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TITLE PAGE

Pharmacokinetics of tranexamic acid (TXA) delivered by expeditious routes in a swine model of polytrauma and hemorrhagic shock

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ABSTRACT

Pharmacokinetics of tranexamic acid (TXA) delivered by expeditious routes in a swine model of polytrauma and hemorrhagic shock

Objective: Hemorrhage is the leading cause of preventable death in civilian trauma centers and on the battlefield. One of the emerging treatment options for hemorrhage in austere environments is tranexamic acid (TXA). However, the landscape is not amenable to the current delivery standard. This study compared the pharmacokinetics of TXA via a standard 10-minute intravenous infusion (IV infusion), intravenous rapid push over 10 s (IV push), and intramuscular injection (IM) in a swine polytrauma and hemorrhagic shock model (trauma group) compared to uninjured controls (control group).

Methods: Thirty swine were randomized to the trauma or control group. Following anesthesia, the trauma group experienced a simulated blast injury and 40% controlled hemorrhage. Subjects in both groups were then randomized to receive 1 g/10 mL TXA via IV infusion, IV push, or IM. Animals were monitored for four hours with serial blood sampling. Serum TXA concentrations were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and analyzed.

Results: The time to maximum TXA concentration (T_{max}) was not affected by trauma in IV infusion or IV push, but was affected in the IM administration with T_{max} significantly slower than the control group (p=0.016). The minimum effective serum concentration of TXA (C_{eff}, 10 µg/mL) was reached in less than one minute with IV infusion and instantaneously with IV push.

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Despite lower bioavailability, the time to reach C_{eff} (T_{eff}) was achieved via IM administration in less than 10 minutes for both groups (6.4 minutes trauma vs. 2.1 minutes control).

Conclusions: In austere prehospital environments, an alternative to intravenous infusion of a life-saving medication is desired. Administration of TXA via all three methods reached the level needed to cause substantial inhibition of fibrinolysis within 10 minutes. The IV push method showed similar pharmacokinetics to IV infusion of TXA but can be delivered quickly without sacrificing an access site for 10 minutes.

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Key words: tranexamic acid, pharmacokinetics, polytrauma, hemorrhage, swine

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MAIN DOCUMENT

Pharmacokinetics of tranexamic acid (TXA) delivered by expeditious routes in a swine model of polytrauma and hemorrhagic shock

INTRODUCTION:

Despite continuous advances in medicine, hemorrhage is still a leading cause of preventable death in civilian trauma centers and on the battlefield. The casualty data from Operation Iraqi Freedom and Operation Enduring Freedom have shown that close to 87% of all injury mortality occurs prior to reaching surgical capabilities with cause of injury most commonly explosions (1). Hemorrhage was shown to make up about 90% of all potentially survivable injuries, predominantly truncal (67.3%) followed by junctional (19.2%) then extremity (13.5%) (1).

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The recognition and concept of trauma-induced coagulopathy, the inability of blood to clot in severely injured patients with hemorrhagic shock, has profoundly altered the treatment of hemorrhage. In addition to tourniquets and blood products, tranexamic acid (TXA) is one of the few non-surgical treatments in trauma-induced hemorrhage that has shown mortality benefit (2-7). Tranexamic acid is an antifibrinolytic, which competitively and reversibly binds to plasminogen, preventing its activation to plasmin, and, therefore, inhibits the breakdown of clot. It has been shown to effectively inhibit fibrinolysis when serum levels are at least 10 µg/mL (8). Tranexamic acid is currently only Food and Drug Administration (FDA) approved for heavy menstrual bleeding and for patients with hemophilia to prevent hemorrhage and reduce the need for factor replacement associated with tooth extraction. Despite this, both the Advanced Trauma Life Support guidelines and Tactical Combat Casualty Care (TCCC) guidelines recommend TXA administration to bleeding patients within three hours of traumatic injury (9, 10).

The renewed interest in TXA for the management of trauma came from the mortality benefit demonstrated in two landmark studies: the 2010 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial and the 2012 Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS). Studied in civilian hospitals in 40 different countries, CRASH-2 showed that TXA reduced all-cause mortality within four weeks of injury by 1.5% (2). It also established the standard TXA IV dosage used in trauma: 1 gram of TXA over 10 minutes followed by 1 gram of TXA over 8 hours (2). The MATTERS study was a retrospective study based on registry data at an American surgical center in Afghanistan from January 2009 to December 2010. Among individuals who required blood products within 24 hours of traumatic injury, mortality was compared between those who received TXA and those

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who did not (6). Although these reported mortality benefits may not seem clinically significant, TXA is overall a low-risk medication with the potential to increase the number of lives saved after traumatic injury.

Although recent studies underscore the beneficial effects and negligible side effects of TXA, its routine administration in patients meeting severe injury criteria remains infrequent (3, 4, 5, 7, 11, 12, 13). A survey of U.S. surgeons revealed that only 38% regularly use TXA for significant traumatic hemorrhage, with usage rates in the military being under 6% (14). The battlefield is a dynamic environment, often not amenable to a 10-minute infusion of 1 gram of TXA followed by an additional 1 gram over eight hours. Similar constraints exist in civilian prehospital settings, despite evidence supporting the feasibility of such treatments (5). This limited use likely stems from the narrow three-hour post-injury administration window, challenges in establishing venous access due to trauma-induced hypotension, and the logistical difficulties associated with the 10-minute intravenous infusion (11)."

Alternative methods of administration have the potential to improve TXA delivery rates in remote or austere prehospital environments if proven to be safe and reach the necessary effective concentrations in trauma patients. The same TXA dose given IV rapidly over 10 s is a possible alternative, however, hypotension has been reported following rapid administration and dangerously high levels of serum TXA could be possible (15). Meanwhile, the peripheral vasoconstriction and altered vascular permeability during hemorrhagic shock have historically precluded the use of IM medications in this population.

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Previous pharmacokinetic studies in swine models of 35% hemorrhage have demonstrated that IV, intraosseous (IO), and IM administration can reach therapeutic concentrations of TXA (16-18). However, these studies are limited by 1) the use of multiple resuscitation adjuncts, including vasopressors, blood products, and resuscitation fluid, confounding the effect of hemorrhagic shock on the pharmacokinetics of TXA, 2) the lack of an uninjured control group preventing comparison of TXA pharmacokinetics to baseline conditions, or 3) the absence of severe trauma resulting in inadequate modeling of the physiologic response.

To overcome these limitations, our study limited volume resuscitation, used uninjured, healthy controls, and paired a 40% hemorrhage with a severe pattern of polytrauma, simulating a catastrophic blast/blunt injury pattern. We hypothesized that severe trauma and hemorrhagic shock would significantly alter the pharmacokinetic profile of TXA in swine treated via standard IV infusion over 10 minutes (IV infusion), intravenous rapid push over 10 s (IV Push), and intramuscular injection (IM) compared to uninjured swine.

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METHODS:

Ethics statement and animal welfare

Research data derived from an approved Naval Medical Center Portsmouth, Virginia IACUC protocol. All procedures were reviewed and approved by the Naval Medical Center Portsmouth, Virginia Institutional Animal Care and Use Committee in compliance with all applicable Federal regulations governing the protection of animals in research, and per the principles in the “Guide

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for the Care and Use of Laboratory Animals," Institute for Laboratory Animal Research, 2011. All procedures were performed in AAALAC-accredited facilities.

Preparation, vascular access, and baseline measures

Following an acclimation period of three to seven days, 30 female Landrace/Yorkshire swine (*Sus scrofa domestica*) weighing 30-75 kg were randomized into six treatment groups. Each of the three TXA administration methods (IV infusion, IV Push, and IM) consisted of five animals each for a total of 15 swine in the trauma group and 15 swine in the uninjured control group.

All animals were pre-medicated with telazol, xylazine, ketamine (0.44 mL/kg) and buprenorphine (0.02 mg/kg) intramuscularly/subcutaneously for sedation and analgesia, followed by 5% isoflurane mask induction. Post intubation, subjects were maintained under anesthesia with 1-5% isoflurane in 100% oxygen and mechanically ventilated with tidal volumes of 10-15 mL/kg and respiratory rates (RR) of 10-15 breaths per minute.

An esophageal probe, foley catheter, electrocardiographic leads, in-line end-tidal carbon dioxide monitor, and pulse oximeter were applied for continuous temperature, urine output, electrocardiographic, capnographic, and oxygen saturation/pulse monitoring, respectively. A peripheral IV was inserted in the swine's ear for TXA administration. The carotid artery and external jugular vein were cannulated with a 7.5 French introducer sheath catheter via ultrasound-guided percutaneous or cutdown methods for invasive blood pressure monitoring and blood collection. Blood pressure (systolic and diastolic), mean arterial pressure (MAP), pulse rate, temperature, and pulse oximetry were monitored. Five minutes after all lines were placed,

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baseline vitals were assessed every five minutes for 15 minutes and then averaged for statistical analysis.

Polytrauma and hemorrhage

Trauma was induced in designated animals according to a standardized protocol (Figure 1). After femoral artery cannulation, tissue dissection was performed in trauma swine on the bilateral lower extremities to expose the periosteum of the femur. The dissection process also functioned as soft tissue trauma. A penetrating bolt gun was used sequentially on the bilateral femurs and fracture was confirmed via palpation and/or visualization. If no fracture was confirmed, further attempts were made with the penetrating bolt gun until successful fracture. Following successful bilateral femur fracture, blunt chest trauma was administered by placing lead and steel plates against the right chest and firing the bolt gun against the plate twice. The resulting injury included rib fracture and pulmonary contusion confirmed by necropsy during protocol development. Control animals did not receive the trauma protocol and were immediately randomized into TXA treatment modes following instrumentation and IV fluids.

After polytrauma completion, the swine underwent a 40% (class IV) total blood volume-controlled hemorrhage through the previously cannulated femoral artery. Hemorrhage was manually maintained at 60 mL/min with a three way stop cock and two 60 mL syringes. The swine were observed for 10 minutes and monitored continuously. Post-injury blood samples were collected and analyzed.

Treatments

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After baseline vitals and labs were collected, swine received a 250 mL infusion of 0.9% sodium chloride (NS). Following randomization, one gram of TXA (100 mg/mL) was administered via one of the three experimental delivery methods:

(1) *IV infusion*: An IV infusion of 10 mL TXA reconstituted in 90 mL NS was administered over 10 minutes.

(2) *IV Push:* A 10 mL IV injection was administered via rapid push over 10 seconds.

(3) *IM:* Two 5 mL IM injections were administered one in each thigh at 20-24 cm caudal to the ischial crest and 15-18 centimeters caudal to the tibia/fibula with the goal location being the semitendinosus/semimembranosus muscles.

To address the 90 mL additional volume in the IV infusion group, the IM and IV rapid push groups received 90 mL NS IV over 10 minutes after TXA administration via the ear vein catheter.

Monitoring after treatment

Subjects were observed for four hours during which time urinary output, vital signs, and laboratory parameters, including blood samples for TXA analysis, were collected. Blood samples for TXA analysis were collected at post-TXA administration times of 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes. Packed cell volume and total protein (PCV/TP), chemistry, and lactate were measured at post-TXA administration times of 30, 60, 90, 120, 150, 180, and 240 minutes. Vital signs (systolic and diastolic blood pressure, MAP, pulse oximetry, temperature, and pulse rate) were measured and recorded every 10 minutes after TXA administration and urinary output was measured every 30 minutes. Animals were continuously monitored for the duration of the study.

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Euthanasia

At the end of the four-hour monitoring period, final blood samples were collected, and the swine were humanely euthanized. If the early endpoint criteria of a MAP < 20 mm Hg for 10 consecutive minutes was met, the swine were humanely euthanized prior to the study endpoint of 240 minutes. Euthanasia was performed via transthoracic intracardiac administration of Euthasol (0.22 mL/kg).

TXA sample analysis

Samples designated for TXA analysis were collected in BD Vacutainer SST tubes and inverted a minimum of five times. Following inversion, samples were allowed to clot by sitting undisturbed at room temperature for up to one hour. Samples were then spun in a centrifuge at 3,500 revolutions per minute for 15 minutes. The resulting supernatant was then carefully decanted into a cryopreservation tube using a Pasteur pipette. These samples were immediately snap frozen in dry ice and transferred to a -80°C freezer for long term storage. The frozen samples were then shipped to Northeast Bioanalytical Laboratories LLC (Hamden, CT) on dry ice. Samples were analyzed using liquid chromatography tandem mass spectroscopy (LC-MS/MS), which generated serum TXA concentration data in µg/mL.

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Statistical analysis

Physiologic and laboratory data analysis

Vital signs (MAP, pulse rate, and temperature), urinary output, as well as laboratory data, including chemistry (glucose, sodium, ionized calcium) and blood gas (lactate, pH, pCO_2) were

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compared between the three administration methods within the trauma group and within the control group separately using repeated measures (RM) analysis of variance (ANOVA). If there were missing values, mixed effects analysis was used. It was expected that there be no difference between the administration methods within each group because the method itself should not affect physiologic parameters. Corrected p-values were reported using Šídák's multiple comparison test. There were no differences in model parameters within conditions between administration methods, so treatment groups were combined, and multiple comparisons were made between conditions using RM-ANOVA with multiple comparisons between time points using Šídák's multiple comparison test.

Urinary output was recorded every 15 minutes after Foley catheter placement and until the end of the experiment and was converted into mL/kg/hr for each swine. The urinary output was averaged for the trauma group and for the control group and compared during three different phases: phase I (urine collected in the 30 minutes post-Foley catheter insertion), phase II (urine collected post-injury/hemorrhage but prior to TXA administration), and phase III (urine collected following TXA delivery).

Pharmacokinetic data analysis

The resultant TXA data in µg/mL were graphed over time. Pharmacokinetic data were analyzed using PKSolver, an add-in program for Microsoft Excel, for each subject to determine area under the curve (AUC), concentration maximum (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$), and plasma clearance rate (CR) (19). Time to reach minimum effective dose (T_{eff}) was estimated from the linear slope of the linear portion of the first 2 to 4 data points of the concentration versus time

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data and solving for time when y = 10 µg/mL. Pharmacokinetic parameters AUC, T_{max}, C_{max}, T_{eff}, $t_{1/2}$ and CR were compared within conditions separately for trauma or control groups using ANOVA and between conditions for each administration method using t-tests, or Mann-Whitney for non-continuous or non-gaussian data. Bioavailability was calculated for IV Push and IM administration by dividing the AUC of each subject by the average AUC of the IV infusion method within each condition. Comparisons were made using t-tests between conditions within treatment methods. All statistical analysis was completed using GraphPad Prism version 9 for Windows (GraphPad Software, San Diego, CA). Data were considered significant at $p < 0.05$.

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RESULTS:

Characterization of the polytrauma and hemorrhagic shock model

The trauma group had a significantly lower MAP (Figure 2A, $p < 0.0001$) and elevated pulse rate ($p < 0.0001$) compared to the control group (Figure 2B); hypotensive episodes were not observed after TXA administration in any treatment group (SF 1A). There was no significant difference in temperature between conditions (SF 1B). The urinary output was variable within and between the conditions with large standard deviations. Although no statistically significant difference was found, overall, there appeared to be a trend toward decreased urinary output in the trauma group compared to the control group (SF 2). All swine had decreased urinary output from baseline measures, possibly due to inhalant anesthesia with isoflurane (20, 21).

The trauma group had elevated lactate levels beginning 10 minutes after completion of the injury and hemorrhage, peaking at 30 minutes post-administration of TXA, and remained elevated, >2

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mM, through the end of the experiment (Figure 2C). Most of the swine in the trauma group (80%) also exhibited an acidosis, defined as a pH < 7.35, post-injury/hemorrhage (Figure 2D). In the control group, two swine had up to two pH measurements < 7.35.

The partial pressure of carbon dioxide (pCO_2) on arterial blood gas was elevated and significantly higher in the trauma group than the control group at t=30 minutes but then trended down with time (SF 3A). Sodium levels in both conditions declined over time, but with a statistically significant decrease in the trauma group compared to the control group starting at t=90 minutes through to the end of the experimental period (SF 3B). Glucose levels were elevated and significantly higher in the trauma group compared to the control group only at 10 minutes post-injury/hemorrhage (SF 3C). There was no statistically significant difference in ionized calcium between conditions (SF 3D).

Pharmacokinetic profiles of TXA

The serum concentration of TXA was plotted over the 240 min study period for all control groups (Figure 3A) and trauma groups (Figure 3B) beginning one minute after administration of TXA.

The AUC was measured over the duration of the 240-minute experimental period (Figure 4A). The swine in the trauma group have approximately 40% less blood volume than the swine in the control group; therefore, the trauma group should have an approximately 166% higher AUC than the control group for each administration method. This was evident in the IV and IV Push administration, which had an increased AUC of 156% (p=0.0025) and 145% (p<0.0001),

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respectively. For IM administration, there was only a 45% increase in the AUC in the trauma group compared to the control group, which was not a statistically significant difference. Within conditions, IV Push displayed significantly higher AUC compared to IM administration (p=0.0004 trauma, p=0.04 control).

Standard IV administration was used to calculate bioavailability for IM administration. The bioavailability of TXA via IM administration was significantly lower in the trauma group at 0.52 (Figure 4B, p=0.033) compared to 0.93 in the control group.

Despite the lower bioavailability of the IM administration, both the trauma group and control group achieved the minimum effective concentration of TXA (C_{eff}, 10 µg/mL) in a relatively short period of time (Figure 5A). In the trauma group, the average T_{eff} was 6.4 minutes (standard deviation (SD) 3.1 minutes) after IM administration, which was significantly slower than in the control group (p=0.0042). For the control group, the average T_{eff} was 2.1 minutes (SD 1.2 minutes) after IM administration (Figure 5B). T_{eff} was also significantly slower for the IM administration compared to IV infusion in the trauma group (p=0.0001). Serum TXA levels reached the minimum effective concentration in both conditions in less than one minute after IV infusion and instantaneously after IV Push. All groups maintained TXA concentrations > C_{eff} throughout the remaining duration of the experiment.

The C_{max} was significantly greater for IV Push compared to both the IV infusion and IM methods within both the trauma group and control group (Table 1). There was no significant difference between C_{max} for the IV infusion and IM methods in either the trauma group or control group;

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however, it took significantly more time for the IM administration to reach C_{max} compared to IV infusion. The T_{max} for the IM administration in the trauma group was a median of 45 minutes (range: 30–180 minutes).

The estimated $t_{1/2}$ was prolonged in the trauma group for all administration methods but it was variable. Despite this trend, due to the variability, statistical significance was found only for the IV Push administration between the trauma group and control group (p=0.0043). The $t_{1/2}$ for all administration methods in the control group were similar to the reported 2-hour half-life of TXA (33). The IM administration for the trauma group only had three of the five swine included in this analysis due to two swine maintaining an unchanged serum TXA concentration by the end time of the experiment.

There was no difference in plasma clearance rates between the different administration methods within either the trauma group or control group. The plasma clearance in the trauma group was significantly reduced compared to the control group in both the IV infusion and the IM methods (p= 0.002 and p=0.012, respectively). There was a trend toward clearance rate reduction in the IV Push method between conditions.

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DISCUSSION:

We evaluated two faster methods of TXA administration, IV Push and IM, compared to the standard 10-minute IV infusion in a polytrauma model of severe shock. Importantly, we included the same three administration methods in healthy, uninjured swine to understand the magnitude of the effect of polytrauma on the pharmacokinetic profile over four hours. The severity of the

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model and control of confounding resuscitation treatments allowed us to isolate the effect of trauma in a worst-case scenario that may be experienced in a remote, austere, or prehospital environment. All three TXA administration methods in the polytrauma group reached minimum therapeutic serum concentrations >10 µg/mL within 10 minutes and were sustained above this level throughout the duration of the experiment.

Rapid infusion of TXA after severe or ongoing hemorrhage could result in potentially unsafe concentrations of the drug, compounded by low blood volume. The Pfizer TXA insert reports that concentrations up to 10 mg/mL had no influence on platelet count, coagulation time, or coagulation factors in whole or citrated blood from healthy subjects (22). Here, we observed the expected transiently high peaks in TXA concentrations immediately upon IV Push administration, reaching up to 1 mg/mL. This concentration is unlikely to influence blood coagulation, however, it is possible that the higher C_{max} after IV Push in a trauma patient could be associated with increased risk of adverse events such as seizures (23). Although the minimum effective dose to inhibit fibrinolysis is estimated to be 10 µg/mL, the maximum plasma concentration before adverse reactions occur is unknown (8).

Literature describing TXA toxicity is associated with use of high dose-regimens (50-100 mg/kg), are complicated by confounders, and are limited to case reports (24-26). Further, the rapid infusion of TXA has been discouraged due to concerns for hypotension, noted in the package insert but not supported by literature (22). Adverse events were not observed or reported during previous military implementations of IV Push ultimately leading the Committee on TCCC to

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recommend IV Push administration in the field (6, 27, 28). Aligning with this, we did not observe hypotensive episodes associated with IV Push TXA administration.

Unsurprisingly, polytrauma and hemorrhagic shock had the greatest effect on uptake of TXA after IM administration. Traditionally, IM administration of TXA has been avoided in shock states due to the compromised microvasculature and peripheral vascular shunting, which impedes drug absorption into the bloodstream. Indeed, in our severe model, IM delivery resulted in a 200% longer T_{max} and 40% decreased bioavailability when compared to healthy controls. This was similar to a study using a class III hemorrhagic shock model in swine that resulted in T_{max} after IM TXA administration 12 times longer than after IV or IO administration (17). Conversely, in a less severe model of ongoing hemorrhage that included significant volume replacement and vasopressors, T_{max} and bioavailability for TXA via IM administration were comparable to our healthy control swine that received IM TXA (16), underscoring the impact of trauma severity on pharmacokinetics.

Several trials have demonstrated a correlation between shorter times to TXA administration and better outcomes (2, 3, 5, 6). Despite the slower drug absorption after IM administration of TXA in our severe trauma and hemorrhagic shock model, therapeutic concentrations were still reached within 10 minutes. IM administration would remove the variability associated with first-attempt IV success rates (42-86%), time required to establish IV access (2.2-13 minutes) in the prehospital setting, and the time required to prepare an infusion (29-33). By removing these barriers, IM administration may result in quicker achievement of therapeutic levels compared to IV administration.

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Our study results are limited to the acute effects of trauma and hemorrhagic shock due to the experimental study duration of four hours, which did not allow for evaluation of long-term survival outcomes. We also did not validate coagulation parameters, including development of fibrinolysis within the four-hour study, which is a limitation of our swine model of polytrauma and hemorrhagic shock. We instead focused on developing a model with severe enough trauma to impact pharmacokinetics and did not attempt to induce consistent levels of fibrinolysis to study the pharmacodynamics of TXA, which may have required treatment with exogenous tissue plasminogen activator to achieve.

Our results in swine indicate that a 1 g dose of TXA given IV or IM achieves minimum therapeutic levels of TXA within 10 min. However, the effective dosage of TXA in trauma patients is an active area of research and dosages of up to 4 g have been reported (34). Further clinical studies are needed to recommend an updated dosing regimen or minimum effective concentration in trauma. Additionally, many medications delivered IM are given at higher doses than when given IV. Increasing the IM dose may result in reaching therapeutic levels faster in trauma or in ultimately reaching a higher C_{max} and could be optimized in future studies. Employment of pre-made autoinjectors of IM TXA would further increase ease of delivery and compliance of TXA administration, particularly in the prehospital environment.

CONCLUSIONS:

In prehospital, austere, and tactical environments where supplies, time, and space are limited, alternatives to a 10-minute infusion of a life-saving medication are desired. Our data suggest

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both rapid IV push and IM modes of TXA administration can achieve minimum therapeutic serum concentrations within 10 minutes without adverse effects. While further research is needed to determine the clinical implications on outcomes, these modes may be viable and efficient alternatives to IV infusions of TXA in the prehospital environment.

Authorship Contributions:

M.W. wrote the first draft and collected data. S.S. conceptualized the study concept, participated in protocol development, collected data, and contributed to manuscript creation. B.L. participated in data collection, data analysis, and manuscript creation. C.M., T.P., R.H., C.T., E.S., and L.G. participated in data collection. P.F. participated in protocol development. E.E.F. analyzed the data, finalized protocol development, and provided critical review of the manuscript. All authors read and approved the final manuscript.

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Disclosure Statement:

The authors report there are no competing interests to declare.

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REFERENCES:

1. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. J Trauma Acute Care Surg. 2012;73(6 Suppl 5):S431-7.

Information Classification: General

2. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23-32.

3. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019 Nov 9;394(10210):1713-1723. doi: 10.1016/S0140-6736(19)32233-0.

4. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of Cryoprecipitate and Tranexamic Acid With Improved Survival Following Wartime Injury: Findings From the MATTERs II Study. *JAMA Surg.* 2013;148(3):218–225. doi:10.1001/jamasurg.2013.764

5. Brown JB, Neal MD, Guyette FX, et al. Design of the study of tranexamic acid during air medical prehospital transport (STAAMP) trial: addressing the knowledge gaps. *Prehosp Emerg Care.* 2015;19:79–86.

6. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012;147(2):113-9.

7. Shiraishi A, Kushimoto S, Otomo Y, Matsui H, Hagiwara A, Murata K; Japanese Observational Study for Coagulation and Thrombolysis in Early Trauma (J-OCTET) investigators. Effectiveness of early administration of tranexamic acid in patients with severe trauma. Br J Surg. 2017 May;104(6):710-717. doi: 10.1002/bjs.10497. Epub 2017 Feb 23. PMID: 28230248.

Accepted Manuscript

Information Classification: General

8. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood Coagul Fibrinolysis. 2019;30(1):1-10.

9. Joint Trauma System TCCC Guidelines. The Committee on Tactical Combat Casualty Care; 2021.

10. Surgeons ACo. Advanced Trauma Life Support : Student Course Manual. 10th ed. Chicago, IL: American College of Surgeons 2018.

11. Fisher AD, Carius BM, April MD, Naylor JF, Maddry JK, Schauer SG. An Analysis of Adherence to Tactical Combat Casualty Care Guidelines for the Administration of Tranexamic Acid. J Emerg Med. 2019;57(5):646-52.

12. Eckert MJ, Wertin TM, Tyner SD, Nelson DW, Izenberg S, Martin MJ. Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). J Trauma Acute Care Surg. 2014 Dec;77(6):852-8; discussion 858. doi: 10.1097/TA.0000000000000443. PMID: 25423534.

13. Rowe S, Liu A, Zagales I, Awan M, Santos R, McKenney M, Elkbuli A. Effectiveness and Safety of Tranexamic Acid Use in Acute Traumatic Injury in the Prehospital and In-hospital Settings: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Ann Surg Open. 2021 Nov 8;2(4):e105. doi: 10.1097/AS9.0000000000000105. PMID: 37637875; PMCID: PMC10455131.

14. Napolitano LM. Prehospital tranexamic acid: what is the current evidence? Trauma Surg Acute Care Open. 2017;2(1):e000056.

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Information Classification: General

15. Hedlund PO. Antifibrinolytic therapy with Cyklokapron in connection with prostatectomy. A double blind study. Scand J Urol Nephrol. 1969;3(3):177-82. doi: 10.3109/00365596909135401. PMID: 4912802.

16. Spruce MW, Beyer CA, Caples CM, DeSoucy ES, Kashtan HW, Hoareau GL, et al. Pharmacokinetics of Tranexamic Acid Given as an Intramuscular Injection Compared to Intravenous Infusion in a Swine Model of Ongoing Hemorrhage. Shock. 2020;53(6):754-60.

17. DeSoucy ES, Davidson AJ, Hoareau GL, Simon MA, Tibbits EM, Ferencz SE, et al. Pharmacokinetics of Tranexamic Acid via Intravenous, Intraosseous, and Intramuscular Routes in a Porcine (Sus scrofa) Hemorrhagic Shock Model. J Spec Oper Med. 2019;19(4):80-4.

18. Lallemand MS, Moe DM, McClellan JM, Loughren M, Marko S, Eckert MJ, et al. No intravenous access, no problem: Intraosseous administration of tranexamic acid is as effective as intravenous in a porcine hemorrhage model. J Trauma Acute Care Surg. 2018;84(2):379-85.

19. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed. 2010;99(3):306-14.

20. Osborn JW, Cruz-Lynch A. Volatile Anesthesia Activates Renal Sympathetic Nerves to Reduce Renal Excretory Function: Implications for Surgically-Induced Acute Kidney Injury. Function (Oxf). 2021;2(6):zqab056.

21. Connolly CM, Kramer GC, Hahn RG, Chaisson NF, Svensen CH, Kirschner RA, et al. Isoflurane but not mechanical ventilation promotes extravascular fluid accumulation during crystalloid volume loading. Anesthesiology. 2003;98(3):670-81.

22. Cyklokapron (Tranexamic Acid). Package insert. New York, NY: Pfizer; 2011.

Accepted Manuscript

Information Classification: General

23. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. Ann Neurol. 2016;79(1):18-26.

24. Merriman B, Mayson K, Sawka A, Akagami R, Flexman AM. Postoperative seizure in a neurosurgical patient: Should tranexamic acid be on the differential? Can J Anaesth. 2013;60(5):506-7.

25. Wang CS, Yang CJ, Chen SC, Chen HC, Huang MS. Generalized convulsion resulted in hyperammonemia during treatment with tranexamic acid for hemoptysis. Ir J Med Sci. 2011;180(3):761-3.

26. Bhat A, Bhowmik DM, Vibha D, Dogra M, Agarwal SK. Tranexamic acid overdosage-induced generalized seizure in renal failure. Saudi J Kidney Dis Transpl. 2014;25(1):130-2.

27. Androski CP, Jr., Bianchi W, Robinson DL, Zarow GJ, Moore CH, Deaton TG, et al. Case Series on 2g Tranexamic Acid Flush From the 75th Ranger Regiment Casualty Database. J Spec Oper Med. 2020;20(4):85-91.

28. Drew B, Auten JD, Cap AP, Deaton TG, Donham B, Dorlac WC, et al. The Use of Tranexamic Acid in Tactical Combat Casualty Care: TCCC Proposed Change 20-02. J Spec Oper Med. 2020;20(3):36-43.

29. Nadler R, Gendler S, Benov A, Shina A, Baruch E, Twig G, et al. Intravenous access in the prehospital settings: What can be learned from point-of-injury experience. J Trauma Acute Care Surg. 2015;79(2):221-6.

30. Chreiman KM, Dumas RP, Seamon MJ, Kim PK, Reilly PM, Kaplan LJ, et al. The intraosseous have it: A prospective observational study of vascular access success rates in patients in extremis using video review. J Trauma Acute Care Surg. 2018;84(4):558-63.

Accepted Manuscript

Information Classification: General

31. Reades R, Studnek JR, Vandeventer S, Garrett J. Intraosseous versus intravenous vascular access during out-of-hospital cardiac arrest: a randomized controlled trial. Ann Emerg Med. 2011;58(6):509-16.

32. Minville V, Pianezza A, Asehnoune K, Cabardis S, Smail N. Prehospital intravenous line placement assessment in the French emergency system: a prospective study. Eur J Anaesthesiol. 2006;23(7):594-7.

33. Prottengeier J, Albermann M, Heinrich S, Birkholz T, Gall C, Schmidt J. The prehospital intravenous access assessment: a prospective study on intravenous access failure and access delay in prehospital emergency medicine. Eur J Emerg Med. 2016;23(6):442-7.

34. Kim, N. (2023). Tranexamic acid in trauma management: A review of evidence. Journal of Acute Care Surgery, 13(3), 85–94. https://doi.org/10.17479/jacs.2023.13.3.85

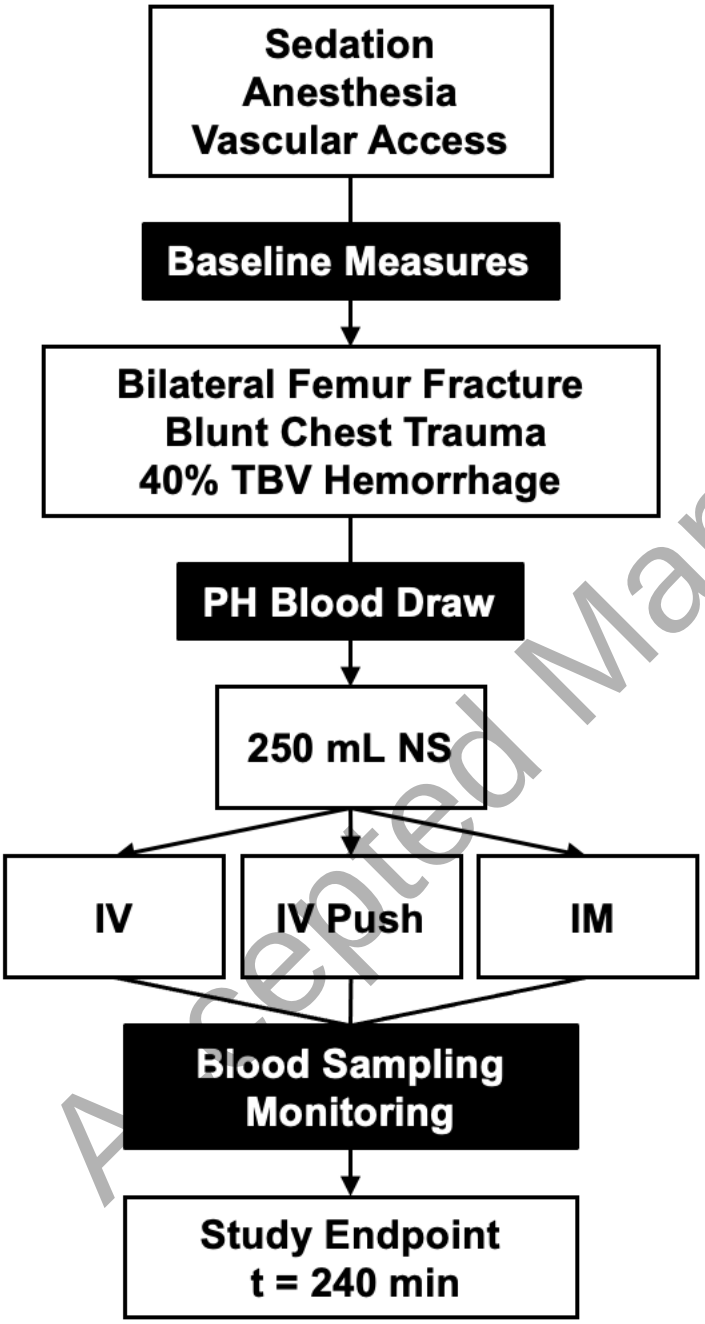
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TABLE AND FIGURE CAPTIONS:

Table 1. Pharmacokinetic parameters. T_{max} data are represented as median (interquartile range (IQR)). All other data are represented as means (standard deviation (SD)).

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Figure 1. Visual representation of experimental procedure for trauma group. Post-hemorrhage (PH) is 10-min post hemorrhage and injury completion. Normal saline (NS).

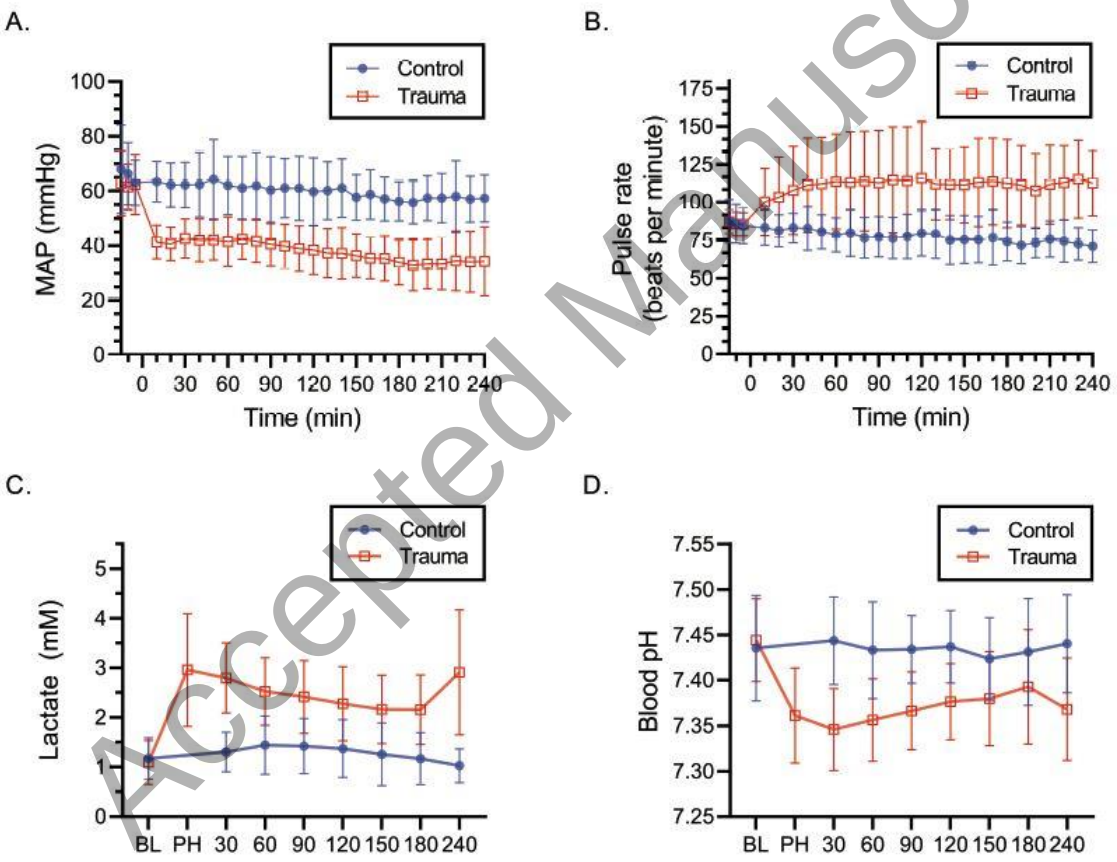


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Figure 2. Physiology and blood chemistry over time.

Figure 2 footnotes: Mean arterial pressure (MAP) (A.) and pulse rate (B.) were plotted at baseline, shown to the left of the dotted line, and in 10-min intervals after TXA administration commenced at t = 0. Lactate (C.) and blood pH (D.) were measured at baseline (BL), 10-minutes post-hemorrhage and injury (PH) and in 30 minute or 1-hour intervals.

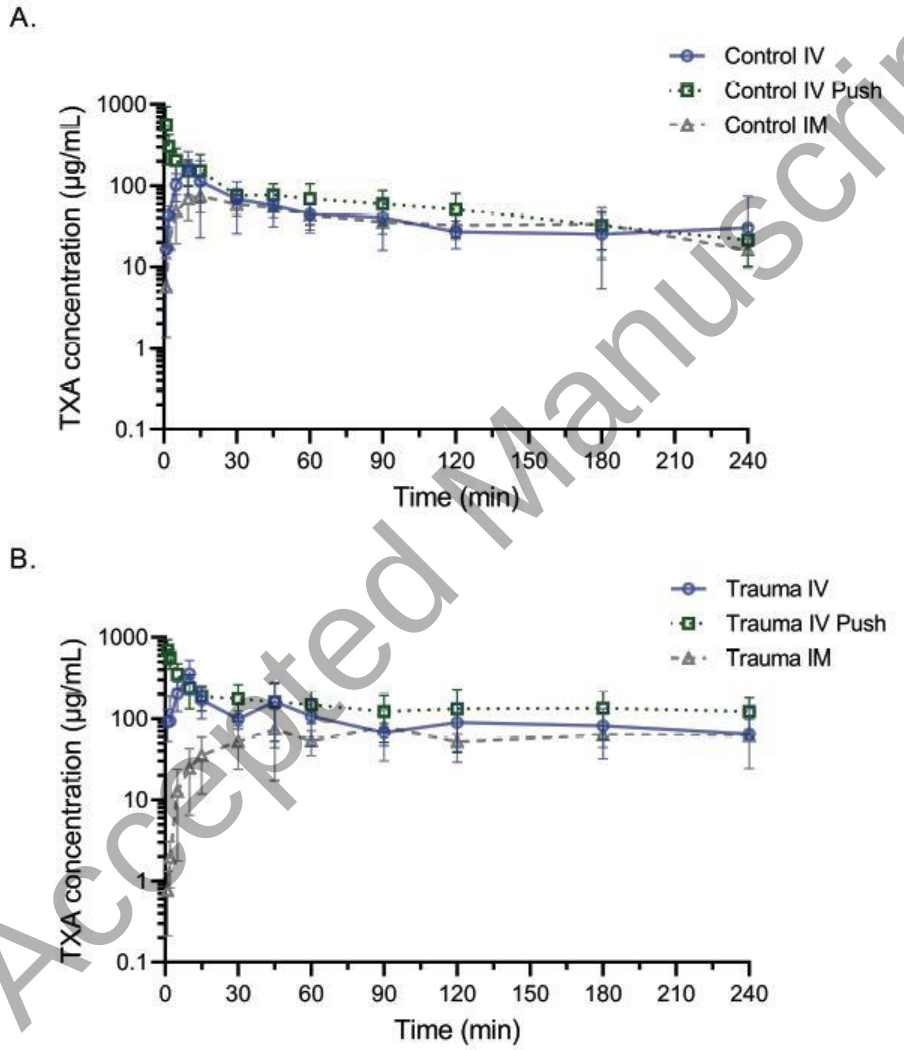


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Figure 3. Pharmacokinetic analysis of TXA detected over time.

Figure 3 footnotes: TXA levels detected in serum using LC/MS in healthy controls (A.) and trauma (B.) animals.

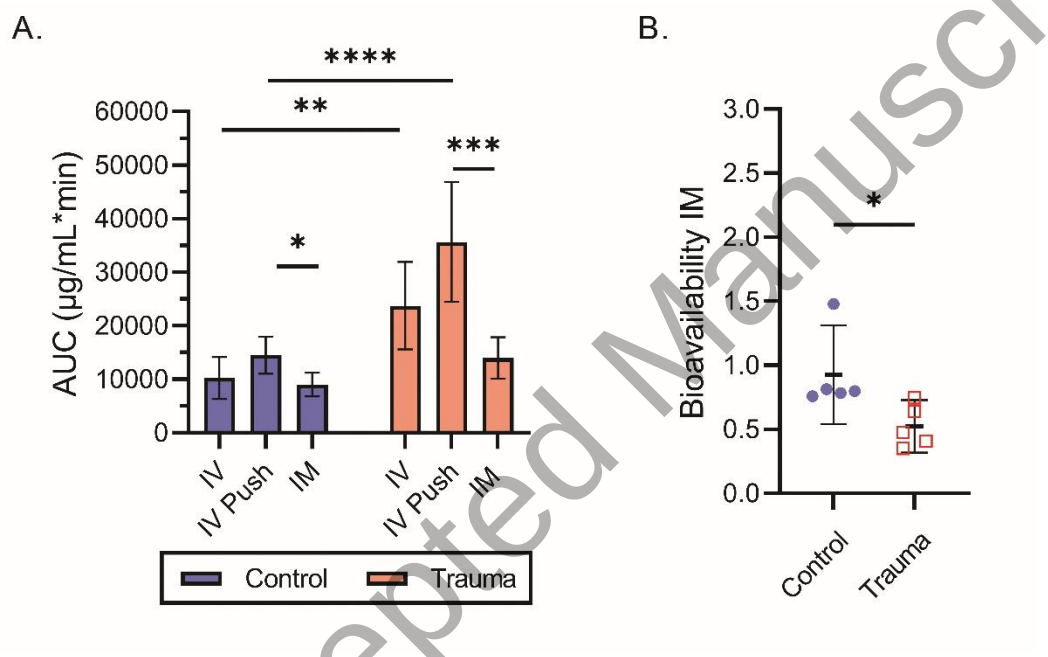


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Figure 4. Bioavailability of TXA.

Figure 4 footnotes: Area under the curve (A.) was calculated over the 240-minute study period, bars represent the mean and error bars represent 95% confidence intervals (CI). Bioavailability after IM (B.) for control and trauma conditions are plotted as individual data points. Horizontal line and error bars represent the mean and 95% CI. *, p < .05; **, p < .01; ***, p < .001; ****, p < .0001; n = 5 swine per treatment and condition.

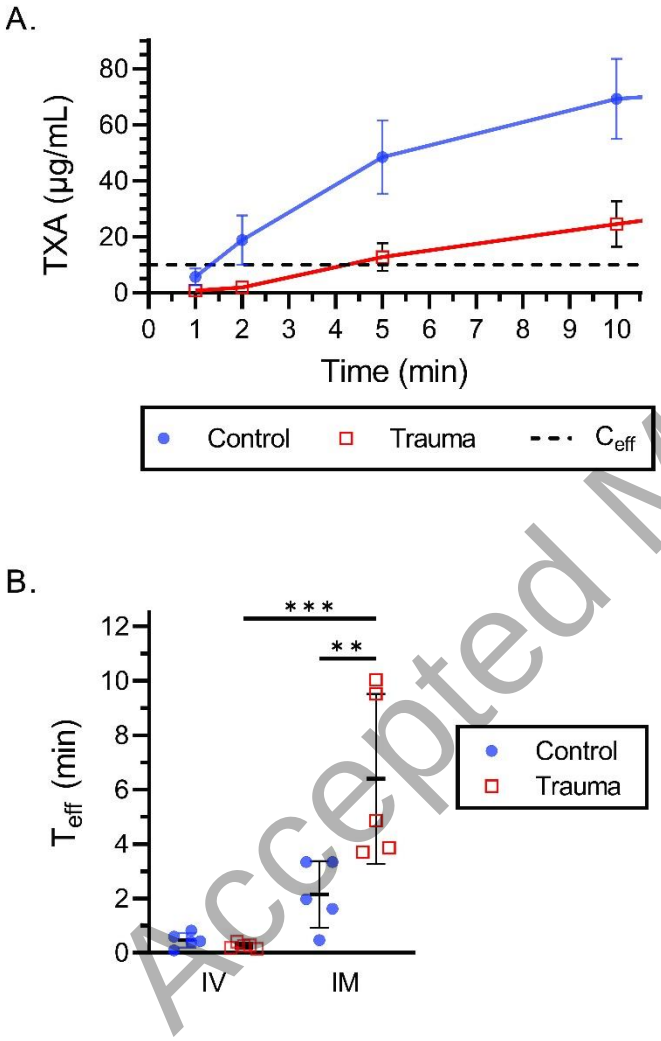


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Figure 5. Effective serum concentration of TXA.

Figure 5 footnotes: (A.) The first 10 minutes after IM administration are plotted along with the minimum effective dose. (B.) Time to reach the effective dose (T_{eff}) was estimated for IV infusion and IM administration. Effective dose was reached instantaneously after IV Push and is not shown. **, p < .01; ***, p < .001; n = 5 swine per treatment and condition.



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	IV	IV Push	IM
T_{max} (min)			
Control	10 (10 – 10)	1 (1 – 2)	15 (5 – 30)
Trauma	10 (10 – 10)	1 (1 – 2)	45 (30 – 180)
C_{max} (µg/mL)			
Control	169.4 (92.1)	570.7 (365.6)	79.8 (27.4)
Trauma	356.8 (160.5)	727.8 (222.0)	101.9 (55.6)
$T_{1/2}$ (min)			
Control	98.4 (17.6)	113.9 (36.6)	121.1 (15.8)
Trauma	198.4 (98.5)	202.6 (24.2)	393.3 (300.0)
CR (mL/min)			
Control	103.4 (44.3)	61.4 (30.2)	94.6 (23.9)
Trauma	33.7 (19.7)	17.4 (10.8)	29.5 (8.7)

Table 1. *Pharmacokinetic parameters.* T_{max} data are represented as median (interquartile range (IQR)). All other data are represented as means (standard deviation (SD)).

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