ABSTRACT

Early tranexamic acid (TXA) administration for resuscitation of critically injured warfighters provides a mortality benefit. The 2019 Tactical Combat Casualty Care (TCCC) recommendations of a 1g drip over 10 minutes, followed by 1g drip over 8 hours, is intended to limit potential TXA side effects, including hypotension, seizures, and anaphylaxis. However, this slow and cumbersome TXA infusion protocol is difficult to execute in the tactical care environment. Additionally, the side effect cautions derive from studies of elderly or cardiothoracic surgery patients, not young healthy warfighters. Therefore, the 75th Ranger Regiment developed and implemented a 2g intravenous or intraosseous (IV/IO) TXA flush protocol. We report on the first six cases of this protocol in the history of the Regiment. After-action reports (AARs) revealed no incidences of post-TXA hypotension, seizures, or anaphylaxis. Combined, the results of this case series are encouraging and provide a foundation for larger studies to fully determine the safety of the novel 2g IV/IO TXA flush protocol toward preserving the lives of traumatically injured warfighters.

KEYWORDS: tranexamic acid; TXA; TXA flush; TXA intraosseous; TXA protocol; Tactical Combat Casualty Care (TCCC)

Introduction

Hemorrhage continues to be the leading cause of death from potentially survivable battlefield injuries.\(^1\) Accordingly, the Department of Defense (DoD) is focused on improving the care of warfighters with active exsanguination.\(^2,3\) To assist in preserving life on the battlefield, TXA is often used because of its proven mortality benefit.\(^4\)

TXA is an antifibrinolytic agent that slows hemorrhage by inhibiting clot lysis. First characterized in 1962, this synthetic lysine derivative inhibits fibrinolysis by blocking the lysine site on plasminogen.\(^5\) TXA use has become an accepted treatment for heavy bleeding in medical domains, ranging from dentistry and postpartum obstetrics to surgery and trauma.\(^4,6-9\)

Empirical evidence supports the efficacy of TXA. For example, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) randomized placebo-controlled trial of 20,211 traumatically injured individuals at 274 hospitals in 40 countries found that TXA reduced all-cause deaths and risk of death due to bleeding when TXA was given within 3 hours of injury. Further, the CRASH-2 trial found no significant differences between intervention and placebo groups in vascular occlusive events and concluded that TXA should be considered in treating bleeding trauma patients.\(^4\) Most recently, the CRASH-3 trial demonstrated mortality benefit in patients with mild-to-moderate traumatic brain injury, with the greatest benefit observed with early TXA administration.\(^6\)

The retrospective Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study, which specifically evaluated warfighters with traumatic battlefield injuries, further demonstrated a mortality benefit with TXA administration. Importantly, this benefit was most evident in patients requiring massive transfusion.\(^10\)

Per Tactical Field Care and Tactical Evacuation Care phases of Tactical Combat Casualty Care (TCCC) guidelines, TXA is recommended for all casualties who require (or are expected to require) significant blood transfusion, have signs of hemorrhagic shock, sustain penetrating torso trauma, sustain one or more amputations, and/or have persistent and severe bleeding.\(^2\) Consistent with civilian hospital protocols, the 2019 TCCC protocols recommend a dose of 1g TXA dripped over 10 minutes, followed by an additional 1g dose dripped over an unspecified amount of time, but presumably over 8 hours (in accordance with previous studied protocols).\(^2,4,6,10\) The reason for this slow infusion rate is to avoid rapid rises in...
intravascular drug concentration of TXA and thereby theoretically reduce the rates of side effects, including hypotension, seizures, or anaphylaxis. However, this slow and cumbersome TXA infusion protocol is not compatible with the operational battlefield environment, which is dynamic, resource limited, and often in low-light conditions. It is therefore not surprising that difficulty in administering TXA as a drip over 10 minutes has been identified as a possible obstacle to compliance, and the Committee on TCCC has been considering modifications to their TXA administration protocol since early 2019.

The 75th Ranger Regiment has anecdotally identified three challenges specific to TXA administration in the battlefield environment. First, an IV drip setup is often difficult or even infeasible in this environment. Second, dosing is often inaccurate due to difficulties in calculating and maintaining the appropriate drip rate. Third, accidental dislodgement of IV access during casualty movement is common.

To overcome these challenges, the 75th Ranger Regiment has been systematically adjusting their TXA protocols. First, in 2014, the 10-minute drip was replaced with a recommendation that the first 1g dose of TXA be administered as a slow IV/IO push over 2 minutes. IO TXA administration is approved by TCCC and has been recommended for human use after demonstrating equal efficacy as IV TXA in porcine models. In 2017, the slow IV/IO push recommendation was replaced with a rapid 1g IV/IO flush, commonly administered from predrawn 10mL syringes filled with 1g TXA and labeled appropriately. In 2019, Ranger medics were given the option to flush with 1g or 2g of TXA. Toward ensuring that patients receive the full 2g dose, recommendations were modified in late 2019 to mandate the single 2g TXA flush.

Figure 1 displays the initial phase of the Tactical Damage Control Resuscitation Protocol currently used by the 75th Ranger Regiment. This step-by-step protocol includes TXA indications and instructions. For blunt or penetrating trauma, the casualty is assessed for signs and symptoms of hypovolemic shock, followed by the 2g TXA flush, followed by rapid blood product infusion.

However, the clinical effects of the 2g TXA flush has not been previously reported in published literature. Therefore, the purpose of this case series is to report the results of six casualties who received 2g TXA flush to treat traumatic battlefield injuries. The primary outcomes of interest were hypotension, seizures, and anaphylaxis immediately following TXA administration.

### Methods

#### Setting and Sample

This case series reviews six casualties receiving a 2g TXA flush dose for treatment of exsanguinating or potentially exsanguinating traumatic injuries suffered on the Afghanistan battlefield in 2019.

#### Process Improvement Procedures

This retrospective case series was conducted as part of a process improvement (PI) project within the 75th Ranger Regiment in December 2019. This PI project evaluated practices of TXA administration in combat settings by the 75th Ranger Regiment from July 2013 to December 2019. Chart review was independently conducted by two trained chart abstractors. Data were collected in a deidentified manner and stored on a secure server. This PI project received approval from the 75th Ranger Regimental command prior to data collection, and all publicly disseminated information was approved by the regimental public affairs officer.

### Chart Abstraction Procedures

A total of 245 charts were screened, 69 of which described casualties who had received TXA. Of these 69 charts, three charts were eliminated for having insufficient TXA documentation, one revealed that no actual TXA was administered due to failure of an IO device, and one described an injury related to a training exercise. Of the 64 remaining charts, 58 were excluded for either receiving only a single 1g flush of TXA (n = 51) or for receiving an initial 1g flush then a second 1g flush prior to evacuation (n = 7), leaving six that met the inclusion criteria for the present case series analysis (N = 6). Of the six qualifying cases, three were US Servicemembers and three were Afghan Servicemembers. All qualifying cases were from 2019.

#### TXA Administration Procedure

For each qualifying case, the flush dose was administered using a novel method in which 2g of TXA was predrawn into two labeled 10mL syringes (1g TXA each) within 7 days prior to mission start. After IV (n = 4) or IO (n = 2) access was established, Ranger medics confirmed placement by first observing aspirate on syringe plunger withdrawal, then slowly administering the first 1–2cc of TXA to assess for extravasation. Once access was confirmed by both visual and tactile inspection, the remainder of the 2g flush dose was rapidly administered.

#### Vitals Assessment Protocol

Vital signs were obtained pre- and post-TXA administration, including heart rate (HR), systolic blood pressure (SBP), respiratory rate (RR), and oxygen saturation (SpO2). Vital signs were measured by the standards of care established by the Ranger Medic Handbook rather than by standardized pre-determined pre- and post-TXA administration intervals. HR was determined via pulse palpation timed with a wristwatch or from portable fingertip pulse oximeter. RR was obtained by visual inspection timed with a wristwatch. SBP estimation was performed in accordance with Ranger medic protocols, with a palpable radial pulse indicating at least 80mmHg (recorded as 80mmHg), and if radial pulse was absent, palpable carotid pulse indicating at least 60mmHg (recorded as 60mmHg). While known to be a non-ideal method, TCCC guidelines and the Ranger Medic Handbook include the palpable radial pulse assessment because the more precise sphygmomanometry method is often not feasible during battlefield care. Diastolic blood pressures were not obtained. SpO2 was obtained from a portable fingertip pulse oximeter.

#### Adverse Outcomes

For the purpose of this PI investigation, the following parameters were used to define adverse outcomes. “Hypotension” was defined as a drop in SBP of 20mmHg or greater using the estimations previously described. “Seizure” was defined as any presence of convulsions that presented after drug administration. “Anaphylaxis” was defined as any development of urticaria, skin flushing, wheezing, or angioedema.
Analysis
Cases are reported individually, with a focus on the initial injury source, initial assessment, casualty care steps, TXA administration specifics, and post-TXA administration casualty assessment. Time from initial assessment to TXA administration are provided, along with time from TXA administration to evacuation. Times are expressed as raw values per case, along with summary means, ranges, and standard deviations (SDs) across cases. The primary outcomes of interest were hypotension, seizures, or anaphylaxis between TXA administration and evacuation.

Results
All six warfighters received care at night, in low-light conditions. Pre-TXA and post-TXA vital sign measures for each case are provided (Table 1). There was no evidence of large changes in vital signs from pre-TXA to post-TXA, except for the RR increase in Case 1, which roughly matched the other cases post-TXA.

Case 1
A US Servicemember sustained injuries from a blast and subsequent building collapse. The Servicemember was entrapped in rubble for approximately 20 minutes before receiving initial care. On initial assessment by the 75th Ranger Regiment medic, the casualty was found to be alert, with initial vital signs of HR 90, SBP 60, RR 14, and no documented SpO₂. Physical examination revealed a possible high thoracic spinal injury, an unstable pelvic fracture, and a right lower extremity crush injury. Spinal precautions and pelvic binder application were initiated prior to extrication and evacuation. While this case had multiple access failures, two IOs were successfully placed and the 2g TXA flush was administered within approximately 45 minutes of casualty assessment. TXA was followed by multiple crystalloid fluid boluses, 1 unit of cold-stored whole blood, and multiple rounds of analgesia medication. There was no documented exacerbation of hypotension, seizures, or anaphylaxis between TXA administration and evacuation.

Case 2
A member of the Afghanistan Armed Forces sustained a blast injury from a presumed improvised explosive device. On initial assessment by the 75th Ranger Regiment medic, he was found to be alert, with initial vital signs of HR 102, SBP 80, RR 20, and SpO₂ of 79%. Physical examination revealed penetrating shrapnel wounds to the right mid back and right trapezius muscle. A decompressive needle thoracostomy was performed at the right midaxillary line. Blood was noticed exiting the needle hub, after which medics elected to perform a right lateral finger thoracostomy. An initial dose of 150mg ketamine was provided for pain control. A nasopharyngeal airway was subsequently placed due to gradually decreasing mentation, followed by establishment of sternal IO access. The 2g IO TXA flush was administered within 5 minutes of casualty assessment, 5 minutes prior to evacuation. There was no documented exacerbation of hypotension, seizures, or anaphylaxis between TXA administration and evacuation.

Case 3
A US Servicemember sustained a blast injury from a grenade while engaged in combat. On initial assessment by the 75th Ranger Regiment medic, he was found to be alert, with initial vital signs of HR 100, SBP 80, RR 22, and SpO₂ of 98%. Physical examination revealed a primary and secondary blast injury pattern to his lower extremities. Bilateral lower extremity tourniquets were immediately applied, and IV access was established. The 2g IV TXA flush was administered within 2 minutes of casualty assessment. The casualty received multiple rounds of analgesic medication as well as anxiolytics during a care period of 108 minutes prior to evacuation. There was no documented exacerbation of hypotension, seizures, or anaphylaxis between TXA administration and evacuation.
Table 1: Pre-TXA and Post-TXA Vital Signs

<table>
<thead>
<tr>
<th>Vital</th>
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<td>96</td>
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HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RR = respiratory rate; SpO₂ = blood oxygen saturation; NR = not recorded.

Case 4
A member of the Afghanistan Armed Forces sustained multiple fragmentation grenade injuries to the face, left chest, left arm, left leg, and right thigh. On initial assessment by 75th Ranger Regiment medics, he was found to be alert with initial vital signs of HR 125, SBP 80, RR 20, and SpO₂ of 97%. Treatment included multiple pressure dressings, a tourniquet to the left lower extremity, 2 units of fresh whole blood, IV analgesics, anxiolytics, and antibiotics. The 2g IV TXA flush was administered within approximately 25 minutes of initial assessment. The casualty sustained a field care period of 115 minutes prior to evacuation. There was no documented exacerbation of hypotension, seizures, or anaphylaxis within TXA administration and evacuation.

Cases 5
A member of the Afghanistan Armed Forces sustained a small arms gunshot wound, suspected to originate from enemy ground forces, 10 minutes into a helicopter flight during mission exfiltration. On initial evaluation, the casualty was alert, with vital signs of HR 128, SBP 80, and no documented respiratory rate or SpO₂. Physical exam revealed a single wound below the sternum. A sternal IO was immediately placed but subsequently failed when flushed with TXA. A right-sided antecubital 16-gauge IV was placed and flushed with 2g of TXA, approximately 2 minutes from initial assessment. The exfiltration helicopter was redirected to a receiving medical facility, so the evacuation time was coded as 0 (zero) because the casualty was already in flight. On arrival to the receiving facility, the casualty was found to have a secondary gunshot wound just below the right gluteus. There was no documented exacerbation of hypotension, seizures, or anaphylaxis following TXA administration.

Case 6
A US Servicemember sustained a gunshot wound to the abdomen and another to the left upper extremity. On initial assessment by 75th Ranger Regiment medics, he was alert, with initial vital signs of HR 110, SBP 80, RR 22, and SpO₂ of 98%. A tourniquet was applied to the left upper extremity and an occlusive dressing was applied to his abdominal wound. IV access was established and the 2g IV TXA flush was administered within 20 minutes of casualty assessment, 10 minutes before evacuation. Post-TXA vital signs were not documented. There was no documented seizure or anaphylaxis following TXA administration and evacuation.

Discussion
The present series examined six cases of flush administration of 2g TXA into warfighters who sustained traumatic wounds. This 75th Ranger Regiment protocol is simpler and much faster than the 2019 TCCC TXA protocol, which requires a drip bag, continuous unobstructed tubing, two levels of sequential dosing (1g over 10 minutes follow by 1g over 8 hours), and continuous elevated fluids without backflow for the duration of TXA administration. This simplified protocol decreases task saturation, reduces cognitive barriers, and provides an executable strategy for tactical medics across a wide range of mission demands.

We found no empirical evidence of increased hypotension, seizures, or anaphylaxis with this novel approach to TXA administration. Though far from conclusive, present findings are encouraging. TXA was administered relatively quickly, well within the 3-hour guideline from time of injury. Further, while the 2019 TCCC TXA protocol is complicated and
makes compliance challenging, the 75th Ranger Regiment TXA protocol was executed in low-light conditions in less than 20 minutes on average from time of assessment. Combined, these limited findings suggest that the 2g TXA flush is potentially faster and easier to execute than the slow and cumbersome 2019 TCCC TXA infusion protocol.

Although the present case series was too small to determine the overall safety of this novel approach, present findings combined with previous literature suggest the possibility that the fears associated with the purported adverse effects of TXA might not be fully congruous with the context of young, healthy warfighters. The two most commonly feared adverse effects associated with TXA administration are hypotension and seizures. Hypotension, which is hypothesized to be related to rate of administration, is described on the TXA package insert with recommendations to not exceed 1mL/min (100mg/min). To our knowledge, only one documented case of hypotension associated with TXA administration has been described in the literature, and it occurred in a patient who had “an earlier tendency to orthostatic symptoms” during a 1969 randomized controlled trial. Seizures related to TXA administration have been predominantly described in cardiothoracic surgery patients. A 2015 meta-analysis of 26,079 patients receiving TXA during cardiac or thoracic surgery found a cumulative incidence of TXA-associated seizure to be 2.7%, with seizure incidence rising with increased TXA dose exposure. The current favored mechanism postulates a TXA-induced antagonism of gamma-aminobutyric acid type A (GABA_A) receptors. Notably, the cohort in the 2015 meta-analysis was older than 60 years, with advanced disease processes necessitating cardiothoracic surgery, which does not align well with the typical military-aged cohort for which TCCC guidelines were designed. The MATTERs study included warfighters with a mean age of 24 years old, none of whom experienced a seizure following TXA administration. Future research is required to determine the side effect profile of a 2g TXA flush in young healthy warfighters. However, the findings of this case series, in addition to current literature, suggests the potential risks of a 2g TXA flush could be outweighed by the known mortality benefit of TXA. In fact, for the 2020 protocol update, the Committee on TCCC has adopted a TXA dosing and administration protocol similar to the one described in this case series. (Danielle Davis, senior administrative assistant for Committee on TCCC, email communication, July 7, 2020)

The 2g TXA dose is somewhat arbitrary. The 2019 TCCC TXA guidelines mirror the landmark CRASH-2 trial protocol of 1g infusion over 10 minutes followed by an intravenous infusion of 1g over the following 8 hours. The CRASH-2 authors relied on cardiac anesthesia literature to develop a fixed dose that was presumed safe and effective for both larger and smaller patients. Subsequent cardiac anesthesia literature has shown greater efficacy with increased doses of TXA. For example, for patients who have an anticipated high risk of bleeding during cardiac surgery, a recommended bolus dose of 30 mg/kg is given over 15 minutes, followed by a 16 mg/kg/h dose until chest closure. This dosage is more than double the TXA package insert recommendations of 10 mg/kg of body weight IV in an individual with normal renal function, which is specific to the US Food and Drug Administration (FDA) approved use of TXA for hemorrhage prevention in hemophilia patients undergoing tooth extraction. The 2g dose investigated in the present case series doubles the 2019 TCCC initial dose guidelines and, if applied to our lightest warfighters, roughly matches the recommendations for high risk cardiothoracic surgery patients, but applied in a single flush rather than over 15 minutes. However, the risk of massive hemorrhage is likely much greater in, for example, an IED blast casualty than for a cardiothoracic surgery patient. Given the empirical evidence that higher levels of TXA can be more effective than lower doses, the optimal dosing of TXA in the traumatically injured warfighter remains an important open area for future research.

Implications

TXA provides a mortality benefit when administered within the first 3 hours of traumatic injury. The present case series suggests the possibility that TXA can be administered at a much faster rate compared to current guidelines. Further, all six patients were treated with TXA in low-light combat conditions and results were consistent across IV or IO administrations. While more research is needed, this simplified method for accelerated TXA administration rates holds potential for improving casualty outcomes and increasing TXA protocol compliance.

Limitations

This retrospective case series was limited by the sample size, which was modest and included only healthy military-aged men from a single US military area of operation with injuries sustained during a brief observational window. All cases met the criteria for TXA administration, and while injuries varied in both mechanism and severity, this case series was not comprehensive. The results of this case series should therefore be generalized only with appropriate caution.

The case series was also limited by the measured variables. This case series did not account for comorbidities unrelated to the traumatic injury. Further, precise vital signs and injury severity data were not acquired. Recorded vitals were documented by 75th Ranger medics, who were providing high levels of care in austere and extremely stressful combat situations. The 75th Ranger medics are instructed to assume a detectable radial pulse as a minimum estimated systolic blood pressure of at least 80mmHg and a carotid pulse as a minimum estimated systolic blood pressure of 60mmHg, which is less precise than pressures obtained by sphygmomanometer. The after-action reports (AARs) lacked the necessary data to calculate standardized Injury Severity Scores (ISS). This retrospective case series investigated occurrences of known TXA adverse effects during a relatively brief period following drug administration, with no evaluation of long-term casualty outcomes.

Finally, this case series was limited by the retrospective design, which included no control or comparison cases or groups that used the standard 2019 TCCC TXA protocol versus the modified 75th Ranger Regiment TXA protocols. All retrospectively evaluated data were obtained from AARs written by the 75th Ranger medics within 48 hours of the time of injury. The stressors of the combat environment and the delay in data recording could have affected documentation detail and accuracy.

Areas for Future Research

It is crucial to determine the optimal TXA dose for traumatically wounded warfighters and for those wounded collaboratively.
The 2g TXA dose described here demonstrated no adverse reactions in young healthy male warfighters, but whether 2g is the optimal TXA dose is an open emul in determining the optimal TXA dose to foster positive casualty outcomes.

It is important to continually assess TXA protocol compliance. The 2019 TCCC TXA protocol is slow and cumbersome, leading to compliance shortfalls. While the simplified 2g TXA flush described here should improve protocol compliance, actual compliance is empirically measurable, and an important focus toward optimizing casualty outcomes. As evident by the lack of documented post-TXA vitals in case 6, it is equally important to develop methods to foster reliable battlefield recordings of vitals and completeness of AARs.

There were no incidences of known TXA adverse effects, including hypotension, seizures, or anaphylaxis, observed in the present case series, but large-sample studies are needed. These studies should include subanalyses to account for comorbidities, such as disseminated intravascular coagulation, nonsteroidal anti-inflammatory drug (NSAID) use, and other factors that could potentially affect coagulation and TXA efficacy. In this context, it is essential to include long-term follow-up to assess the full efficacy and safety of TXA when administered via this novel method.

Finally, research is needed to determine optimal route for TXA administration in the context of battlefield medicine. Establishing and maintaining IV or IO access on a dynamic battlefield is challenging, each requiring time, equipment, and dexterity. IO access can be obtained by feel alone, which is advantageous in low light or darkness conditions. However, marrow fat emboli are common with IO infusions, particularly at higher pressures. Further, practitioners vary greatly in their speed of IO infusion, which is important because faster infusion rates are associated with higher pressures, and therefore with greater fat intravasation. Rubal et al. suggests that it may be prudent to train IO users with an instrumented IO push preparation so that they can directly observe the relationship between the rates of infusion and the pressures they are generating. The efficacy of this training strategy is an important area for future research.

The potential of administering TXA via the intramuscular (IM) route could dramatically increase both the simplicity and ease of TXA administration and protocol compliance. A recent review article found that no published studies to date had focused on the clinical application of IM TXA for traumatically injured patients. Future researchers should aim to identify the effectiveness and safety of IM-administered TXA in trauma casualties. Furthermore, it is possible that TXA has a sufficiently long shelf life, which opens the potential to create dedicated long-life 2g TXA injectors that can both simplify administration and further assist in TXA administration speed, consistency, and protocol compliance, whether via IV, IO, or IM access.

Conclusion
This case series of six battlefield-injured warfighters revealed no evidence of hypotension, seizures, or anaphylaxis immediately following a 2g IV or IO flush of TXA at point of injury. This case series provides a foundation for larger investigations towards determining the efficacy of this more tactically feasible method of TXA administration compared to the present slow and cumbersome protocol.

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Disclosure
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Author Contributions
CA, WB, DLR, and RK conceived the process improvement investigation concept. CA, WB, and DLR coordinated and collected data. CA, WB, DLR, GJZ, CM, TD, BD, and RK analyzed data. CA, WB, and GJZ wrote the manuscript. SG provided medic review of the data and provided subject matter expertise. All authors made significant edits to the manuscript.

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