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The Use of Tranexamic Acid in Tactical Combat Casualty Care

TCCC Proposed Change 20-02

Brendon Drew, DO[1]; Jonathan Auten, DO[2]; Andre Cap, MD, PhD[3]; Travis Deaton, MD[4]; Benjamin Donham, MD[5]; Warren Dorlac, MD[6]; Joseph DuBose, MD, FACS, FCCM[7]; Andrew D. Fisher, MD, PA-C[8]; Alan J. Ginn[9]; James Hancock, MD[10]; John B. Holcomb, MD[11]; John Knight, MD[12]; Ryan Knight, MD[13]; Albert "Ken" Koerner, MD[14]; Lanny Littlejohn, MD[15]; Matthew J. Martin, MD[16]; John Morey[17]; Jonathan Morrison, MD[18]; Martin Schreiber, MD[19]; Philip C. Spinella, MD, FCCM[20]; Benjamin Walrath, MPH, MD[21]; Frank Butler, MD[22]*

ABSTRACT

The literature continues to provide strong support for the early use of tranexamic acid (TXA) in severely injured trauma patients.[1] Questions persist, however, regarding the optimal medical and tactical/logistical use, timing, and dose of this medication, both from the published TXA literature and from the TCCC user community. The use of TXA has been explored outside of trauma, new dosing strategies have been pursued, and expansion of retrospective use data has grown as well. These questions emphasize the need for a reexamination of TXA by the CoTCCC. The most significant updates to the TCCC Guidelines are (i) including significant traumatic brain injury (TBI) as an indication for TXA, (ii) changing the dosing protocol to a single 2g IV/IO administration, and (iii) recommending TXA administration via slow IV/IO push.

KEYWORDS: *TXA; tranexamic acid; hemorrhage; hemostatics; antifibrinolytics; hemorrhagic shock; traumatic brain injury; traumatic injury*

Proximate Reason for This Proposed Change

Since the publication of the CRASH-2 and MATTERs studies, the medical literature regarding the use of TXA has grown exponentially. Initially a drug developed to treat menorrhagia and subsequently adopted for use in cardiac surgery and trauma, it is now used in orthopedic surgery,[2–25] spine surgery,[26–30] plastic surgery,[31,32] ophthalmology,[33] otolaryngology,[34,35] gastroenterology,[36] maxillofacial surgery,[37–39] pediatric trauma,[40–42] and post-partum hemorrhage.[43]

Recently, evidence has been obtained from two randomized, controlled trials studying the use of TXA in trauma patients with TBI. The results from both the international CRASH-3 Trial, and a completed US trial[44] with novel dosing strategy, require consideration of TXA for this indication as well.

The TCCC change team working on this proposed change identified a number of specific questions that needed to be addressed in this review.

- *Should a TBI Indication Be Added to the TXA Recommendations in the TCCC Guidelines and the Dose Increased to 2 Grams?*
- *Is There a Need to Reinforce the Timely Administration of TXA When Indicated?*
- *Is a Second Dose of TXA Needed to Improve Outcomes When Used for Bleeding Trauma Patients?*
- *Is TXA Effective When Administered via the IM route 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 (1-minute) 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?*
- *Is There a Need for a Second Dose of TXA to be Administered as Part of TCCC, Given the Discussion of the Pharmacokinetics of TXA Mentioned Above?*
- *And – If a Second dose of TXA Is Needed, Should the Second Dose Be Given Like the First?*
- *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?*

Background

Updating the TCCC TXA Dosing Protocol.

Feedback from the field reveals that the current administration protocols are logistically burdensome in TCCC and may be

*Correspondence email and affiliations are given on page 42.

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contributing to lower than expected compliance with guidelines.[45,46] The logistical burden comes in several dimensions: the weight and volume of the additional reconstitution fluid bags, the time it takes to mix the drips and the need to initiate and continue a prolonged infusion while avoiding IV tube interference and displacement during patient movement.

The logistical challenges of the current dosing protocol in TCCC motivated the group to explore updated dosing strategies in trauma. The dosing protocol most widely used, including in the CRASH-2 and CRASH-3 Trials, dates back 25 years. Referred to as the "Horrow Protocol," this dosing strategy was compared to others for use in cardiac surgery, with patients on ECMO, and with the first dose being administered prior to the initial surgical incision.[47] More recent literature supports single dose regimens as well, even in cardiac surgery, with one study noting that a single 1g dose of TXA provided adequate prevention of hyperfibrinolysis compared to 3g + weighted dose or a single 5g dose.[48] Several articles from the orthopedic surgery literature have validated the use of single dosing regimens.[2,49–52] A meta-analysis including 57 studies, published in 2020, that included several surgical disciplines, also found single dose regimens to be effective.[53] The TCCC change team acknowledges that caution should be exercised in translating findings from these patient populations to trauma patients.

Discussion

TXA administration has been shown in multiple studies to be safe and effective when used for bleeding trauma patients. TXA was incorporated into the TCCC Guidelines in 2011.[54] It has since been used in prehospital EMS systems in the United States,[55,56] Scandinavia,[57] Canada,[58] Switzerland,[59] France,[60] England,[61] Germany[62] and Israel[63] among others. Literature continues to support the early use of TXA in trauma consistent with the findings from CRASH-2 and MATTERs.[59,60,64] TXA has been documented repeatedly in the previously referenced publications to reduce blood loss in elective surgery, and the sooner blood loss is slowed or stopped in bleeding trauma patients, the more favorable the expected outcome.[65]

TXA for Casualties with TBI.

As far back as 2012, data suggested "that TXA administration might improve outcomes in TBI patients and provide grounds for evaluating this hypothesis in future research."[66] The inclusion of patients with concomitant trauma not isolated to the head prevented a definitive conclusion from the investigators. In 2014, a lack of evidence of benefit was cited as rationale for not giving TXA in TBI.[67] A meta-analysis published the same year noted a "statistically significant reduction in ICH progression with TXA and non-statistically significant improvement of clinical outcomes in ED patients with TBI."[68] Dosing was 1g over 10 minutes followed by an additional 1g over eight hours, which is the same as the CRASH-2 trial and the current TCCC Guidelines. As recently as 2016, there was a continued call for research to investigate optimal TXA dosing in TBI.[69] Several studies have examined the use of TXA in patients with identified intracranial hemorrhage (ICH), but these studies were not designed to treat all TBIs and the TXA was given once the ICH was identified on CT (not prehospital). Dosing was the same as the current TCCC Guidelines. In two studies that found no benefit from TXA administration to TBI patients, one made no mention of the time of administration[70] and in the other only 10% of the patients who received TXA were treated within 3 hours of injury.[71]

A retrospective review of 651 patients at a civilian trauma center published in 2019 concluded that TXA use was an "independent factor associated with lower 30 day mortality in cerebral contusions or traumatic subarachnoid hemorrhage."[72] Another retrospective review, this one of military trauma patients, also concluded that TXA was independently associated with decreased mortality and improved outcomes in head trauma. In this review, 174 of 265 massive transfusion cases received TXA. The TXA patients had "significantly higher ISS, lower presenting GCS, higher incidence of severe head injury and higher transfusion requirements . . . and lower mortality (0% vs 10.1%)."[73]

A large meta-analysis published in 2018 explored TXA for TBI and concluded that TXA "lower(ed) the mortality rate and improv(ed) favorable neurologic outcomes.[74] Another retrospective review found a lower mortality rate for the neurotrauma patients that received TXA."[64]

In 2019, the results of the largest randomized control trial of TXA in isolated TBI was completed. The CRASH-3 Trial was conducted between 2012 and 2019 in 175 hospitals in 29 countries and used the Horrow Protocol for TXA dosing. 12,737 patients were included in the study and 6,406 received TXA. The criteria for TXA administration included (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 18.5% in the TXA group and 19.8% in the placebo group. After excluding severe head injury (GCS 3 or non-reactive pupils) the mortality from head injury was 12.5% in the TXA group and 14% in the placebo group. In a comment published in the same journal, the author noted that "the use of 28-day head injury-related mortality as the primary endpoint probably biased the treatment effect towards the null because tranexamic acid is most likely to benefit patients with TBI with intracranial bleeding at risk of early mortality."[75]

A recent US randomized controlled trial found a survival benefit when 2g of TXA was administered in the prehospital phase of care to casualties with moderate to severe TBI. In the subset of patients who were later noted to have intracranial hemorrhage (ICH) on initial CT scan, 2g prehospital administration of TXA resulted in a significantly improved 28-day mortality of 18% compared to 28% mortality in the 1g TXA bolus + 1g maintenance infusion group and 28% mortality in the placebo group. For 2g TXA bolus vs placebo, the difference in outcome was highly significant for those diagnosed with ICH (p = .0035). The 1g infusion followed by 1g over 8 hours was not different from placebo. For the entire cohort (identified prehospital based on criteria of GCS 3-12, one or two reactive pupils and SBP ≥ 90), there was no negative effect of giving TXA for potential ICH based on both mortality and thrombotic complications.[44]

Should a TBI Indication for TXA Be Added to the TXA Recommendations in the TCCC Guidelines and the Dose Increased to 2 Grams?

In addition to previously discussed work supporting a 2g dose for TXA in TBI, there is evidence of a 1g dose not being sufficient in severe trauma.[76] Grassin-Delyle et al noted that a 1g

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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.[77–79] It is also important to recognize that a 2g dose has not been specifically studied in patients already in hemorrhagic shock but has been studied in severely injured patients.[88] A recently completed randomized study of prehospital TXA administration in the US[81] compared three dosing strategies, and found that the higher dose regimen (2g bolus followed by 1g infusion) was associated with lower 30 day mortality versus the lower dose regimens or placebo.[82] Studied dosing outside of the trauma literature varies considerably. Most important, however, is the observation that symptomatic VTE and other adverse effects are not increased with dosing up to 30 mg/kg.[2,83–87] TBI researchers also found no difference in VTE rate between the 1g and 2g prehospital dose.[44] Although a recent review noted the safety and effectiveness of the current dosing protocol, the recommendation to continue with the current TXA dosing regimen did not take into account TBI, the logistical burden of the dosing, and the safety profile of a potential change in protocol.[88]

Does a higher initial dose of TXA cause seizures? There is a historical concern that TXA is associated with an increased seizure risk, but clinically significant seizures have historically been associated with the much higher doses (>50mg/kg) used in cardiac surgery, rather than the smaller dose of TXA used in trauma patients.[77,89–97] A recent large randomized controlled trial of TXA in TBI patients noted an increased rate of seizures at the 2g dose, but these seizures were not found to be associated with an increase in adverse outcomes.[44] In CRASH-3, the observed seizure rate was similar in TXA (3.2%) and placebo groups (3.0%).[98]

Ensuring appropriate criteria for administration of TXA in the prehospital setting for TBI was challenging. The change group considered the safety profile of TXA and feedback from prehospital and emergency medicine providers at the September 2019 CoTCCC meeting[99] in finalizing the recommended guidelines. The initial proposed wording: "If the casualty manifests signs of significant TBI (blast injury or blunt trauma with loss of consciousness or altered mental status)," was too liberal given patients in the Emergency Department would not receive a head CT based on the criteria above. Utilizing the Glasgow Coma Scale (GCS) was proposed as well, but this is cumbersome in the prehospital setting. The updated TCCC Guidelines recommend TXA "If the casualty has signs or symptoms of significant TBI or has altered mental status associated with blast injury or blunt trauma." In clarifying specific criteria to apply quickly and efficiently in the prehospital setting, trauma literature supports the use of only the motor component of the GCS.[100] An inability to follow commands, which represents a GCS motor score of 5 or less, is an efficient way to determine the threshold for TXA administration in the prehospital setting. CRASH-3 identified the greatest benefit of TXA in patients with mild to moderate head injury.[98] In CRASH-3, the GCS was assessed, but the individual components were not reported. The Emergency Medicine literature has also provided potential algorithms, but most included the use of CT scans, which are rarely available in the prehospital deployed setting.[101]

How Do We Reinforce the Need for Timely Administration of TXA when Indicated?

Some studies have questioned the benefits of TXA in trauma but based their recommendation on TXA administered well after the time of injury. One study stated that "For the highest injury acuity patients, TXA was associated with increased, rather than reduced, mortality, no matter what time it was administered."[102] In this study, however, TXA was administered at a mean time of 97 minutes after arrival at the hospital. The range of times was 0 to 886 minutes after arrival. These times are problematic in that they do not include the elapsed time from injury occurrence until 911 call, the delay to dispatch after the call is received, transit time to the scene of the injury, time on scene, or transport time from the scene to the trauma center. This study also suffered from selection bias, resulting in more severely injured patients in the TXA group, which cannot be adequately controlled for even with multivariate regression techniques. In another published study that concluded there was no difference between prehospital and ED administration of TXA, the prehospital group was noted to receive TXA 51 minutes after EMS dispatch while the ED group received TXA 29 minutes after EMS dispatch.[103] In a retrospective review of TXA use in France, TXA administration did not demonstrate in-hospital mortality improvement.[60] These studies highlight the challenges in translating data from mature civilian trauma systems to TCCC.

Other studies have reinforced the findings of the CRASH-2 timing subgroup analysis that the timing of TXA administration is critical when the possibility of life-threatening bleeding is considered likely.[104] 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; $p < .0001$). 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."[105] Post-hoc analysis of CRASH-2 data has shown improvement in functional outcomes as well.[106] 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."[107] The recently reported pre-hospital STAAMP Trial also found that administration of TXA within 1 hour was associated with reduced 30-day mortality compared to alternative administration or placebo.[82]

In three studies evaluating endotheliopathy in trauma injury, the effect of TXA was found to be time-dependent and the authors supported early administration.[108–110] A large meta-analysis evaluating TXA use in TBI also supported early administration.[74] TXA has also been shown to have anti-inflammatory effects in humans[111–114] and in rodent models.[115–119] These papers suggest that the additional mechanisms of TXA may also be time-sensitive. Updated civilian trauma guidelines continue to emphasize administration as early as possible following trauma.[120]

Is a Second Prehospital Dose of TXA Really Needed to Improve Outcomes When Used for Bleeding Trauma Patients?

Recent literature has questioned the need to initiate an 8 hr infusion of a second gram of TXA as part of the prehospital care rendered.[121] Based on the pharmacokinetics of TXA, there is time after the first dose of TXA to have the casualty arrive at

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the hospital and be evaluated for possible ongoing hemorrhage before deciding whether or not to administer another dose of TXA. A paper describing the prehospital use of TXA in three EMS systems in Cincinnati, Oklahoma City, and Tulsa notes that paramedics are encouraged to initiate TXA administration when indicated, regardless of how close they are to a trauma center.[56] This paper goes on to note that none of these 3 systems call for a second dose of TXA in the prehospital setting, based both on the relatively short transport times, but also on TXA's pharmacokinetics. TXA has a half-life of about two hours, maintaining antifibrinolytic action in some tissues for up to 17 hours and in the blood for approximately 7–8 hours.[56]

Is TXA Effective When Administered IM to Bleeding Trauma Patients?

Although the CRASH-2 and MATTERS studies, as well as most of the reports on pre-operative TXA in elective surgery, call for TXA to be administered IV, authors have noted that it would be faster to administer TXA by autoinjector.[122,123] Is there evidence to support this route of administration for TXA, in particular for casualties who may in hemorrhagic shock? An in-depth review of this topic in 2018 was unable to specifically recommend for or against IM administration of TXA.[79] There is very scarce literature evaluating the IM administration of TXA, and none of the studies included patients in shock. Bioavailability and pharmacokinetics studies date back to the 1970s and 1980s.[124,125] In one study, 3 healthy volunteers were given TXA and bioavailability of IM and IV TXA was 100%. Peak serum concentrations of IM TXA were not noted until 40–60 minutes, whereas the peak levels of IV TXA were reached in 5 minutes.[126] A 2019 meta-analysis of available data regarding IM administration of TXA in healthy patients also found a total of 6 participants in 2 studies, which demonstrates a continued lack of available human data.[127] Two recent studies of TXA pharmacokinetics in a porcine shock model have demonstrated similar bioavailability of IM and IV TXA, but with inconsistent results of peak serum concentrations. One recent study noted peak concentration of IV TXA at 5 minutes and IM TXA (given in two IM doses at separate sites) at 10 minutes[128] with another demonstrating peak concentration of IV/IO TXA at 5 minutes and IM TXA at 60 minutes.[129] The current TXA packaging is only available in 100mg/1mL, which would require IM dosing at 10mL for each 1g of TXA to be administered. Given the time sensitive nature of TXA administration and the lack of consistent data evaluating TXA absorption in shock states, there is not enough evidence to recommend IM TXA administration in TCCC at the present time.

Is TXA Effective When Administered Via the IO Route to Bleeding Trauma Patients?

The current TCCC Guidelines do not include IO administration of TXA, but there are no known contraindications to administering intravenous medications intraosseously. IO administration of TXA has been reviewed without identified complications to 82 patients in the pre-hospital setting.[130] The IO route of administration was also included in the Cal-PAT study, but was not discussed in depth.[55] The 75th Ranger Regiment currently administers TXA via the IO route and has no documented complications from this protocol.[131,132]

In swine models, IO and IV TXA have been shown to have equivalent pharmacokinetics as well as anti-fibrinolytic activity.[129,133,134]

Questions from the TXA User Community

Can TXA Be Safely Given as a Slow (1-minute) IV Push Rather Than over 10 minutes?

Combat medics and their supervising physicians have repeatedly posed the question about giving the first dose of TXA by slow IV push rather than as a 10-minute infusion, as was done in the CRASH-2 study.[135] TXA was administered as an IV bolus in the MATTERs patient population without documented adverse effects.[136] The need for a 10-minute infusion of TXA was mentioned as a possible factor in the reported poor compliance with TCCC recommendations regarding TXA. One of the co-authors reported personal experience with safe slow IV push and advocated for this update to the TCCC Guidelines.[45] One paper that directly addressed clinically significant hypotension is from 1969.[137] Two small porcine studies have administered TXA over 5 minutes[134] and by push[129] without adverse outcomes or observed hypotension. Neither the authors of the MATTERs study (also authors of this change) nor the 75th Ranger Regiment have observed or reported any episodes of clinically significant hypotension with this dosing strategy.[132] We recommend that TXA administration should be an IV/IO slow push. This bolus should be given over approximately 1 minute.

Can TXA Be Given in the Same IV/IO Line as Blood or Blood Products?

There are no specific studies addressing this concern and there is no known contraindication to administration of TXA with blood or blood products. There are also no reports of complications from TXA being administered with blood products. There should be no compatibility problems expected, since TXA typically mixes with blood immediately after being given IV. The authors' recommendations are to administer TXA as soon as possible after injury. If blood or blood products are being given, the authors recommend giving TXA in the port closest to the skin. The Ranger Regiment's administration protocol uses TXA as the flush after initial IV/IO access is obtained.

Is There a Need for a Second Dose of TXA to be Administered as Part of TCCC, Given the Discussion of the Pharmacokinetics of TXA Mentioned Above?

And – If a Second dose of TXA Is, In Fact, Needed, Should the Second Dose Be Given Like the First?

The CRASH-2 trial administered the second dose of TXA as 1g given over 8 hours. This dosing protocol was adopted from the cardiac surgery community[47] and more current research supports simplified administration protocols as discussed in other areas of this paper.

Should the Second Dose of TXA Be Administered If More Than 3 Hours Have Elapsed Since the Time of Wounding

The CRASH-2 timing subgroup analysis found that mortality was actually increased when TXA was given more than 3 hours after the time of injury. Does the 3-hour caveat apply only to the first dose? There is no evidence to date suggesting that late administration (>3 hours after injury) of TXA is beneficial.

What Is "Initial Fluid Resuscitation?" as Mentioned in the TCCC Guidelines with Respect to TXA? And when does it end?

The TCCC Guidelines (dated 1 August 2019) call for the second 1g dose of TXA to be administered "after initial fluid

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resuscitation has been completed." This requires a clarification how "initial fluid resuscitation" is defined. TXA should be administered as early as possible after the injury, taking the tactical situation and prioritization of interventions (MARCH) into account. The phrase "after initial fluid resuscitation has been completed" has been removed from the updated TCCC Guidelines. The updated administration recommendations and dosing protocol eliminate the need for this decision point.

Should the Dose of TXA as Administered in TCCC Be Modified in the Presence of Ongoing Hemorrhage?

In the presence of ongoing hemorrhage and massive transfusion, the impact of both decreased renal clearance of TXA and loss of a portion of the TXA dose through blood loss must be considered. A recent paper noted that: "Scenarios involving large patients requiring massive transfusion may benefit from a replacement strategy."[138] Replacement dosing schemes should be identified using simulations and tested in large animal model." However, this paper also demonstrated that TXA levels were relatively preserved during hemorrhage, with only a 25% decrease after one total body blood volume loss and replacement. In the WOMAN Trial, a second dose of TXA (or placebo) was only given if bleeding continued after 30 minutes[43] or restarted within 24 hours. The World Health Organization updated dosing recommendations for TXA based on this trial in 2017 and currently recommends a second dose of TXA for ongoing bleeding after 30 minutes or if bleeding restarts within 24 hours of completing the first dose.[139] Less than 30% of the patients who received one dose received a second dose and whether or not the second dose provided clinically significant benefit was not explored or discussed.[43]

Based on limited available evidence and the personal experience of the authors, an evidence-based recommendation for redosing of TXA in the prehospital setting cannot be made at this time. Measuring fibrinolytic status to guide TXA dosing continues to be debated in the literature reported out of trauma centers, but the technology required to measure fibrinolytic status is not available in the prehospital setting. The change group recommends exploration of this topic in future studies, along with more investigation of the most effective serum concentration required for trauma. In a Prolonged Casualty Care scenario, redosing may be considered in conjunction with personal expertise or through access to remote teleconsultation.

Can TXA Be Administered through the Same Line as Hextend?

Although the preferred resuscitation fluid in TCCC is whole blood, Hextend is still, at the time of this writing, a TCCC-recommended resuscitation fluid if no blood products are available and medics 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." Hextend is not mentioned. Recent studies however, found that "There was no evidence of incompatibility between the solutions of Hextend and TXA by either visual inspection or by digital turbidimeter."[140,141]

What Is the Current State of Evidence that TXA Causes an Increase in the Risk of Deep Venous Thrombosis and Pulmonary Embolism?

The studies of TXA use in elective surgery—when TXA is routinely given pre-operatively 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.[23,85,86,142–148] Orthopedic trauma surgery studies have also not found an increase in VTE.[5,149–151] A review of cardiac surgery also found no increase in VTE.[89] Some newer studies of use in trauma have not shown an increase rate of VTE[1,64,105,152,153] while some have noted an increase.[103,154] When given to over 10,000 patients with post-partum hemorrhage, no increase in VTE was noted.[43] A large meta-analysis including 22 studies and over 49,000 patients who received TXA for non-surgical bleeding noted no increase in venous or arterial thrombotic events.[155] The discussion is further complicated by historical data showing that trauma patients have higher rates of VTE than non-trauma patients[156–158] and a recent review of the Joint Trauma Registry concluding that TXA may increase non-fatal VTE but "potential mortality benefit likely outweighs the potential risks of fatal PE."[159] In a large meta-analysis evaluating TXA use in TBI published in 2018, the authors noted no effect on VTE rates.[74] In the TAMPITI trial, active screening for VTE was completed on all patients with an increase noted in the TXA group in a dose dependent manner.[80] Given the time-sensitive nature of TXA administration and the challenges of delivering care in austere environments, it is reasonable to anticipate that patients may receive TXA who ultimately are determined not to need it. In one retrospective review of military TXA use, overuse was estimated at 6.4% and was associated with an increased risk of VTE.[160] Two recent reviews also noted variation in the incidence of VTE after TXA administration[161,162] with one concluding that "the application of TXA to trauma patients may pose a certain risk for possible thromboembolic complications."[162] In CRASH-3 (isolated TBI), no difference in VTE rate between TXA and placebo groups was noted.[98] A large meta-analysis of the over 28,000 patients from the CRASH-2 and WOMAN trials published in 2020 found "the risk of vascular occlusive events was similar according to baseline risk categories."[107]

It is the opinion of the authors of this change that administering a 2g initial dose of TXA in trauma will require careful attention to appropriate thromboprophylaxis and close observation for venous thromboembolic disease.

Conclusions

The conclusions of this working group include the following answers to the posed questions:

- *Should a TBI Indication Be Added to the TXA Recommendations in the TCCC Guidelines and the Dose Increased to 2 Grams?*
  Yes
- *Is There a Need to Reinforce the Need for Timely Administration of TXA When Indicated?*
  Yes
- *Is There a Need for a Second Dose of TXA to be Administered as Part of TCCC, Given the Discussion of the Pharmacokinetics of TXA Mentioned Above?*
  No, there is not enough evidence to support a second dose in TCCC.
- *Should the Second Dose of TXA Be Administered If More Than 3 Hours Have Elapsed Since the Time of Wounding.*
  No, there is not enough data at the present time to recommend redosing in the prehospital setting.

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– *Is TXA Effective When Administered IM to Bleeding Trauma Patients?*
  No, it is not supported in TCCC by the current evidence.
– *Is TXA Effective When Administered Via the IO Route to Bleeding Trauma Patients?*
  Yes
– *Can TXA Be Safely Given as a Slow (1-minute) IV Push Rather Than over 10 minutes?*
  Yes
– *Can TXA Be Given in the Same IV/IO Line as Blood/Blood Products?*
  Yes
– *What Is "Initial Fluid Resuscitation?" as Mentioned in the TCCC Guidelines with Respect to TXA? And when does it end?*
  TXA should be administered as early as possible after the injury, taking the tactical situation and prioritization of interventions (MARCH) into account. The phrase "after initial fluid resuscitation has been completed" has been removed from the updated TCCC Guidelines. The updated administration recommendations and dosing protocol eliminate the need for this decision point.
– *Should the Dose of TXA be Modified in the Presence of Ongoing Hemorrhage?*
  Based on the limited available evidence at present and the personal experience of the authors, an evidence-based recommendation for redosing of TXA in the prehospital phase of care (TCCC) cannot be made at this time. In-hospital administration of TXA should be guided by the casualty's fibrinolytic status as measured clinically.
– *Can TXA Be Administered through the Same Line as Hextend?*
  Yes. Although the preferred resuscitation fluid in TCCC is whole blood, Hextend is still—at the time of this writing—a TCCC-recommended resuscitation fluid if no blood products are available. A recent study of this issue found no evidence that Hextend and TXA are incompatible.
– *If removed from glass vials in preparation for administration, how long can TXA be kept in a syringe?*
  Although TXA is very stable throughout a range of temperatures for several days,[163,164] 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 draw and store 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.

Given the volume of active TXA research, the authors recommend that the CoTCCC consider another review of updated TXA literature within 2 years of this change.

Current Wording

Care Under Fire
None.

Tactical Field Care
c. Tranexamic Acid (TXA)
- If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding):
  – Administer 1g of tranexamic acid in 100mL normal saline or lactated Ringer's as soon as possible but NOT later than 3 hours after injury. When given, TXA should be administered over 10 minutes by IV infusion.
  – Begin the second infusion of 1g TXA after initial fluid resuscitation has been completed.

TACEVAC
c. Tranexamic Acid (TXA)
- If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding):
  – Administer 1g of tranexamic acid in 100mL normal saline or lactated Ringer's as soon as possible but NOT later than 3 hours after injury. When given, TXA should be administered over 10 minutes by IV infusion.
  – Begin the second infusion of 1g TXA after initial fluid resuscitation has been completed.

PROPOSED CHANGE

Care Under Fire
None.

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 metal status associated with blast injury or blunt trauma:
  – Administer 2g of tranexamic acid via slow IV or IO push as soon as possible but NOT later than 3 hours after injury.

TACEVAC
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 metal status associated with blast injury or blunt trauma:

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– Administer 2g of tranexamic acid via slow IV or IO push as soon as possible but NOT later than 3 hours after injury (if not previously administered).

Level of evidence:
The levels of evidence used by the American College of Cardiology and the American Heart Association were outlined by Tricoci P, et al.[165]:

Level A: Evidence from multiple randomized trials or meta-analyses.
Level B: Evidence from a single randomized trial or non-randomized studies.
Level C: Expert opinion, case studies, or standards of care.

2g dose of TXA in TBI = B
2g dose of TXA in hemorrhagic shock = C
Single dose of TXA in TBI = B
Single dose of TXA in hemorrhagic shock = C
Administration of TXA through IO access = C
Administration of TXA through slow IV push = C
Redose of TXA = C
Administration of TXA with blood/blood products = C

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Disclaimers
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Defense Health Agency or the Department of Defense. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Disclosures
The authors have nothing to disclose.

Release
This document was reviewed by the Chief of the Joint Trauma System and by the Public Affairs Office and the Operational Security Office at the DoD's Defense Heath Agency. It is approved for unlimited public release.

References can be found online at https://jsom.us/2Z2io0G

*Corresondence to brendon.g.drew.mil@mail.mil

[1]**CAPT Drew, DO, USN,** is the chair of the Joint Trauma System Committee on Tactical Combat Casualty Care. He currently serves as the 1st Marine Expeditionary Force Surgeon and the Navy Emergency Medicine Specialty Leader. He has eight deployments across Asia, Afghanistan, Iraq, and Africa and 11 ships in support of both USMC and SOCOM units. [2]**CDR Auten, DO, USN,** is the program director of the Emergency Medicine Residency at Naval Medical Center San Diego and director, Combat Trauma Research Group West. He has served as a Carrier Airwing Flight Surgeon, US Marine Corps Shock Trauma Platoon leader, and Detachment OIC for SOUTHCOM humanitarian efforts. He has a wide area of research involvement in prehospital and austere medicine with specific interests in pediatric trauma, hemostatic resuscitation, and intraosseous blood transfusion. [3]**COL Cap, MC, USA,** is division chief, Acute Combat Casualty Care Research, US Army Institute of Surgical Research. He first trained and worked as an EMT, and then as an internist, hematologist, oncologist, and specialist in stem cell transplantation, coagulation disorders, and transfusion medicine. He is the hematology and oncology consultant to the Army Surgeon General and has consulted extensively for the Joint Trauma System and Special Operations Command. He serves as co-chair of the NATO Blood Panel. [4]**CDR Deaton, MD, USN,** is the 1st Marine Division surgeon and most recent chair of Emergency Medicine at Naval Medical Center San Diego. As a prior flight surgeon and dive medical officer, he has 13 deployments in support of USMC and SOCOM units. [5]**MAJ Donham, MD, USA,** is the director of operational medicine at the Carl R. Darnall Army Medical Center's Emergency Medicine Residency Program and has multiple deployments with austere surgical teams in support of overseas contingency operations. [6]**Col (Ret) Dorlac, USAF,** is a trauma and critical care surgeon and medical director with the University of Colorado Health system. In his 26 years of service with the Air Force, he served in numerous positions to include the trauma consultant to the USAF surgeon general, director of the CSTARS military-civilian program at the University of Cincinnati, trauma medical director at Landstuhl, Germany, from 2004 to 2007, and as the Joint Theater Trauma System deployed director for CENTCOM in 2009. He is currently a subject matter expert for the Department of Defense's Committee on TCCC. [7]**Colonel DuBose, USAF,** serves as director, Center for the Sustainment of Trauma and Readiness Skills (CSTARS) at R Adams Cowley Shock Trauma Center/University of Maryland in Baltimore, MD. He is a professor of surgery at USUHS and the University of Maryland and is board certified in general surgery, vascular surgery and surgical critical care. He has over 230 published peer-reviewed publications as an active duty military surgeon with the US Air Force and has deployed seven times as a trauma surgeon to combat theaters in both conventional and JSOC roles. [8]**MAJ Fisher, PA-C, ARNG,** is a physician assistant in the Texas Army National Guard, a recent graduate from the Texas A&M University College of Medicine, and a general surgery resident at the University of New Mexico School of Medicine. He previously served on active duty as a physician assistant within USASOC. [9]**SSG Ginn, USA,** is a Special Operations combat medic and NREMT Paramedic. He has extensive experience as a point of injury care provider over multiple interagency and joint task force deployments. He is currently serving as a company senior medic with the 1st Battalion, 75th Ranger Regiment.

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[10]**RDML Hancock, USN,** is an emergency physician with multiple combat deployments. He has served as a flight surgeon, as OIC of a fleet surgical team and as OIC of a shock trauma platoon. He is currently serving as the medical officer of the Marine Corps/director, Health Services, Headquarters Marine Corps with additional duty as the chief of the Medical Corps for the Navy. [11]**COL Holcomb, USA (Ret),** is a trauma surgeon who deployed with the Joint Special Operations Command for a decade, is a former commander of the US Army Institute of Surgical Research, and was the Army Surgeon General's trauma consultant for 6 years while serving on active duty for 23 years. He is now a professor of surgery at the University of Alabama at Birmingham. He has been a member of the Department of Defense's CoTCCC since 2001. [12]**Maj Knight, USA,** is a former Special Forces Green Beret medic having served in various Special Operations units. After 17 years he transitioned to physician and is now an emergency medicine physician who has completed a point-of-care ultrasound fellowship, served as faculty in the DoD's only Level I trauma center, deployed with Joint Special Operations Command, and is now completing a second fellowship in EMS and disaster medicine. [13]**LTC Knight, USA,** was an Infantry platoon leader, leading platoons in Afghanistan and Iraq, prior to becoming a physician. As an emergency physician, he served 7 years at Ft. Bragg, NC deploying numerous times to Afghanistan and austere locations in Africa with a Joint Task Force. He has extensive experience training medics, APPs, and physicians in austere/operational medicine. Ryan is currently serving as the regimental surgeon for the 75th Ranger Regiment and is the primary author of the 2019 and 2020 *Ranger Medic Handbooks*. [14]**Major Koerner** is a trauma anesthesiologist with the US Air Force. He has been practicing anesthesiology for more than 20 years and currently holds an appointment as an assistant clinical professor at the University of Maryland R Adams Cowley Shock Trauma Center. He is attached to the 711 HPW C-STARS unit in Baltimore and teaches the ground surgical team-austere course, TCCC, trauma anesthesia, and the CMRP course as a subject matter expert in trauma care. Additionally, he is a NOAA/UHMS dive medicine physician and supports the Hyperbaric and Dive Medicine Center at Shock Trauma. [15]**CAPT Littlejohn, USN,** is a prior US Marine who now serves as an emergency physician for the US Navy. He has served as a flight surgeon, diving medical officer, shock trauma platoon leader, and command surgeon for multiple US Marine Corps and US Special Operations Command units. He is currently the force surgeon for Naval Special Warfare Command. [16]**Colonel Martin, US Army (Ret)** is a trauma and acute care surgeon at Scripps Mercy Hospital and the Navy Medical Center San Diego. He recently retired from active military service as the trauma director and director of surgical research at Madigan Army Medical Center, where he established and directed a highly productive basic science and translational trauma research lab. He served in a variety of clinical and leadership positions during five deployments in support of combat operations in Iraq and Afghanistan. [17]**HMCS Morey, USN,** is a Special Operations independent duty corpsman (SOIDC) and advanced tactical paramedic, currently serving as the medical leading chief petty officer for Tactical Development Squadron 2, Naval Special Warfare Development Group. [18]**Dr Morrison** is a vascular and trauma surgeon at the R Adams Cowley Shock Trauma Center, with a particular interest in hemorrhage control research. He has served in the British Army since in 2003 with multiple deployments to Iraq and Afghanistan. [19]**Dr Schreiber** is chief of trauma, critical care, and acute care surgery at Oregon Health & Science University. He is on the American College of Surgeons Board of Governors and he is the chair of the Grassroots Advocacy Engagement Workgroup. He has been deployed to Iraq and Afghanistan and has served as the Joint Theater Trauma System Director. Dr Schreiber also directs the Trauma Research Laboratory at OHSU. [20]**Dr Spinella** is a professor of pediatrics at Washington University in St Louis and director of the Critical Care Translational Research Program. He separated from the US Army after 12 years of active duty. He is part of a team of investigators that was awarded the US Army's Best Invention in 2008 for the development of the concept of hemostatic resuscitation. He is an accomplished clinical trialist in the area of hemorrhagic shock resuscitation. He is a co-founder of the THOR Network, and consults for the US Army and Norwegian Navy Blood Research Programs. [21]**CAPT Walrath, USN, is** the chair of emergency medicine at Naval Medical Center San Diego and the director for Navy Medicine West Emergency Medical Services. He is the chair of the Committee on En Route Combat Casualty Care Clinical Practice Guideline Sub-Committee and the co-chair of the En Route Care Sub-Community to the BUMED Trauma Advisory Board. He recently completed a deployment to AFRICOM as the team leader for a damage control surgical team. [22]**CAPT (Ret) Butler, USN,** was a Navy SEAL platoon commander before becoming a physician. He is an ophthalmologist and a Navy underseas medical officer with more than 20 years of experience providing medical support to Special Operations Forces. Dr Butler has served as the command surgeon at the US Special Operations Command and was the chairman of the Department of Defense's Committee on TCCC for 11 years. He currently serves as a consultant to both the JTS and the CoTCCC.

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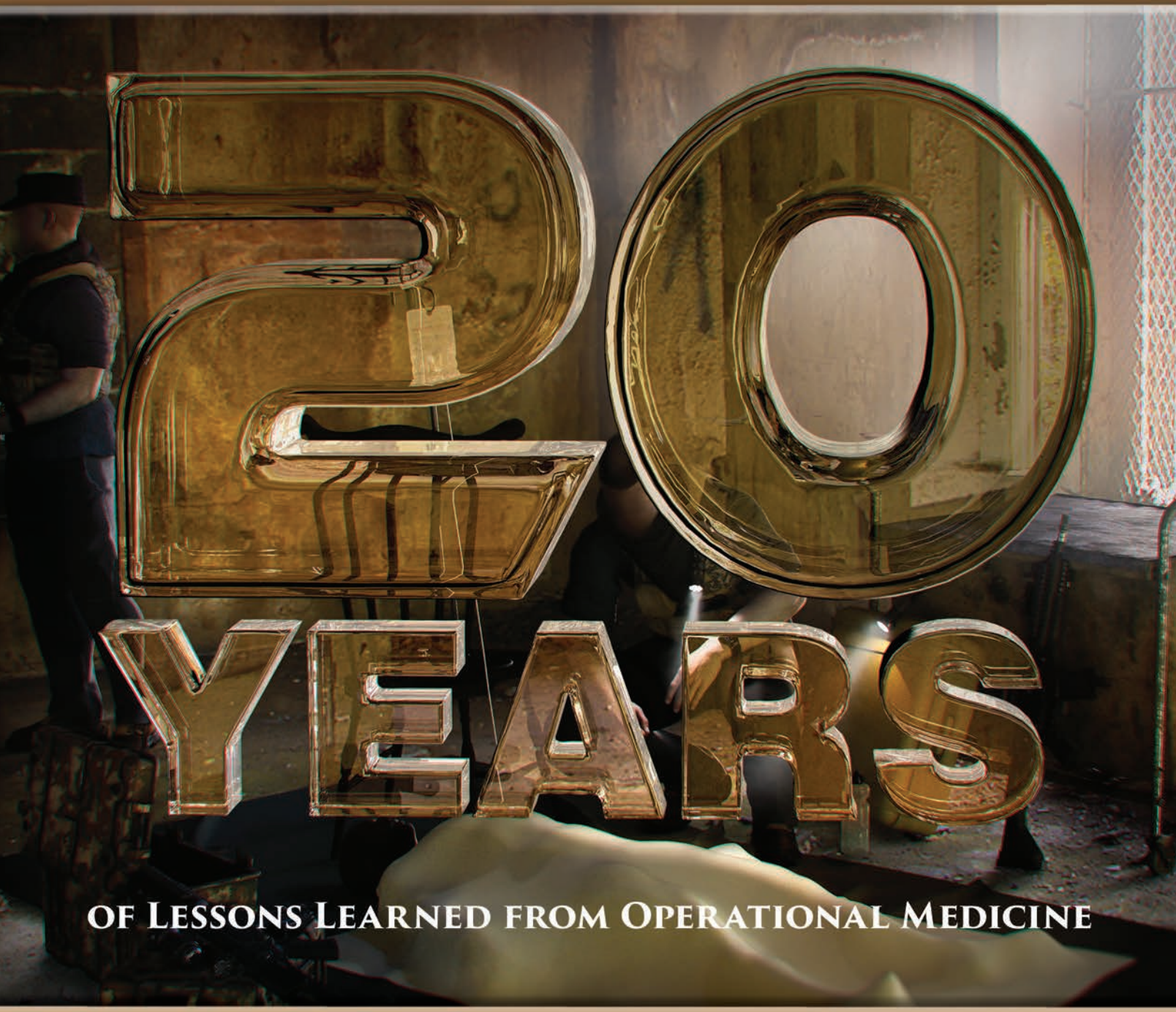

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