporated into trauma clinical practice guidelines and treatment protocols…. TXA should be adopted for use in bleeding trauma patients because it is the only drug with prospective clinical evidence to support this application.” A later study using a swine model found that TXA is also effective when administered by the intraosseous route. (Boysen 2017)

In the years following the CRASH-2 study, a number of studies examining the use of TXA in elective surgery appeared in medical literature. A 2013 meta-analysis reviewed 46 randomized controlled trials involving 2925 patients and found that the use of TXA in elective major orthopedic surgery reduced total blood loss by a mean of 408 mL. (Huang 2014) In his 2017 study, Sabbag noted that “IV TXA has gained substantial popularity in primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) and is now commonly used for revision hip and knee arthroplasties as well.” (Sabbag 2017) This paper addressed the question of whether or not TXA was safe to use in patients who had a previous history of DVT. Their retrospective study of 1,262 patients who had undergone either THA or TKA found that patients who had a history of venous thromboembolism (VTE) did not have an increased risk of recurrent VTE when TXA was used as an adjunct to their surgery. Ramirez et al state that “Currently, TXA may be the best pharmacologic option for prehospital hemostatic interventions, and its administration in the field has been shown to be feasible in both civilian and military settings.” (Ramirez 2017)

The finding of the CRASH-2 timing subgroup analysis that TXA given more than 3 hours after injury increased mortality (CRASH-2 Early Treatment, 2011) has unfortunately led to the misperception that giving TXA at any time before the 3-hour point is equally acceptable when using this drug in trauma patients. A best-practice summary published in Annals of Emergency Medicine states: “According to the available evidence, tranexamic acid has been shown to significantly decrease mortality in bleeding trauma patients, with no significant increase in serious prothrombotic complications if administered within 3 hours of injury” and recommends its use in patients who require resuscitation with blood products, especially
massive transfusion patients. (Harvey 2014) This approach does not reflect the fact that CRASH-2 showed that the greatest benefit from TXA use in trauma was seen when it was given within one hour of injury. Furthermore, the studies of TXA given before elective surgery produced Level A evidence that TXA reduces blood loss and does not increase the risk of thromboembolic complications when given before the bleeding starts in elective surgery. The best way to prevent death from hemorrhage is to prevent the causative hemorrhage. COL John Kragh found in his 2009 tourniquet study that when tourniquets were applied before the onset of shock, survival was 90%. When shock was already present at the time of tourniquet application, survival dropped to 10%. (Kragh 2009) The implication for TCCC is that to obtain the maximal survival benefit from the hemostatic effect of TXA, TXA should be given as soon as possible after injury (Figure XX-1). This is reflected in the wording of the 2020 TCCC Guidelines shown above. (Drew 2020)

The second dose of TXA is typically given after the casualty arrives at a Role 2 or Role 3 medical facility. This dose may be given in the field if evacuation is delayed and fluid resuscitation is completed before arrival at the medical facility. If the second dose of TXA is administered during Tactical Field Care or Tactical Evacuation Care, it should be given just as directed for the first dose.

The question of whether or not TXA can be safely mixed with Hextend™ has been raised. A 2016 study was performed to address that issue.21 The authors found that mixing TXA with Hextend caused no evidence of incompatibility on visual inspection or by digital turbidimeter. To date, this study has resulted in no change in the PDR recommendations20 nor a change in the TCCC recommendation to mix TXA in normal saline or Lactated Ringer’s solution.

In October of 2013, the Assistant Secretary of Defense expanded prehospital use of TXA from Special Operations forces to all forces in the U.S. Military. The approval letter noted that TXA is not FDA-approved for trauma and is therefore considered an off-label use subject to a provider's clinical judgment. The letter required the military services to establish service-specific policies regarding TXA administration, to develop training and education plans, to accumulate outcome data and monitor adverse events associated with TXA use, and to assume all costs for implementation. (Woodson 2013)

The Joint Trauma System recently examined the data in the DoD Trauma Registry to further evaluate the impact of TXA in combat casualties. Howard’s 2017 study examined the use of TXA in 3,773 combat casualties. (Howard 2017) All of these casualties received at least one unit of RBCs. The authors did not find a significant impact of TXA use on mortality, but they did note that TXA use was associated with a higher rate of deep venous thrombosis. Caveats in this study included a note that physicians and combat medical providers have been cautious about the use of this new medication and have received training that suggests that TXA should only be given to the most seriously injured patients. (Howard 2017) If TXA administration is delayed until the casualty is in shock, the time for maximal benefit has likely passed. (Kragh 2009, Gayet-Ageron 2018) Additionally, Howard’s study did not include a subgroup analysis based on elapsed time from injury until TXA administration, as the CRASH-2 timing subgroup analysis did. (Howard 2017) Finally, the preponderance of undocumented prehospital care makes it difficult to determine what was or was not done in the prehospital phase of care, when TXA administration would be expected to have had the most benefit. (Kotwal 2017, Butler 2017, Kotwal 2013)

A civilian TXA study examining the prehospital use of TXA found a benefit from using this medication early in the continuum of care for trauma patients. (Wafaisade 2016) In this study, early (24-hour) mortality was found to be significantly lower in the TXA group (5.8 %) than the control group (12.4%). The most pronounced mortality difference was observed in patients who were more severely injured.

A review of TXA use in austere environments (Huebner 2017) produced the following recommendation: “Our recommendation based on the current literature advocates the use of early bolus TXA in the prehospital setting in those patients at risk of significant uncontrolled bleeding. The benefit is most pronounced when given early after injury (less than 1 hour) and, combined with the extensive literature on prophylactic administration in elective surgery, may be most beneficial when given before the development of hemorrhagic shock. We recommend withholding repeat dosing until coagulation status has been
determined and redosing at that time for a LY30 greater than 43% on TEG.”

A large meta-analysis of trauma and post-partum hemorrhage patients treated with TXA found that: “Immediate treatment improved survival by more than 70% (OR 1.72, 95% CI 1.42–2.10; p<0.0001). Thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit.” There was no increase in vascular occlusive events with tranexamic acid use. (Gayet-Ageron 2018)

Despite the power of the amassed evidence as discussed, the novelty of TXA in prehospital trauma care has resulted in its continued underuse or delayed use in battlefield trauma care, as recently noted by Schauer and his co-authors. (Schauer 2017)

TXA Update 2020

Traumatic Brain Injury (TBI) is another major cause of death in trauma. While in the past, this cause of death has not necessarily been considered preventable, as external hemorrhage is. But two recent randomized, controlled trials have shown that many TBI deaths can be avoided by the early administration of TXA. (Drew 2020) One was the international CRASH-3 Trial; (CRASH-3, 2020) the second was a U.S. study (Rowell 2020) that used a single 2 gm dose of TXA in the prehospital setting. This new evidence requires consideration of TXA for this indication as well.

In developing this proposed change to the TCCC Guidelines, the TCCC change team identified a number of specific questions that needed to be addressed: (Drew 2020)

- Should a TBI indication for TBI be added to the TXA recommendations in the TCCC Guidelines and the dose increased to 2 gms?
- Is there a need to reinforce the need for timely administration of TXA when indicated?
- Is a second dose of TXA really needed to improve outcomes when used for bleeding trauma patients?
- Is TXA effective when administered IM to bleeding trauma patients?
- Is TXA effective when administered via the IO route to bleeding trauma patients?
- Can TXA be safely given as a slow IV push rather than over 10 minutes?
- Can TXA be given in the same IV/IO line as blood/blood products?
- Should the second dose of TXA be administered if more than 3 hours have elapsed since the time of wounding?
- What is "Initial Fluid Resuscitation?" as mentioned in the TCCC Guidelines with respect to TXA? And when does it end?
- Should the dose of TXA be modified in the presence of ongoing hemorrhage?
- Can TXA be administered through the same line as Hextend?
- If removed from glass vials in preparation for administration, how long can TXA be kept in a syringe?
- What is the current state of evidence that TXA causes an increase in the risk of deep venous thrombosis and pulmonary embolism? (Drew 2020)

After an extensive review of the TXA literature and a number of teleconferences dedicated to this topic, these questions were answered as follows:

- Should a TBI indication for TBI be added to the TXA recommendations in the TCCC Guidelines and the dose increased to 2 gms?

Yes. Studies dating back to 2012, have suggested “that TXA administration might improve outcomes in TBI patients and provide grounds for evaluating this hypothesis in future research.” (Perel 2012)
Multiple studies since then have suggested a benefit from TXA administration to TBI patients. (Chan 2019, Morte 2019, Weng 2018, Cornelius2018)
The 2019 CRASH-3 trial was the largest randomized control trial of TXA in isolated TBI performed to date. It was performed from 2012 to 2019 in 175 hospitals in 29 countries and continued to use the Horrow Protocol (1 gm TXA over 10 minutes initial dose followed by another 1 gm dose administered over 8 hours.) There were 12,737 patients in the study and 6,406 were randomized to receive TXA. The criteria for TXA administration were: 1) presentation within 3 hours of injury; 2) Glasgow Coma Scale of 12 or less with any intracranial bleeding on CT; and 3) no extracranial bleeding. Overall mortality from head injury was found to be 18.5% in the TXA group as compared to 19.8% in the placebo group. When patients with severe head injury (GCS 3/non-reactive pupils) were excluded, the mortality from head injury was then 12.5% in the TXA group as compared to 14% in the placebo group. (CRASH-3 2019)

More recently, a paper by Rowell et al that has been accepted for publication in JAMA at the time of this writing describes a triple-armed randomized, controlled trial (placebo, 1 gm TXA initial dose followed by another 1 gm TXA over 8 hours, and 2 gm initial TXA dose only) conducted in the US. This study found a survival benefit when a 2 gm dose of TXA was administered in the prehospital phase of care to patients with moderate to severe TBI. (Rowell 2020) For the cohort of patients who were subsequently found to have intracranial hemorrhage on initial CT scan, the 2 gm prehospital administration of TXA resulted in a 28-day mortality of 18%; in patients who had received the 1 gm TXA initial dose followed by a subsequent 1 gm dose, the mortality was 28%; and the mortality in the placebo group was also noted to be 28%. In comparing the 2 gm TXA prehospital bolus to placebo, the difference in outcome was highly significant ($p = .0035$). The 1 gm initial dose of TXA followed by another 1 gm over 8 hours was not different from placebo. (Rowell 2020). Figure 3 is an image of a subdural hematoma, one type of intracranial bleeding.

![Subdural Hemorrhage](image)

The Physicians Desk Reference lists TBI as an indication for TXA as follow: “For intracranial bleeding prophylaxis after traumatic brain injury” but recommends a dose smaller (PDR Website, 2020)

In addition to previously discussed work supporting a 2 gm dose for TXA in TBI, there is evidence of a 1 gm dose not being sufficient in severe trauma (Grassin-Delyle 2018). Grassin-Delyle et al noted that a 1 gm dose resulted in serum concentrations that may not be beneficial past 90 minutes. It is important to note, however, that an optimal serum concentration of TXA in trauma has yet to be determined. (Taam 2020, Picetti 2019, Vu 2018). It is also important to note that a 2 gm dose of TXA has not been specifically studied in patients already in hemorrhagic shock but has been studied in severely injured patients. (Spinella unpublished data) A recently completed randomized study of prehospital TXA administration in the U.S. (STAAMP Trial) compared three dosing strategies, and found that the higher dose regimen (2 gram bolus followed by 1 gram infusion) was associated with lower 30 day mortality versus the lower dose regimens or placebo. (Guyette 2020) Doses used for indications other than trauma vary considerably, but it is important to note that symptomatic VTE has not been noted in multiple studies using TXA doses up to 30 mg/kg in elective surgery procedures. (Mannan 2018, Apipan 2018, Wang 2016, Volquind 2016, Baker 2015,
Hourlier 2014) TBI researchers also found no difference in VTE rate between the 1 gm and 2 gm prehospital dose (Rowell 2020). Although a recent review noted the safety and effectiveness of the current dosing protocol, the recommendation to continue with the current TXA dosing regimen was based on studies of the use of TXA for hemorrhage and did not take into account the recent Rowell findings regarding the use of TXA in TBI. (Stansfield 2019)

- Is there a need to reinforce the need for timely administration of TXA when indicated?

Yes. The evidence to date consistently supports the premise that the timing of TXA administration is key to improving outcomes in trauma patients.

The CRASH-2 timing subgroup analysis found that the timing of TXA administration is critical when the possibility of life-threatening bleeding is considered to be high. (CRASH 2 Collaborators 2011) More recent studies have reinforced that finding. A large meta-analysis of trauma and post-partum hemorrhage patients treated with TXA found that: “Immediate treatment improved survival by more than 70% (OR 1.72, 95% CI 1.42–2.10; p<0.0001). Thereafter, the survival benefit decreased by 10% for every 15 min of treatment delay until 3 h, after which there was no benefit. There was no increase in vascular occlusive events with tranexamic acid…” (Gayet-Ageron 2017) Post-hoc analysis of CRASH-2 data has shown improvement in functional outcomes with early administration of TXA as well (Nishijima 2019). A meta-analysis of over 28,000 patients published in 2020 found that “about one-quarter of deaths from bleeding occurred in patients who initially appeared to have a low risk of death.” The authors emphasized early administration of TXA and specifically recommended that TXA “use should not be restricted to the most severely injured or bleeding patients.” (Ageron 2020) Other potential mechanisms through which TXA may benefit trauma patients may also be time-dependent. (Diebel 2018, Nauman 2018, Weng 2018, Diebel 2017, Diebel 2015, Jimenez 2011, Levy 2010, Jimenez 2007).

A study at Ryder Trauma Center in Miami reported that “For the highest injury acuity patients, TXA was associated with increased, rather than reduced, mortality, no matter what time it was administered.” (Valle 2014) Of note, however, is that TXA in this study was administered at a mean time of 97 minutes after arrival at the hospital. The range of elapsed times from arrival at the hospital to TXA administration was 0 to 886 minutes. (Drew 2020, Valle 2014) Further, these times do not include the elapsed time from injury occurrence until the 911 call; the time delay to dispatch after the call is received; ambulance or helicopter transit time to the scene of the injury; time on scene for the first responders; or the transport time from the point of injury to the trauma center. Thus, this study reinforces the findings of CRASH-2 that delayed administration of TXA is not associated with a survival benefit.

Like TCCC, updated civilian trauma guidelines continue to emphasize administration of TXA as early as possible following trauma (Spahn 2019). Medics should be trained to understand that timing is critical for casualties with known or suspected hemorrhage and/or moderate to severe TBI: DONT DELAY WITH TXA!

- Is a second dose of TXA really needed to improve outcomes when used for bleeding trauma patients?

No. Although the often-quoted CRASH-2 study used an initial dose of TXA followed by a second dose of TXA given over 8 hours, more recent literature has questioned the need for the second dose of TXA to be included in prehospital care protocols. (Huebner 2017, Goodloe 2013) The pharmacokinetics of TXA are such (a half-life of two hours) that subsequent doses of TXA could be given in the hospital, optimally based on the patients fibrinolytic status and the presence or absence of ongoing hemorrhage. Additionally, the multiple studies of TXA use in elective surgery cited above that have consistently demonstrated a reduction in surgical blood loss typically use a single pre-op dose of TXA.
- Is TXA effective when administered IM to bleeding trauma patients?

The CRASH-2 and MATTERS studies, as well as most studies in which preoperative TXA is given to reduce bleeding in elective surgery, called for TXA to be administered IV. Other authors, however, have raised the question of whether TXA would still be efficacious at reducing mortality in bleeding patients if administered intramuscularly, in particular by an autoinjector. (Wright 2014, Culligan 2011) A review of this topic conducted in 2018 was unable to definitively answer that question, but did make a recommendation that “Balancing the available data and risk/benefit ratio, IM TXA should be considered a viable treatment option for tactical and combat applications.” (Vu 2018)

The literature on IM administration of TXA is not robust, and none of the studies reviewed used IM TXA for patients in shock. In a 1985 study, TXA was administered to 3 healthy volunteers. Bioavailability of both IM and IV TXA was 100%, but peak serum concentrations of IM TXA were not seen until 40-60 minutes after administration, whereas peak levels of IV TXA were achieved in 5 minutes. (Puigdellivol 1985). TXA is currently supplied only as 100mg/1mL solution, which would require a very large IM volume of 20mL to achieve the desired 2 gm dose. Given the currently available evidence and the lack of a more concentrated formulation of TXA, IM TXA administration is not currently recommended in TCCC.

- Is TXA effective when administered via the IO route to bleeding trauma patients?

The TCCC Guidelines in the past have not included IO administration of TXA, but there are no known contraindications to administering intravenous medications intraosseously. (Drew 2020) In swine models, IO and IV administration of TXA have been shown to have both equivalent pharmacokinetics as well as anti-fibrinolytic efficacy. (Lallemand 2018, Boysen 2017, DeSoucy unpublished data) One case series of prehospital TXA administered via the IO route found no complications in 82 patients. (Lewis 2015) IO administration of TXA was included in the Cal-PAT study, but the authors did not discuss that aspect of the study in depth. (Neeki 2018) The 75th Ranger Regiment currently allows the IO route to be used for TXA administration and has had no documented complications from this practice. (LTC Ryan Knight, personal communication – date?).

- Can TXA be safely given as a slow IV push rather than over 10 minutes?

The CoTCCC has been asked frequently by combat medical personnel and their supervising physicians about whether or not it would be acceptable to give the initial dose of TXA by slow IV push rather than as a 10-minute infusion, as was done in the CRASH-2 study. (CRASH 2 Collaborators 2010) Combat medic compliance with the TCCC recommendation for TXA administration has been found to be poor and the need for a 10-minute infusion of TXA was mentioned as a possible factor for that finding. One of the co-authors of that paper reported his personal successful experience with safe slow IV push administration of TXA and recommended that this item be changed in the TCCC Guidelines. (Schauer 2017) IV bolus dosing of TXA was used in the MATTERs study with no adverse effects noted from that practice, but the time over which the bolus was delivered was not specified and the dose delivered was 1 gm rather than the now-recommended 2 gms. (Morrison 2011)

There is concern that administering TXA too rapidly may result in hypotension or seizures. The Physicians Desk reference recommends that TXA not be administered more rapidly than 1000 mg/minute. (PDR website, 2020) A small porcine study administered TXA (30 mg/kg) IV or IO over 5 minutes using a digitally programmable syringe driver. (Boysen 2017) without adverse outcomes or observed hypotension. The 75th Ranger Regiment has used a dose of 1 gm given slow IV push without any episodes of clinically significant hypotension with a slow IV push strategy. (Personal Communication LTC Ryan Knight) The time suggested for the slow IV administration of TXA in the text of the TCCC change paper was “approximately 1
minute,” (Drew 2020) but the specific time over which the 2 gm dose should be given was not part of the wording in the approved change to the TCCC Guidelines. The Rowell paper (Rowell 2020) had a study arm in which a 2 gm dose of TXA was administered “via IV bolus in the out-of-hospital setting followed by a placebo infusion,” but the time over which the bolus was administered was not specified. According to the senior author on the paper, the bolus of TXA was administered by dissolving 2 grams of TXA in 20 cc of water and then adding the solution to a 250 ml bag of normal saline. Medics were trained to infuse the 250ml over 20 minutes but frequently the infusion was given wide open. (Personal communication, Dr. Marty Schreiber – 7 July 2020) Using this dosing regimen in 345 patients, the only adverse outcome noted was that “participants in the bolus-only group were more likely to experience seizures (5%) than participants in either the bolus-maintenance group (2%) or placebo group (2%).” (Rowell 2020) Despite the

The TCCC change team recommended that slow IV or IO push be allowed for TXA administration and this was subsequently approved by the CoTCCC. Alternative approaches that might be useful in some circumstances are to administer the initial 2 gm dose of TXA by injecting it into a 250 cc IV piggyback bag and allowing that to run in wide open, as was done in the Rowell study or to use a timed-infusion device set for approximately 5 minutes as per the 2017 Boysen study.

- Can TXA be given in the same IV/IO line as blood/blood products?

Yes. Although the PDR website states that TXA should not be mixed with blood, the TCCC change paper on the update to TXA dosing found no specific studies that addressed this question. (Drew 2020), but also noted that no reports of complications from TXA being administered with blood products were found. Since TXA typically mixes with blood immediately after being given IV, no compatibility issues would be expected. Drew and his co-authors recommended that TXA be given as soon as possible after injury and that giving it in the same line as blood products is acceptable. (Drew 2020) If TXA is to be given with blood products, the IV port closest to the skin should be used to administer the bolus.

- Should the second dose of TXA be administered if more than 3 hours have elapsed since the time of wounding?

No. In the 2011 CRASH-2 timing subgroup analysis, mortality was actually found to be increased when TXA was administered more than 3 hours after the time of injury. (CRASH-2 Early Treatment, 2011) While this finding referred to the initial dose of TXA, there has been no evidence found to date that suggests that additional doses given in the prehospital setting more than 3 hours after injury are beneficial and these delayed doses of TXA are not recommended in TCCC. (Drew 2020)

- What is "Initial Fluid Resuscitation?" as mentioned in the TCCC Guidelines with respect to TXA? And when does it end?

The TCCC Guidelines prior to the present change called for a second 1 gm dose of TXA to be administered “after initial fluid resuscitation has been completed” but this would require defining what is meant by “initial fluid resuscitation.” The most important aspect of TCCC administration is that TXA be given as soon as possible after the injury, given the tactical situation and prioritization of TCCC interventions according to the “MARCH” acronym. There is now no second dose of TXA recommended in TCCC and the reference to “after initial fluid resuscitation has been completed” has been removed the present TCCC Guidelines.

- Should the dose of TXA be modified in the presence of ongoing hemorrhage?

No. Should ongoing hemorrhage and a resultant massive transfusion be present in the casualty, the question has been raised in the medical literature whether or not the dose of TXA should be modified to compensate
for the loss of a portion of the administered TXA through ongoing hemorrhage and hemodilution of the remainder of the TXA dose. (Drew 2020) One recent study noted that: “Scenarios involving large patients requiring massive transfusion may benefit from a replacement strategy. (Derickson 2018) Replacement dosing schemes should be identified using simulations and tested in large animal model.” This study went on to note, however, that TXA levels were relatively preserved during hemorrhage, with only a 25% decrease after one total body blood volume loss and replacement. The WOMAN study called for a second dose of TXA (or placebo) only if bleeding was still present after 30 minutes (WOMAN Collaborators 2017) or if it had restarted within 24 hours. The World Health Organization current recommendations on TXA dosing reflect those used in the WOMAN study mentioned above. The present TCCC Guidelines do not call for a modification of TXA dosing in the presence of ongoing hemorrhage.

- Can TXA be administered through the same line as Hextend?

The preferred resuscitation fluid in TCCC is whole blood, but Hextend at present remains on the (bottom of the) list of recommended fluids with which to treat hemorrhagic shock, if no blood products are available. Medics and physicians therefore on occasion ask if it is possible to administer TXA in Hextend infusions. The Physicians’ Desk Reference states that TXA “may be mixed with most solutions for infusion such as electrolyte, carbohydrate, amino acid, and dextran solutions.” (PDR website, 2020) Hextend is not specifically mentioned. Two recent studies however, have found that TXA is compatible with Hextend. (Fillingham 2018, Studer 2016) Studer noted that “There was no evidence of incompatibility between the solutions of Hextend and TXA by either visual inspection or by digital turbidimeter.” In the event that Hextend is used to resuscitate a casualty, TXA may be given with the Hextend. It should be noted, however, that there is at present a proposed change to the TCCC Guidelines that may include the removal of Hextend from the list of recommended resuscitation fluids.

- If removed from glass vials in preparation for administration, how long can TXA be kept in a syringe?

Despite the abundant evidence that TXA increases survival in casualties with ongoing bleeding or moderate/severe TBI, use of TXA in these clinical situations is still considered “off-label” by the FDA. There are, therefore, at present no manufactured 2 gm TXA unit-dose vials or pre-mixed piggyback IV doses commercially available. The PDR website specifies that the “diluted admixture may be stored for up to 4 hours at room temperature.” (PDR website, 2020) Although TXA is very stable throughout a range of temperatures for several days (Donnelly 2018, de Guzman 2013), there are no studies to support storage outside of the original packaging (for example, in a pre-drawn syringe). Under routine conditions, medications are given within a few hours of being prepared. Operational units should evaluate the need to predraw TXA prior to missions or operations and adjust practice based on the tactical and/or logistical situation. Providers should consult their medical director for guidance regarding drawing and storing medications prior to administration.

- What is the current state of evidence that TXA causes an increase in the risk of deep venous thrombosis and pulmonary embolism?”

Use of TXA to reduce blood loss in elective surgery (especially orthopedic and cardiac surgery) - when TXA is routinely given preoperatively or before the time of tourniquet release in extremity surgery - have repeatedly found that TXA use decreases bleeding without increasing the risk of DVT and PE. (Lack 2017, Gausden 2017, Amer 2017, Evangelista 2017, Li 2017, Myles 2017, Farrow 2016, Huang 2017, Volquind 2016, Baker 2015, Yu 2015, Valerio 2015, Huang 2014, Karam 2014, Charoencholvanich 2011). When TXA was given to over 10,000 patients with post-partum hemorrhage, no increase in VTE was noted (WOMAN Trial Collaborators 2017). A large meta-analysis that included 22 studies and over 49,000 patients who received TXA for non-surgical bleeding noted no increase in venous or arterial
thrombotic events. (Chornenki 2019)

Trauma patients are, however, at increased risk for VTE and PE (Ekeh 2010, Reif 2009, Adams 2008) and the MATTERS study found that TXA increased that risk. (Morrison 2011) Despite the increased risk of VTE and PE associated with TXA use in that study, however, there was still a net increase in survival with TXA use, especially in patients who required a massive transfusion. (Morrison 2011) Some newer studies of TXA use in trauma have not shown an increased rate of VTE (Glover 2019, Khan 2018, El-Menyar 2018, Cornelius 2018, Gayet-Ageron 2018) while others have in fact noted an increase in this condition. (Boudreau 2019, Myers 2019)

In light of the above data, use of TXA is recommended in patients with the hemorrhagic or TBI indications noted, but these patients should receive the appropriate thromboprophylaxis once bleeding is controlled and should be monitored closely for venous thromboembolic disease.

Case Study - Solution

The Setting
- A small unit is moving outside of a village
- There is a single shot from somewhere in the village
- No other hostile fire

The Casualty
- Single gunshot wound to abdomen
- The casualty is alert and in moderate pain
- There is no life-threatening external hemorrhage
- There is a normal radial pulse

Casualty Status
- AVPU Alert
- Airway Patent
- Breathing RR 18 and unlabored
- Radial Pulse Strong
- O2 Saturation 97%

Question: What is the NEXT action you should take?
1. Start an IV and administer TXA immediately
2. Start an IV and administer a unit of freeze-dried plasma
3. Administer 50 mg of ketamine IM
4. Administer an 800ug fentanyl lozenge

Case Study Correct Response:

1. Start an IV and administer TXA immediately

This casualty may have life-threatening intra-abdominal hemorrhage. The next action should be to immediately start an IV and infuse 1 gm of TXA over 10 minutes.
References


Butler FK. Military history of increasing survival: The U.S. military experience with tourniquets and hemostatic dressings in the Afghanistan and Iraq conflicts. Bull Am College Surg. 2015 Sep;100 (1 Suppl): 60-64.


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