No IV, No Problem: Intraosseous Administration of Tranexamic Acid is as
Effective as Intravenous in a Porcine Hemorrhage Model

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ABSTRACT

BACKGROUND: The acute coagulopathy of trauma is often accompanied by hyperfibrinolysis. TXA can reverse this phenomenon, and, when given early, decreases mortality from bleeding. Establishing IV access can be difficult in trauma and IO access is often preferred for drug administration. Currently, there is no data on the efficacy of IO administered TXA. Our objectives were to compare serum concentrations of tranexamic acid (TXA) when given IV and intraosseous (IO) and to compare the efficacy of IO administered TXA to IV at reversing hyperfibrinolysis.

METHODS: Using a porcine hemorrhage and ischemia-reperfusion (IR) model, 18 swine underwent hemorrhagic shock followed by a tissue plasminogen activator (tPA) infusion to induce hyperfibrinolysis. Animals then received an IV or tibial IO infusion of TXA over 10 minutes. Blood was then analyzed using ROTEM to monitor reversal of hyperfibrinolysis. Serum was analyzed for drug concentrations.

RESULTS: After hemorrhage and IR, there were no significant differences in MAP (48 vs 49.5), lactate (11.1 vs 10.8), and pH (7.20 vs 7.22) between groups. Intraosseous TXA corrected the lysis index at 30 minutes in EX-TEM and IN-TEM, like IV infusion. Peak serum levels of TXA after IV and IO administration show concentrations of 160.9µg/mL and 132.57µg/mL respectively (p=0.053). Peak levels occurred at the completion of infusion. Drug levels were tracked for four hours. At the end of monitoring, plasma concentrations of TXA were equivalent.

CONCLUSION: Intraosseous administration of TXA is as effective as intravenous in reversing hyperfibrinolysis in a porcine model of hemorrhagic shock. Intraosseous administration was associated with a similar peak levels, pharmacokinetics, and clearance. Intraosseous administration of TXA can be considered in hemorrhagic shock when IV access cannot be established.
LEVEL OF EVIDENCE: III

STUDY TYPE: Therapeutic Study

KEY WORDS: tranexamic acid, hyperfibrinolysis, coagulopathy, porcine model, intraosseous, hemorrhage control
BACKGROUND

Trauma induced coagulopathy (TIC) is a complex and highly morbid complication that is associated with severe injury and large volume hemorrhage. TIC is classically attributed to a combination of acidosis, hypothermia, hyper-activity and consumption of clotting factors, and dilution of the same factors\(^1\)\(^2\) during resuscitation. As the understanding of traumatic coagulopathy has advanced it has come to light that there is a subset of patients that present in the acute phase of trauma with an established coagulopathy, which has been termed the acute traumatic coagulopathy (ATC). The mechanism for the development of ATC is multifactorial, but thought to be due to a combination of a robust activation of protein C, fibrinolysis, inflammation, and platelet dysfunction\(^3\)\(^-\)\(^5\). Patients with ATC have been shown to have increased transfusion requirements, longer ICU stays, more ventilator days, and a greater number and degree of organ dysfunction. It is also associated with a significantly increased risk of mortality of three to four fold when matched with patients who do not have ATC, and an eight-fold increase in mortality within the first 24 hours after injury.\(^6\)

Tranexamic acid (TXA) is a synthetic lysine analogue drug that has marked anti-fibrinolytic properties\(^7\)\(^,\)\(^8\). This agent has been shown to reduce mortality in both civilian and military trauma patients with proven or suspected major hemorrhage,\(^9\)\(^-\)\(^11\) and is now routinely used in the military setting. TXA has been incorporated into the military clinical practice guideline for massive transfusion at forward combat hospitals, and is also carried by special operations forces (SOF) medics in the deployed environment. In both civilian and military trauma patients who are hypotensive and hemorrhaging, establishing intravenous (IV) access can be difficult and often leads to delays in initiation of resuscitation or pharmacologic therapies including TXA.\(^12\) An additional relatively common consideration in modern battlefield trauma are the injury patterns produced by major blast mechanisms, such as those seen with improvised explosive devices. The most severe of these has now been characterized as the “dismounted
complex blast injury” or DCBI. This complex is characterized by multiple mangled or amputated extremities, complex perineal wounds and pelvic fractures, spine fractures, and multiple truncal penetrating fragment injuries.\textsuperscript{13} These patients are among the highest risk for major hemorrhage and requiring massive transfusion, but also present an extremely difficult target for establishing intravenous access. Intraosseous access for the administration of intravenous fluids, medications, and even blood products is widely utilized in select civilian trauma patients, and has found an even greater use in the battlefield setting. The administration of most fluids and some medications via the intraosseous route has been shown to be safe and effective, although there is significantly less data compared to the intravenous route.\textsuperscript{14-16}

The combination of the potential mortality benefit with TXA administration, and the need to administer the drug early (within 3 hours of injury) for optimal efficacy, calls for further research on optimal timing and delivery options. There are several ongoing trials examining the pre-hospital administration of TXA, and also efforts to evaluate this drug in the combat pre-hospital environment.\textsuperscript{17-19} Given the above-cited problems with early IV access, this would likely require IO administration of TXA in a subset of civilian and military patients. In addition, a 2013 Department of Defense expert panel identified major existing “gaps” in research regarding TXA, which included the complete lack of data on the pharmacology and efficacy of TXA when administered via an intraosseous route.\textsuperscript{20} Thus, the primary objective of this study was to evaluate the pharmacodynamics and efficacy of TXA in the IO versus IV routes in a large animal model that mimics post-traumatic hemorrhagic shock physiology. We hypothesized that when given through the intraosseous route, TXA will reach similar serum concentrations compared with intravenously delivered TXA, and that IO delivery will have equal efficacy in terms of reversal of hyperfibrinolysis compared to the standard intravenous route.
METHODS

This study was performed at an American Association for Laboratory Animal Science-accredited large animal research facility following protocol approval by the Institutional Animal Care and Use Committee (IACUC). Eighteen adult swine (35-55kg, *Sus scrofa*) underwent a hemorrhage and ischemia reperfusion injury protocol that has been previously validated to produced systemic acidosis, coagulopathy, and shock physiology with marked hyperfibrinolysis. They were then randomized to either an IV dose of TXA (n=9) or a tibial IO dose (n=9).

**Preparation and Invasive Monitoring**

After the induction of general anesthesia all animals underwent placement of invasive monitoring devices. A neck dissection was performed and the right carotid artery and right internal jugular veins were identified. An arterial line was placed in the carotid artery to obtain continuous blood pressure monitoring. A Cordis was placed in the right internal jugular vein and a pulmonary artery catheter was floated from this site to give continuous hemodynamic monitoring. A laparotomy was then performed and a Cordis infusion catheter was placed in the IVC. The aorta was then identified and controlled with a vessel loop via an incision in the diaphragm. The abdomen was then temporarily closed using penetrating towel clamps.

**Injury and Ischemia-Reperfusion Phase**

After the set-up phase each animal underwent a controlled, 35% blood volume hemorrhage (26cc/kg). This hemorrhage was done as tolerated until the animal’s mean arterial pressure (MAP) dropped below 40mmHg. If the MAP dropped below 40mmHg the rate of hemorrhage was slowed. The maximum allowed time for hemorrhage was 30 minutes. If the hemorrhage could not be completed in this time the hemorrhage was stopped at this point and the experiment proceeded. All animals in the study completed the entire hemorrhage within the allotted 30 minute time period.
After the hemorrhage had been performed a supra-celiac aortic cross clamp was placed. This was kept in place for a duration of 45 minutes. When the aortic occlusion time reached 45 minutes the cross-clamp was slowly released over a period of five minutes. An epinephrine infusion was initiated at the start of cross-clamp release and was turned down as tolerated by the animal, insuring that the MAP stayed above 40mmHg.

**Drug Delivery and Monitoring Phase**

After the release from of the supra-celiac aortic cross-clamp the subjects underwent a four hour resuscitation and monitoring phase where they were given intravenous fluids and vasopressors (epinephrine) as needed to keep their MAP above 40mmHg. After release of the cross-clamp the animals were stabilized for 30 minutes. At 30 minutes post cross clamp release we induced a state of hyperfibrinolysis via an injection of 100mg of tissue-plasminogen activator (tPA) through the internal jugular Cordis. This induces an immediate and profound hyperfibrinolytic state as validated previously by our lab, and mechanistically appears similar to human post-traumatic hyperfibrinolytic states that Chapman and colleagues have demonstrated to be secondary to massive endogenous tPA release. After the injection was completed a blood sample was drawn and rotational thromboelastometry (ROTEM) was performed in order to confirm the existence of a hyperfibrinolytic state. Five minutes after the injection of the tPA the animals were given a one gram dose of TXA over ten minutes. This was the only dose of TXA given, and was not followed by a continuous infusion as we wished to assess the response to the single bolus dose only. In the animals that were randomized to the IV group the TXA was given through the right internal jugular cordis. The animals randomized to the IO group received TXA through an IO placed in the tibial plateau.

Hemodynamics and labs values (MAP, pH, lactate, INR) were monitored to assess the animals’ physiologic state at the removal of the cross-clamp, immediately before tPA delivery, 1 hour after cross-clamp removal, and 4 hours after cross clamp removal. ROTEM analysis was
performed immediately after the tPA dose was given, at 1 hour after cross-clamp release (15 minutes after completion of TXA dose), and 4 hours after cross-clamp release.

In order to assess plasma concentrations of TXA we used a custom-made and validated high performance liquid chromatography assay for tranexamic acid levels developed by the University of Washington. To test for serum drug concentrations and establish a pharmacokinetic response curve we drew samples at 0, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes from the start of the TXA infusion in both study groups.

**Statistical Analysis**

All statistical analyses were performed with standard statistical software. T-test analysis was used to determine significance which was determined by a p-value of less than 0.05. A power analysis was conducted by our local biostatistician and it was found that a minimum of eight animals in each arm would be needed to detect differences in serum concentrations and drug effect.

**RESULTS**

Eighteen animals were used to conduct this study, and randomized to one of two groups; IV (N=9) or IO (N=9). Baseline hemodynamic (MAP, HR, Cardiac Index) and laboratory (pH, lactate, base deficit, INR), parameters prior to drug delivery were similar among the two groups (Table 1). After giving tPA all animals became hyperfibrinolytic (Table 1, Figure 1).

**Baseline Hemodynamic and Physiologic Parameters**

At the time of randomization to either the IV or IO arms of the experiments all animals demonstrated shock physiology and there were no differences in the measured baseline characteristics of MAP, pH, lactate, base deficit, or INR. The mean baseline MAP was 48 in the IV arm and 49.5 for the IV arm (p=0.16). The starting pH for the IV group was 7.20 and 7.22 for the IO group (p=0.14). There were also no differences in the baseline lactate, base deficit or INR
of IV and IO arms (lactate 11.3 vs 10.8, p=0.10, base deficit -9.1 vs -8.3, p=0.37, and INR 1.6 vs 1.6, p=0.37).

**Serum TXA Concentration**

Serum TXA concentrations were measured immediately before infusion of the drug and then up to 240 minutes after the completion of the infusion. In both the IV and the IO infusion groups there was an initial spike in serum concentrations that peaked at the 10 minute post TXA infusion lab draw and then slowly tapered off throughout the 4 hours monitoring phase of the experiment. The mean peak concentration in the IV group was 160.9µg/mL and 132.57µg/mL in the IO group (p=0.053). At the end of the 4 hour monitoring phase the serum concentrations of TXA were 20.59 µg/mL and 23.53 µg/mL in the IV and IO groups, respectively. There were no statistically significant differences in serum drug concentrations between IV and IO infusions at any of the measured time points (Figure 2).

**Effect on Fibrinolysis:**

As previously discussed all animals became hyperfibrinolytic after being given the 100mg bolus of tPA with EXTEM lysis index at 30 minutes of 0.88 and 0.22 in the IV and IO groups (p=0.11); the INTEM lysis index at 30 minutes in the IV and IO groups was 0.44 and 0.11 (p=0.14). In both the IV and the IO groups the EXTEM and INTEM lysis indices at 30 minutes corrected with the administration of TXA. In the EXTEM analysis the IV lysis index at 30 minutes corrected to 99.8 from 0.88 and to 100 from 0.22 in the IO group (p=0.44)(Figure 3). Similar results were seen when analyzing the INTEM. The lysis index at 30 minutes corrected from a mean of 0.44 to a mean of 98.4 in the IV group and from a mean of 0.11 to a mean of 98.3 in the IO group (p=0.44) (Figure 4).
DISCUSSION

The benefits of administering TXA and its subsequent decrease on mortality from hemorrhage have been well established in the literature\textsuperscript{9-11}. The benefits of improved survival with earlier administration, and the potential for worse outcomes with administration of the drug after three hours from injury make having a reliable way to infuse the drug as early as possible of paramount importance.\textsuperscript{9} This is even more important for the military austere or other rural settings where both pre-hospital transport and transfer to a tertiary care facility are significantly longer than in the usual urban civilian setting. Both US and international military forces have successfully used intraosseous access for infusions in combat zones\textsuperscript{22-24} and the techniques are used in both adult\textsuperscript{25} and pediatric\textsuperscript{26} civilian trauma patients. Intraosseous access and infusion has become particularly important in the modern military setting due to the change in the predominant mechanism of wounding from standard projectiles to improvised explosive devices. The resultant massive and often multi-system blast injury pattern typically includes multiple mangled or amputated extremities, which makes standard peripheral intravenous access much more difficult or even impossible. The worst of these types of injuries, now commonly referred to as the “dismounted complex blast injury” (DCBI), carries an exceedingly high risk of massive hemorrhage and massive transfusion.\textsuperscript{13,27-29} The current Tactical Combat Casualty Care (TCCC) doctrine emphasizing early hemorrhage control with tourniquets and hemostatic dressings and liberal use of intraosseous access (typically sternal or humeral) has resulted in a significant improvement in battlefield survival, but also a heavier reliance on intraosseous infusion.\textsuperscript{30-32} Therefore, it is critically important to have both clinical and animal data validating the safety and efficacy of fluids or therapeutics administered via this route.

Based primarily off of results from the civilian CRASH-2 and then the military MATTERS-1 and MATTERS-2 studies, the U.S. forward medical treatment facilities began using TXA as an adjunct in patients with major hemorrhage.\textsuperscript{9-11} Similarly, the updated Joint
Trauma System CPG on Massive Transfusion codified this as a theater-wide best practice for both Iraq and Afghanistan. In the civilian trauma community, TXA was also widely adopted in massive transfusion protocols, and subsequently is being studied in the pre-hospital or aeromedical transport phases of care. Among patients in all of these settings who do not have immediate intravenous access, TXA has anecdotally been delivered via an IO route, but without any existing data validating a similar systemic absorption, duration of action, or efficacy for reversing hyperfibrinolysis. In recognition of the lack of data validating the pharmacodynamics and therapeutic efficacy of intraosseous TXA infusion compared to the intravenous route, a 2013 report of a DOD scientific panel identified this as one of the key “gaps” in research for TXA. In response to this well identified gap and our lab’s interest in TXA, we designed this study which is the first to our knowledge that examines the efficacy and pharmacokinetics of TXA when administered via intraosseous infusion in a hemorrhagic shock model. By studying the profile of TXA administered through the intraosseous route, this data provides much-needed scientific evidence to support its safety and efficacy, and allay concerns of a marked alteration of the well-described profile seen with IV administration. In addition, this data provides support (from a pharmacologic standpoint) for the use of TXA in various civilian and military out-of-hospital settings where the need for IO infusion would likely be much greater.

When looking at our data, the peak serum concentration of the IV group trended toward statistical significance, however it did not reach it. The likely mechanism that contributes to this finding is that in a hypovolemic shock state the blood flow to the bone decreases, potentially allowing less of the drug to be absorbed. However, this was only a trend and not statistically significant.

While the peak concentration trended toward significance, from a functional standpoint, it does not seem to matter. When given through an IO the similar serum concentration of the drug is high enough to reverse hyperfibrinolysis, even when in a hypovolemic shock state.
There is data to question the use of TXA in patients without demonstrated hyperfibrinolysis. Moore et al. describe three types of fibrinolysis after trauma, hyperfibrinolysis, physiologic, and fibrinolysis shutdown\textsuperscript{34}. Their group went on to demonstrate that the shutdown phenotype is likely the most common phenotype (46%, compared to 18% for hyperfibrinolysis) and does incur an increased mortality compared to physiologic fibrinolysis; however they also acknowledge the mortality in the setting of hyperfibrinolysis\textsuperscript{35} (34%) is over twice that of physiologic fibrinolysis (14%)\textsuperscript{35} and suggest a selective approach to the administration of anti-fibrinolytic therapy.

While the potential battlefield applications of the intraosseous administrating of TXA, particularly among blast-injured or multiple-amputation patients, are clear, we believe this also has significant civilian trauma applications. There are multiple scenarios where intravenous access, particularly early in the evaluation and resuscitation process, may be difficult or significantly delayed and an IO is required in the meantime. Known factors such as obesity, advanced age, and prior intravenous drug use may complicate attempts at IV access, and in many protocols the next option for immediate access is placement of an IO line. Another obvious civilian application comes in the setting of pediatric trauma, where intraosseous infusion is more commonly required due to the difficulties of IV access in smaller children or babies.\textsuperscript{36} In 2014, Eckert et al. evaluated the use of TXA in a large sample of severely injured pediatric trauma patients from a forward hospital in Afghanistan. While they note that TXA was only given in a small percentage of patients, they found that it was independently associated with a decreased mortality rate and improved survival and neurologic status at discharge. In addition, they also demonstrated no concerning adverse events, thrombotic complications, or medication related complications\textsuperscript{37}.

There are several limitations to our study. The first is the use of animal model. While our ischemia reperfusion model does create a shock physiology and an acidosis, it does not, on
its own create a massive, autologous release of tPA, prompting our use of the drug to create hyperfibrinolysis. The researchers were also not blinded as to which infusion route was performed on each animal. In order to combat any bias the resuscitation of the animals was performed by the veterinary staff during these phases of the experiment. We also did not perform post-mortem tissue analysis of the bone in which the TXA was infused. While we believe the drug would behave similar to other drugs (ie ACLS drugs) infused in this manner we cannot definitively determine that.

Conclusions:

Intraosseous route of infusion is a reliable way to reach effective plasma levels of TXA administered via a single bolus dose. There are clear implications of this finding to tactical combat casualty care (T-CCC) and could be utilized immediately by advanced providers and combat medics who find themselves caring for casualties in austere environments. We also feel that there is an obvious application to the civilian trauma setting, particularly in any setting where IV access can be exceptionally difficult, or in rural/austere settings where transport to a major trauma center and establishment of reliable intravenous access may significantly delay the administration of TXA beyond the currently accepted 3-hour window of early administration.
AUTHOR CONTRIBUTION

All authors meet authorship criteria for this manuscript as described below. All authors have seen and approved the final manuscript as submitted. The senior author (Martin) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Martin, Lallemand, Moe, Loughren, Eckert

Acquisition of data: Martin, Lallemand, Moe, McClellan, Loughren, Marko

Analysis and interpretation of data: Martin, Lallemand, Moe, Loughren, Eckert

Drafting of the manuscript: Lallemand, Martin, Loughren

Critical revision of the manuscript: Martin, Loughren

Statistical expertise: Martin, Lallemand, Moe, McClellan

Administrative, technical, or material support: Marko, Martin, Lallemand, Moe, Loughren

Supervision: Martin, Marko, Eckert
REFERENCES:


FIGURE CAPTIONS AND LEGENDS:

Table 1: Baseline physiologic and hematologic data for test subjects with mean ± standard deviation in IV and IO arms.

Figure 1: Representative ROTEM demonstrating hyperfibrinolysis after administration of 100mg tPA

Figure 2: Plasma concentration curves of TXA.

Figure 3: Representative EXTEM after TXA administration

Figure 4: Representative INTEM after TXA administration
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Table 1. Baseline physiologic and hematologic data for test subjects with mean ± standard deviation in IV and IO arms.