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Tranexamic Acid is Associated with Increased Mortality in Patients with Physiologic Fibrinolysis

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Abstract

Introduction—Tranexamic acid (TXA) administration following trauma has not been proven to improve survival in the US. Trauma patients present to the hospital with a spectrum of fibrinolytic activity, in which a physiologic levels of fibrinolysis are associated with the lowest mortality. We hypothesize that trauma patients who present to the hospital with physiologic levels of fibrinolysis will have increased mortality if they receive TXA.

Material and Methods—Severely injured trauma patients followed prospectively from 2014 to 2016 we included in the analysis. The patient's first thrombelastography (TEG) was used to stratify patients into fibrinolysis phenotypes which included fibrinolysis shutdown, physiologic fibrinolysis, and systemic hyperfibrinolysis. The primary outcome was in hospital mortality.

Results—232 patients were analyzed (11% received TXA) with an overall mortality rate of 20%. TXA administration was associated with a higher new injury severity score (NISS 49 vs 28 $p=0.001$) massive transfusion rate (69% vs 12% $p<0.001$) and mortality (52% vs 17% $p<0.001$). Hyperfibrinolysis and shutdown had higher mortality rates than physiologic (24% vs 30% vs 14% $p=0.050$). The effect of TXA within phenotypes, was not significant for shutdown (28% vs 38% $p=0.604$) but was significant in the physiologic group (11% vs 63% $p<0.001$) and systemic hyperfibrinolysis (19% vs 55% $p=0.023$). After adjusting for NISS, TXA remained a significant predictor of mortality for patients with physiologic fibrinolysis ($p=0.018$).

Conclusion—There was no clear benefit of receiving TXA in this study, and patients who present to the hospital with physiologic levels of fibrinolysis, who received TXA, had the highest

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mortality. The role of TXA in mature trauma systems remains unclear, and emerging data supports it may have adverse effects.

Keywords

Tranexamic acid; Fibrinolysis; Trauma; Trauma Induced Coagulopathy; Fibrinolysis Shutdown

Introduction

Trauma patients present to the hospital with a diverse range of injury patterns and degree of shock which results in a spectrum of fibrinolytic activity (1). A moderate level of fibrinolytic activity is associated with improved survival (2) while high levels of fibrinolysis (hyperfibrinolysis) are associated with increased mortality rates attributed to hemorrhagic death (3–5). Tranexamic acid is an anti-fibrinolytic medication that was associated with a reduction in mortality following trauma in the CRASH-2 trial(6). The protective role of TXA to reverse hyperfibrinolysis in trauma is suggested by a retrospective analysis of TXA use in severely injured patients in which patients in shock benefited from this medication (7), a risk factor for hyperfibrinolysis(1). TXA in elective cardiac (8) and orthopedic(9) surgery has also been associated with a reduction in blood product transfusion.

However, fibrinolysis inhibition (shutdown) after injury is associated with increased mortality(1, 2) and patients that remain in fibrinolysis shutdown for a week following injury have an even higher rate of mortality(10). The protective effect of fibrinolysis to maintain microvasculature patency has previously been demonstrated in animals in near lethal shock(11). Moreover, the potential dangers of blocking fibrinolysis with TXA were recently reported from the Miami group in which there was a two-fold increase in mortality when TXA was used non-selectively (12). It also remains perplexing that there is no benefit of goal-directed TXA use in trauma patients who are hyperfibrinolytic(13). The question remains which patients benefit from receiving this medications, and a selective use has been advocated (14).

The effects of TXA and impact of mortality when taking into consideration a patient's fibrinolytic phenotype have not been assessed previously beyond hyperfibrinolysis (13). While our trauma center emphasizes thrombelastography (TEG) to guide the administration of TXA, clinicians often administer this medication before coagulation tests results are available. As fibrinolysis appears to have a protective effect following severe injury, we hypothesize that TXA in patients with a physiologic level of fibrinolysis will have an increase in mortality compared to other fibrinolytic phenotypes.

Methods

Patient population

Adult trauma patients (age > 18 years) meeting criteria for the highest level of activation at our level 1 trauma center (Denver Health Medical Center/University of Colorado) from 2014 to 2016 with a new injury severity score (NISS) >15 were included in this analysis. All patients had samples collected under protocols approved by the Colorado Multiple

Institutional Review Board for prospective evaluation of coagulation in response to trauma. Patient demographics, injury mechanism, laboratory results, and transfusion requirements were recorded by professional research assistants (PRA) who provide onsite, continuous coverage of the emergency department (ED).

Blood collection

Blood was collected in 3.5-mL tubes containing 3.2% citrate in the ambulance or upon arrival to the ED. Pre-hospital or emergency department (ED) healthcare workers drew study patient blood samples concurrently with the first set of blood samples used for in-hospital laboratory analysis. PRAs performed TEG assays within 2 hours of blood draw. TEGs were drawn for research purposes and not used for clinical management.

Outcomes

PRAs collected all clinical and demographic data on patients from the time they arrived to the ED until discharge or death. Blood transfusion requirements and TXA administration were recorded in the ED to 1, 1 to 2, 2 to 4, 5 to 6, 6 to 12, and 12 to 24 hour intervals from injury. Delayed use of TXA was categorized as TXA used from the 4–6 hour time interval or later. Massive transfusion was defined as >10 units RBC within 6 hours of injury. Mortality was determined during hospitalization, in addition to time from TXA administration to death, and cause of mortality.

Thrombelastography Assays

Viscoelastic assays were completed by a team of trained PRA with extensive experience in multiple types of TEG assays. Citrated blood samples were analyzed using the TEG 5000 Thrombelastography Hemostasis Analyzer (Haemonetics Corp., Niles, IL, USA). The following indices were obtained from the tracings of the TEG: reaction time (*R*-time min.), angle (°), maximum amplitude (MA [mm]), and lysis 30 min after MA (LY30 [%]). Fibrinolysis phenotypes were based on LY30 and previously reported ranges of phenotypes (1); shutdown LY30 <0.9%, physiologic 0.9–2.9%, and hyperfibrinolysis >2.9%.

Statistical Analysis

SPSS version 23 (IBM, Armonk, NY, USA) was used for statistical analysis. TEG measurements and clinical variables are presented as median and interquartile values. Patients who received TXA were contrasted to patients who did not receive TXA with Mann-Whitney U test for continuous variables and chi square or Fisher's exact test for dichotomous variables. Fibrinolysis phenotypes characteristics were contrasted with a Kruskal-Wallis test for continuous variables or chi square/Fisher's exact test for categorical. Alpha was set to 0.05 for all tests. Logistic regression analysis was used to adjust for injury severity between phenotypes. Additional variables to adjust for confounding were not feasible due to limited number of mortalities within phenotypes.

Results

Patient population

During the study time period 232 consecutive trauma activations with a NISS >15 were encountered. The patients were predominantly male (78%), young adults (median 33 years 26–49) with 33% sustaining penetrating injuries, and a median NISS of 33 (IQR 22–47). There were 43 (19%) patients who underwent a massive transfusion, and the overall mortality rate was 20%. TXA was administered in 11% (n=26) of these patients. A second drip of TXA was administered in 7 patients who received their first bolus of TXA without obtaining a second TEG before initiation of the TXA drip. Variables contrasting patients who received TXA versus no TXA are presented in Table 1. Those patients who received TXA were overall more severely injured (NISS 49 vs. 28 $p=0.001$) with a higher rate of massive transfusion (69% vs. 12% $p<0.001$) and mortality (50% vs. 17% $p<0.001$).

Fibrinolysis Phenotype and TXA Administration

Physiologic fibrinolysis was the most common phenotype in this patient population (49%) followed by hyperfibrinolysis (28%) and shutdown (23%). TXA was more commonly administered in hyperfibrinolytic (16%) and shutdown patients (15%) than physiologic (6%), but this administration was not significantly different overall ($p=0.143$). Patients in shutdown and hyperfibrinolysis receiving TXA more frequently and earlier (Log rank $p=0.087$ Figure 1). However, in patients who received TXA, the delayed use of TXA was not significantly different between phenotypes (shutdown 25% physiologic 13% hyperfibrinolysis 20% $p=0.999$).

Blood Product Utilization and TXA

When evaluating patients who required a massive transfusion (n=25 no TXA vs. 17 TXA), patients given TXA received more red blood cells ($p=0.036$), plasma ($p=0.003$), and cryoprecipitate ($p=0.026$) within 24 hours of injury (Table 2). Overall, TXA was not associated with improvement in mortality, when given to patients who required a massive transfusion (non-TXA 40% vs TXA 61% $p=0.346$) despite different, but not significant, NISS between groups [no TXA 38 (34–50) vs TXA 50 (40–57) $p=0.104$]. The median number of red blood cells transfused before or concurrent with TXA use in resuscitation was 9 units (4–16), with a median of 5 units of plasma (3–8) and the majority of patients had not received platelets or cryoprecipitate. Total blood products administered after TXA (until 24 hours after injury) was a median of 2 units of RBC (0–24), 6 units of plasma (0–15), and 1 of unit platelets (0–4), and the majority of patients did not receive cryoprecipitate. However, of the patients who received TXA, 26% went on to require another massive transfusion (10 or more units of RBC within 24 hours of injury after TXA) or were dead within 24 hours of injury. The percent of deaths associated with hemorrhage was higher in patients who received TXA (55% vs. 23% $p=0.060$) but no differences could be assessed within phenotypes due to a low overall number of deaths due to hemorrhage.

TXA Impact on Outcomes

The overall mortality was different between phenotypes ($p=0.050$); hyperfibrinolysis (24%) and shutdown (30%) had higher mortality rates than physiologic (14%). When patients were stratified by TXA vs. non-TXA, non-TXA patients had improved survival (hyperfibrinolysis 19% vs. shutdown 28% vs. physiologic 11% $p=0.023$) compared to no difference in TXA patients (hyperfibrinolysis 56% vs. shutdown 38% vs. physiologic 63% $p=0.585$). The effect of TXA within phenotypes, was not significant for shutdown (28% vs. 38% $p=0.604$) but was significant in the physiologic group (11 vs. 63% $p<0.001$ Figure 2) and hyperfibrinolysis (19% vs. 55% $p=0.023$). After adjusting for injury severity (NISS) TXA remained a significant predictor of mortality for patients with physiologic levels of fibrinolysis ($p=0.018$) but was no longer significant for hyperfibrinolysis ($p=0.116$) and unchanged with shutdown (0.597). When evaluating patients who received at least one unit of blood ($n=120$), the same association of increased mortality in patients who received TXA in physiologic fibrinolysis ($p=0.024$ Figure 3) but not shutdown ($p=0.999$) or hyperfibrinolysis ($p=0.245$). Patients that received a second dose of TXA as a bolus had a mortality rate of 43% which was not significantly different than the overall TXA cohort ($p=0.0665$). In the 13 patients who died after TXA use, 10 clinical TEGs was ordered before TXA was administered and available in the patient's medical record. In this cohort there were only 3 patients with evidence of hyperfibrinolysis on their clinical TEG. In these remaining patients 7 patients TXA was given before completion of LY30 and was ordered most commonly by the trauma surgeon ($n=5$), 1 time by neurosurgery, and 1 time by anesthesia.

Discussion

Despite our institution's protocol of LY30 to guide TXA administration, there were similar percentages of patients with their first TEG reflective of hyperfibrinolysis or shutdown who received this medication, with the lowest number of patients with physiologic levels of fibrinolysis. This administration of TXA without TEG data is likely due to the obligatory time to obtain the LY30 read out, which is nearly an hour after blood is assayed in the Haemonetics 5000 device. In patients who did not receive TXA, physiologic fibrinolysis was associated with the lowest mortality rate. However, TXA was associated with increased mortality in this group, with no effect on shutdown patients, consistent with the hypothesis that a moderate level of fibrinolysis is protective after injury. After adjusting for injury severity, TXA was associated with increased mortality in trauma patients who presented to the hospital in a physiologic state of fibrinolysis, which also persisted when only including patients who received a blood transfusion within 24 hours of injury. TXA was not associated with an overall improvement in mortality in patients whom underwent a massive transfusion. Within the patients who received TXA, bleeding remained the most common cause of death.

Our findings are consistent with the report from the Houston group (13) that TXA did not improve survival in patients who presented with hyperfibrinolysis, and have perhaps identified a population of patients who are harmed by this medications, as described by the Miami group (12). Our results are concerning in that the use of this medication does not appear to be reflective of the patient's fibrinolytic status, rather their physiologic status.

While the temptation to inhibit fibrinolysis in an actively bleeding patient seems rational, it may have lethal consequences. The protective role of fibrinolysis has been proven in animal models in the 1960's. Hardaway demonstrated that irreversible shock was associated with impaired fibrinolysis (15), a process that could be reversed by increasing fibrinolysis (16).

TXA use during massive transfusion was associated with higher overall blood product use compared to those patients who did not receive TXA, but received a MT, and a 26% rate of needing an additional 10 or more units of blood after the medication was given or death within 24 hours of injury. While TXA can reduce plasma fibrinolytic activity within 30 minutes, specific organs can paradoxically have increased fibrinolytic activity early after the medication is given, with some organs having sustained inhibition after plasma levels have appeared to normalize within 90 minutes after administration (17). Thus, administration of this medication may paradoxically increase organ specific bleeding, while causing fibrinolysis shutdown in others. Given that systemic inhibition of fibrinolysis appears to have adverse effects, a role of topical TXA, which in orthopedic surgery has the same efficacy of reducing blood products (18), would be worthy of investigation in future studies.

Alternatives resuscitation strategies can attenuate fibrinolysis in a more physiologic manner, such as plasma first resuscitation. Plasma is an effective buffer of fibrinolytic activity (19) and effectively reverses hyperfibrinolysis and reduces mortality in hyperfibrinolytic rodents (20). This effective colloid also has been shown to enhance metabolic recovery (21) from hemorrhagic shock, restore the endothelial glycocalyx (22), reduce pulmonary injury (23) and reduce gastrointestinal damage (24). Additional blood products that impact fibrinolysis include cryoprecipitate, which has been found to have a similar survival advantage as TXA (25).

There is no current study from the United States that has demonstrated a survival advantage with TXA. The CRASH-2 study (6) was predominantly conducted in developing countries, that did not have the same blood bank capacity as in the United States. Difference in transfusion strategies may also explain why a benefit of TXA is apparent in Europe (7, 26) but not the United States (12, 13). European resuscitation strategies rely on recombinant fibrinogen and prothrombin complex during resuscitation (27). These products do not contain the numerous antifibrinolytic proteins found in plasma (19). In a sense, this European strategy of resuscitation needs an antifibrinolytic therapy during resuscitation, as it may dilute fibrinolytic regulators. The effect of plasma dilution of these regulatory proteins with increased fibrinolysis is evident *in vitro* (19) and clinically (4). Therefore, in the absence of early plasma, TXA may have a role, but is not without some inherent risks to the patient. Furthermore, the majority of severely injured patients may develop a second wave of fibrinolysis resistance after resuscitation, and the time that these patients remain in shutdown is a risk for postinjury complications (28) and mortality (10).

This analysis of trauma patients with the selective use of TXA is inherently biased to treating patients in whom bleeding is not controlled. Despite our institutions algorithm to treat patients based on their TEG LY30 values, a similar number of patients in shutdown received TXA as patients who were hyperfibrinolytic. TXA appeared to be used in dire situations the majority of the time, and may have been used to treat patients who were

bleeding because they were dying, and not dying from bleeding. This question has been investigated previously, finding the majority of trauma deaths from hemorrhage are not attributed to TIC (29). TXA does not inhibit major bleeding, as was documented in the current data because 26% of these patients were dead or underwent a massive transfusion after TXA was delivered.

While studies in the past have suggested a modest improvement in survival when using this medication, the benefit may not be applicable to mature urban trauma centers (6, 25). More importantly, trauma patients present to the hospital with a spectrum of coagulation abnormalities (30, 31). Individualized coagulation resuscitation guided by viscoelastic assays reduces mortality by 50% in patients undergoing massive transfusion (32). Employing a goal-based resuscitation strategy can improve mortality as opposed to resuscitation with fixed ratios of red blood cells, plasma and platelets which does not improve overall survival (33). Finally, trauma patients do not share the same pathophysiology as elective surgery. TXA has been shown to reduce blood loss in elective surgery (34), however, in the setting of massive bleeding from injury where profound tissue ischemia exists there does not appear to be the same beneficial effect. This study is also limited to 26 patients whom received TXA and has limited power to control for multiple potential confounding variables. As previously discussed, the increase in mortality in patients who received TXA could be related to a last ditch effort to salvage patients, rather than a direct cause of increased mortality.

While this study represents a single center experience, the results are consistent with previously published literature in the United States that TXA use does not benefit all trauma patients. Several multicenter randomized control trials with TXA in trauma are currently being conducted in the United States in a variety of clinical settings, which further support that the indications for using this medication remain unclear. Until the results of these studies are available, empiric use of TXA in trauma patients in this country remains a questionably beneficial practice.

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Figure 1. Timing of TXA per Phenotype

Figure 1 the temporal association of the administration of TXA after injury is shown stratified by fibrinolysis phenotype. The Y axis represents the cumulative incidence of patients that received TXA, while the X axis represents time from injury until the patient received this medication. No patient received TXA beyond 9 hours from injury.

Figure 2. TXA Effect on Mortality between Phenotypes

*=P<0.05; Hyper = hyperfibrinolysis

Figure 2 The non-adjusted association between phenotypes and mortality contrasting the effects of tranexamic acid is shown. The Y axis represents the percent mortality and X axis are fibrinolysis phenotypes. In the shutdown phenotype there were 54 patients (8 received TXA), in the physiologic phenotype there were 114 patients (8 received TXA), and in the hyperfibrinolytic phenotype there were 64 patients (10 received TXA).

Figure 3. TXA Effect on Mortality between Phenotypes in Patients Requiring Blood Product Resuscitation

*= $P < 0.05$; Hyper = hyperfibrinolysis

Figure 3 The association between fibrinolytic phenotypes and mortality contrasting the effects of tranexamic acid on patients required blood products during resuscitation is illustrated. The Y axis represents the percent mortality and X axis are fibrinolysis phenotypes. In the shutdown phenotype there were 33 patients (8 received TXA), in the physiologic phenotype there were 48 patients (8 received TXA), and in the hyperfibrinolytic phenotype there were 39 patients (10 received TXA).

Table 1

Patients Receiving TXA Compared to No TXA

	No TXA (n=206)	TXA (n=26)	P
Age	34(27–49)	27 (24–54)	0.214
Male	77%	85%	0.362
Penetrating	32%	42%	0.377
NISS	29 (22–43)	48 (29–57)	0.001
INR	1.2 (1.1–1.3)	1.4 (1.2–1.8)	<0.001
Plt Count	255 (209–305)	166 (133–237)	<0.001
TEG- ACT	121 (113–132)	128 (121–136)	0.010
TEG- Angle	71 (66–75)	63 (60–72)	0.003
TEG- MA	62 (57–67)	54 (48–59)	>0.001
TEG-LY30	1.9 (1.0–2.9)	2.1 (0.6–9.4)	0.324
Massive Transfusion	12%	69%	<0.001
Mortality	17%	50%	<0.001

Table 2

Blood Product use in Patients Undergoing MT

	No-TXA (n=25)	TXA (n=18)	P
RBC	19 (13–28)	28 (17–51)	0.036
FFP	8 (6–15)	15 (14–28)	0.003
PLT	2 (1–3)	3 (2–9)	0.124
CRYO	0 (0–2)	2 (1–4)	0.024
NISS	38 (34–50)	50 (39–57)	0.104
Mortality	40%	61%	0.346