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February 6, 2018

Howard Backer, MD, MPH, FACEP, Director
Emergency Medical Services Authority
10901 Gold Center Drive, Suite 400
Rancho Cordova, CA 95670

Dear Dr. Backer:

On behalf of Doctors Benson, Neeki, Sporer and myself, please accept this report on the trial study "*Tranexamic Acid in Prehospital Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study*".

We are prepared to present this at the March 21, 2018, Commission on EMS meeting with the recommendation to add Tranexamic Acid to Local Optional Scope of Practice for Paramedics in California.

If you have any questions or need additional information, please do not hesitate to contact me.

Sincerely,

Reza Vaezazizi, MD
Medical Director

RV/jlm

Enclosure

c: Peter Benson, MD, Napa County EMS
Michael Neeki, MD, Arrowhead Regional Medical Center
Karl Sporer, MD, Alameda County EMS
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Tranexamic Acid in Prehospital Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study

FINAL REPORT

February 6, 2018

Prepared for:
State EMS Authority

By:
Michael Neeki, MD, Arrowhead Regional Medical Center

Reza Vaezazizi, MD, Medical Director
Inland Counties Emergency Medical Agency/ Riverside County Emergency Medical Services Agency

Tranexamic Acid in Prehospital Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study

Short title: **TXA in Prehospital Traumatic Hemorrhagic Shock**

Word Count: 3,780

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No conflicts of interest.

This manuscript has not been presented at prior conferences or meetings.

No funding was received.

ABSTRACT

BACKGROUND: The California Prehospital Antifibrinolytic Therapy (Cal-PAT) study seeks to evaluate the safety and efficacy of TXA use in the civilian prehospital setting in cases of traumatic hemorrhagic shock.

METHODS: The Cal-PAT study is a multi-centered, prospective, observational cohort study. From March 2015 to July 2017, patients ≥ 18-years-old who sustained blunt or penetrating trauma with signs of hemorrhagic shock identified by first responders in the prehospital setting were considered for TXA treatment. A control group was formed of patients seen in the five years prior to data collection cessation (June 2012 to July 2017) at each receiving center who were not administered TXA. Control group patients were selected through propensity score matching based on gender, age injury severity scores, and mechanism of injury. The primary outcome measured was mortality. Secondary outcomes measured included the total blood products transfused, the hospital and intensive care unit length of stay, and the incidence of known adverse events associated with TXA.

RESULTS: A total of 724 patients were included in the final analysis, with 362 patients in the TXA intervention and control group. Improved mortality was noted at 28-days in the TXA intervention in comparison to the control group (3.6% vs 8.3% for TXA intervention and control, respectively, $p<0.0075$). The mortality difference was greatest in severely injured patients. A trend toward a decreased mortality at 24-hours and 48-hours was also observed in the TXA intervention group, although these differences were not statistically significant (1.9% vs 3.6%, $p=0.1737$, and 2.8% vs 4.4%, $p=0.2308$, respectively). Furthermore, a significant reduction in total blood product transfused was observed after TXA administration ($p<0.0001$).

CONCLUSIONS: Findings from the Cal-PAT study suggest that TXA use in the civilian prehospital setting may safely improve mortality outcomes in patients who have sustained traumatic injury with signs of hemorrhagic shock.

Introduction:

In the United States, traumatic injury is the leading cause of death and disability among those aged one to 44 years old.[1] Amongst trauma victims, hemorrhage accounts for 30% to 40% of the mortality.[2-4] Within the prehospital setting, hemorrhage is one of the top causes of death and comprises the largest portion of preventable deaths.[2,3] Significant blood volume loss leads to the depletion of coagulation factors and activation of the coagulation system. Combined, these factors threaten the body's ability to maintain hemodynamic stability and may result in cardiovascular collapse. The burden of trauma-induced acute coagulopathies has been demonstrated in more than half of trauma patients following arrival to trauma centers and has been associated with a significant increase in the risk of trauma-induced mortality.[5-9] Historically, paramedics have not had access to medications that specifically target the reversal of acute coagulopathies secondary to trauma.[3,4] As biotechnological advances enable better detection and understanding of trauma-induced coagulopathies, a significant portion of patients have been identified that may benefit from early reversal of traumatic coagulopathies, leading to a possible reduction in associated mortality.[10-12]

Tranexamic acid (TXA) is a synthetic derivative that inhibits fibrinolysis and has been shown to be efficacious when administered in the hospital setting in the treatment of hemorrhagic shock. In 2010, the CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2) study suggested that TXA was associated with a 1.5% reduction (14.5% vs. 16%) in all-cause mortality at 28 days when administered within eight hours of injury without an increase in thromboembolic events.[13] In 2011, a post-hoc analysis showed that early TXA treatment within three hours from the time of injury in the hospital setting resulted in a

1.6% decrease in death due to bleeding; the reduction in mortality increased to 2.4% if administered within one hour from injury.[14]

Despite evidence surrounding TXA use in the hospital setting, a gap in knowledge exists surrounding the prehospital use of TXA in the civilian setting. Multiple small studies have demonstrated the feasibility of TXA administration in the prehospital setting and ability of paramedics to identify signs of hemorrhagic shock.[15-18] Two recent investigations focusing on civilian injuries in Germany and Japan further suggest that prehospital TXA use may reduce mortality in severely injured trauma victims.[19,20] The retrospective nature of these studies and lack of standardized dosages and algorithms for TXA administration limits the generalizability of these findings. This paucity of data has limited the widespread implementation of TXA in the United States civilian prehospital setting.

The California Prehospital Anti-fibrinolytic Therapy (Cal-PAT) study was designed to evaluate the safety and efficacy of TXA use in the civilian prehospital setting in cases of traumatic hemorrhagic shock. A preliminary report during ongoing data collection from the Cal-PAT study was published in 2017.[21] The current study updated the original Cal-PAT findings following expanded data collection.

METHODS:

Cal-PAT Study Overview

The Cal-PAT study is a multi-centered, prospective, observational cohort study. The study was initiated in March 2015 in two Southern California counties – San Bernardino and Riverside. In early 2016, Alameda County joined the study. All eight receiving centers are designated Level I and Level II county trauma centers. A total of 30 EMS agencies were

involved across all counties. Current data collection for this study in all counties concluded in July 2017. Notably, Napa County joined the study in 2016; however, no administration of TXA was recorded during this study period. All prehospital protocols were approved by the California Emergency Medical Services Authority (EMSA) and carried out with close supervision and oversight at both the local and state level. Hospital TXA administration protocols were approved by the Institutional Review Boards of each participating receiving trauma center. At each institution, TXA was incorporated into the massive transfusion protocol as a standard of care for trauma patients.

Data collection, Protocols, Outcomes

All patients ≥18-years-old who sustained blunt or penetrating trauma with signs and symptoms of hemorrhagic shock were considered for TXA treatment upon meeting inclusion criteria (Table 1). Patients receiving TXA were enrolled into the TXA intervention group. Patient selection in the prehospital setting was determined by paramedics on ground ambulances and by registered nurses on helicopter transport units. Paramedics and registered nurses underwent a standardized training session that included guidelines for TXA candidate identification, protocol for TXA administration, and the medication side effect profile. They were also educated on the inclusion and exclusion criteria of this study and had access to real-time consultation with physicians at the participating trauma centers to address any concerns regarding patient selection or TXA administration.

TXA was delivered in two doses following the protocol utilized in the CRASH-2 trial.[13,22] The first dose was 1 gram of TXA in 100 ml of 0.9% normal saline infused over 10 minutes via intravenous or intraosseous access. This first dose was administered by ground paramedics or registered nurses as soon as feasible after patient assessment and screening.

Identification of study patients receiving TXA was achieved through a wristband labeled “TXA”, verbal communication at patient hand off by EMS, and/or by EMS run sheet. Following arrival to a participating trauma center, patients who received prehospital TXA were identified and re-assessed by trauma team members for signs of continued hemorrhagic shock. Patients that continued to meet the study criteria (Table 1) received a second dose of 1 gram of TXA in 100 ml of 0.9% normal saline infused over eight hours via intravenous infusion. A patient may have received only one dose of TXA if they arrived to the trauma center and no longer met study inclusion criteria (Table 1). Patients who were deceased upon arrival (declared dead on arrival with minimal resuscitation effort or failed to respond to resuscitation after 15 minutes in the ED), those who received TXA for non-trauma indications, and those who received TXA and were determined to be less than 18 years old upon arrival were excluded from the study.

The control group was formed of patients seen at each receiving center within five years prior to the conclusion of data collection for this report (June 2012 to July 2017). Patients included those who were not administered TXA because they were brought in by an EMS provider group not carrying TXA or because they were transported to the hospital by any means other than a designated EMS provider (e.g. friends, family, self). The control group patients met the same study criteria (Table 1) as those in the TXA intervention group. The control group patients were matched to TXA intervention group patients through utilization of propensity scoring based upon gender, age, injury severity score (ISS), and mechanism of injury.

The primary outcome of this study was mortality, measured at 24 hours, 48 hours, and 28 days. Secondary outcomes included total blood products transfused during resuscitation efforts and during the hospital stay, the hospital and intensive care unit (ICU) length of stay, and the incidence of known adverse events associated with TXA administration including

thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism), myocardial infarction, and neurological events (e.g. stroke, seizure).

Statistical Analysis

All statistical analyses were conducted using the SAS software for Windows version 9.3 (Cary, North Carolina, USA). Descriptive statistics were presented as means and standard deviation for continuous variables, along with frequencies and proportions for categorical variables. Chi-square analyses were conducted to identify if there is a difference on the mortality at 24 hours, 48 hours, and 28 days between the control and intervention groups. Independent T-tests were conducted to identify whether there were differences of continuous variables (e.g., age) between the control and intervention groups. Wilcoxon rank sum tests were conducted to identify whether the median of some continuous variables (e.g., hospital length of stay) was different between the control and intervention groups. Three subgroup analyses were conducted to assess outcomes of patients, including (1) those who received one dose of TXA in comparison to two doses of TXA; (2) those who were severely injury (ISS $\geq$16), and (3) those who sustained significant blood loss ($\geq$10 units of total blood products transfused). All statistical analyses were two-sided. P-value<0.05 was considered to be statistically significant.

Results:

A total of 362 patients were included in the final intervention group (Figure 1). To eliminate the confounding effect of age, ISS, and mechanism of injury, a propensity matching was conducted based on these three factors to select 362 patients as the control group. As a result, 724 patients were included in the final analysis. As expected per the propensity matching process, there was no statistically significant difference in age (37.96 vs 37.64 years for intervention and control, respectively, p=0.7904), ISS (16.08 vs 17.15 for intervention and

control, respectively, p=0.2009), and mechanism of injury (percentage of blunt trauma was 36.4% for both intervention and control, respectively, p=1).

Clinical outcomes were compared between the intervention and control group. The analysis results were presented in Table 2. Analysis demonstrated a trend toward a lower mortality rate in the intervention group at 24 hours (1.9% vs 3.6%, p=0.1737), 48 hours (2.8% vs 4.4%, p=0.2308), and 28 days (3.6% vs 8.3%, p<0.0075). The overall mortality at 28 days yielded a statistically significant difference between the intervention and control group. Additionally, the intervention group received fewer units of total blood products transfused (median of 1 vs 3 units, p<0.0001), had shorter hospital length of stay (median of 4 vs 8 days, p<0.0001), and shorter intensive care unit (ICU) length of stay (median of 4 vs 5 days, p=0.0047). No differences in the incidence of thromboembolic, myocardial infarction, or neurologic events were noted between the intervention and control group.

A subgroup analysis was conducted to identify the difference between patients who received one dose versus two doses of TXA. The analysis results were presented in Table 3. Compared with patients who received one dose of TXA, those who received two doses of TXA required more blood transfusions (median of 0 vs 3 units of blood product, p<0.0001). There is no statistically significant difference on mortality, hospital and ICU LOS between one dose versus two doses of TXA.

A second subgroup comparison of intervention versus control was conducted among patients who required massive transfusion (≥ 10 units of blood product). The analysis results were presented in Table 4. The intervention group showed a trend toward lower mortality at 24 hours (5.6% vs 8.7%, p=0.4819) and 48 hours (7% vs 13%, p=0.2367). The overall mortality at 28 days (8.5% vs 23.2%, p=0.0166) yielded a statistically significant difference between the

intervention and control group. There is no statistically difference on other clinical outcomes, including total blood products transfused, hospital and ICU LOS, between the intervention and control group (all p-values>0.05).

A third subgroup comparison of TXA versus control was conducted among patients with ISS score ≥ 16. The analysis results were presented in Table 5. The intervention group had lower mortality at 24 hours (4.2% vs 4.7%, p=0.8278), 48 hours (5.4% vs 6.4%, p=0.6842). The overall mortality at 28 days (6% vs 14.5%, p=0.0092) yielded a statistically significant difference between the intervention and control group. There is no statistically difference in other clinical outcomes, including total blood products transfused, hospital length of stay, and ICU length of stay between the control and TXA groups (all p-values>0.05).

Lastly, the median time for paramedics to administer TXA from the estimated time of injury was 33 minutes (interquartile range: 26 min, 46 min).

DISCUSSION

This prospective investigation examining the use of prehospital TXA in cases of traumatic hemorrhagic shock suggests that prehospital TXA use is associated with improved mortality outcomes. Reduced mortality was demonstrated at 28 days and a trend toward reduced mortality was noted at 24 and 48 hours. To our knowledge, this is the first large-scale civilian study to systematically examine prehospital TXA administration in trauma patients in the North America.

Reduced mortality noted in this study may be attributed to the antifibrinolytic properties of TXA. Though disputed in the literature, evidence suggests that up to 15% of trauma patients may be in a state of hyperfibrinolysis at the scene as noted on rotational thromboelastometry

(ROTEM) while more than half of trauma patients may be in a state of moderate to severe fibrinolysis upon arrival to the hospital.[5,7-9,12,23] These coagulopathies often begin within minutes of injury and worsen during transportation from the scene to the hospital.[7,9,12] This can threaten clot integrity and result in increased blood loss, morbidity, and mortality.[8,9] The antifibrinolytic properties of TXA may act to slow or stop progression of coagulopathies that contribute to excessive blood loss and disruption of hemodynamic stability. The current study showed a reduction in the total blood products transfused in those administered TXA. However, TXA appears to exert an effect beyond 24 hours, after the risk of bleeding has decreased.[3] This may be a result of the antiinflammatory effects of TXA that are mediated through a reduction in the magnitude of the plasmin level, thus reducing the pro-inflammatory effect of plasmin.[24,25] This may be responsible for the observed trend toward decreased mortality at 48 hours and greater. Though the exact mechanism is not clear, current evidence demonstrates that the therapeutic mechanism of TXA is likely multifactorial in nature.

In particular, severely injured trauma patients appear to benefit most from TXA. This may be attributed to an increased incidence of acute coagulopathies among patients who have sustained severe traumatic injury as detected on ROTEM.[7,9,26] Kunze-Szikszay et al. assessed for acute coagulopathies noted on ROTEM in severely injured trauma patients before and after prehospital TXA administration.[12] Despite no ROTEM changes following prehospital TXA, authors concluded that TXA might have reduced unnecessary fibrinogen consumption due to fibrinolysis after comparing the results to those of Theusinger et al.. This study showed significant deterioration of relevant ROTEM clot parameters between the scene and hospital when TXA was not administered.[7] However, the study by Kunze-Szikszay et al. was limited by a small sample size. Additionally, Moore et al. demonstrated that TXA use in severely injury

patients might result in adverse outcomes in select patients in a state of fibrinolysis shutdown or hyperfibrinolysis.[8] Nonetheless, multiple other investigations of TXA use in the civilian prehospital and hospital setting found that TXA was most beneficial amongst severely injured trauma patients.[19,20,27] Two additional retrospective studies of adults and children injured in the combat setting, the MATTERS (Military Application of Tranexamic Acid in Trauma Emergency Resucitation) study and PED-TRAX (Pediatric Trauma and Tranexamic Acid), respectively, echoed this observation as well.[28,29] Though TXA use in severely injured trauma patients may be beneficial, it appears both the exact candidate selection criteria and mechanism of action conferring benefit remain unclear.

To date, CRASH-2 represents the only randomized controlled trial assessing TXA in civilian adult trauma.[13] Investigators enrolled 20,211 adult trauma patients with signs of hemorrhagic shock across 274 hospitals in 40 countries. The CRASH-2 findings suggested that TXA given in the hospital within three hours of injury led to a significant decrease in all-cause mortality at 28 days. Yet, the effectiveness and impact of the CRASH-2 conclusions are controversial.[23,30] Lack of standardized inclusion protocols between hospitals, many of which were part of underdeveloped trauma systems, along with unclear reporting of adverse events and other variables has contributed to the unclear nature of the CRASH-2 findings. Additionally, few retrospective and prospective studies with varying conclusions regarding the impact of prehospital TXA use have further contributed to the slow implementation of TXA in trauma systems within the United States and other developed countries.[19,20]

In regards to assessing the known side effect profile associated with TXA use, the majority of studies note a limited incidence of adverse events. Though controversial, the CRASH-2 trial reported no increase in thromboembolic events in patients given TXA in the

hospital setting.[13] Among other observational studies assessing prehospital TXA in the civilian setting, no increase in multiple organ failure, sepsis, or thromboembolic events were noted.[19,20] Notably, the MATTERs study noted a slight increase in thromboembolic events in patients administered TXA; however, authors postulated that a higher injury burden within the combat setting may be associated with an increased incidence of thromboembolic events.[12] The current study showed no increase in thromboembolic events, myocardial infarctions, or neurologic events among patients receiving TXA. In one case in this study, a young male patient who received TXA following a head-on, high-speed, motor vehicle accident with multiple long bone fractures experienced a hemisphere ischemic stroke forty hours after admission. Repeat computed tomography (CT) scan of his head revealed a new large ischemic infarct in the right middle cerebral artery distribution with moderate mass effect and midline shift. Suspecting traumatic vascular injury, a computed tomography angiography (CTA) study was ordered but not completed after a family decision to instate a do not resuscitate (DNR) order. Without this definitive imaging study, a thromboembolic complication secondary to TXA could not be ruled out; however, it was considered remote since its relationship with respect to presentation and timing make it unlikely. An additional case of ischemic stroke occurred in an elderly individual following a high-speed motor vehicle accident where the patient presented with altered mental status, scalp lacerations and a possible small subdural hematoma as well as multiple long bone fractures. On hospital day two, the patient was diagnosed with an ischemic stroke which neurosurgery attributed to fat emboli from long bone fractures. Similar to the previous case, a severe mechanism of injury leading to an ischemic stroke with likely etiology made an adverse event directly resulting from TXA administration less likely. Additionally, no increase in

hospital or ICU stay was noted in the current study, further supporting a relatively non-complicated course among patients administered TXA.

The exact dosing of TXA in the setting of traumatic injury remains unclear.[23] A fixed 1 gram dose administered in the field followed by a possible maintenance dose was deemed most practical in an emergency situation.[13] In the current study, 64.9% of patients were only administered the first dose of TXA. This may have occurred when a patient no longer satisfied the inclusion criteria for a second TXA dose upon arrival to a participating trauma center, or less often, due to lack of adherence to research protocol. No difference in mortality was observed between those receiving one dose versus two doses of TXA; however, this observation may be limited by a small sample size. Nonetheless, if sufficient antifibrinolytic and antiinflammatory effects occur with only a single dose of TXA, this challenges the apparent need for a maintenance dose. The exact half-life and duration of action is unclear in present literature; few past reports have indicated two to eight hours depending on the dosage.[31-33] Further studies are warranted to determine the optimal dosage following traumatic injury.

This study emphasizes the feasibility and effectiveness of prehospital TXA administration within a developed trauma system. In the majority of cases, first responders (e.g. paramedics and registered nurses) were able to accurately identify TXA candidates within the prehospital setting and effectively administer TXA. This adds to a growing body of literature supporting the feasibility of prehospital TXA administration within developed trauma systems.[15-20] TXA is also a highly cost effective drug. For this study, one dose of TXA cost between $16 to $50 depending if it was administered in the prehospital or hospital setting. In comparison, the raw cost for one unit of pRBCs is approximately $210.74 with the mean charge to the patient of $343.63.[34] With regards to mortality at 28 days in this study, the number needed to treat (NNT)

was 22 (NNT at 24 hours and 48 hours was 59 and 63, respectively). To place this in context, the number of patients requiring treatment with TXA to achieve a mortality benefit of 1 was 22 patients. Coupled with the potential reduced transfusion among patient administered TXA that was observed in this study, TXA appears to represents a cost effective means to reduce the health care system financial burden as well as improve trauma mortality outcomes overall.

Lastly, our study did not employ coagulation testing before prehospital TXA administration to determine if patients were indeed in a state of hyperfibrinolysis. This significantly limited our ability to administer TXA in a selective fashion. Given the study design and current limitations of point-of-care thromboelastography (TEG) or ROTEM testing, it would have been infeasible to employ such testing in the prehospital setting. Further, previous studies note the incidence of moderate to severe fibrinolysis at the scene and upon hospital arrival to be over 50%, with fibrinolysis steadily worsening from the scene to the hospital when measured on ROTEM.[7,9] Theusinger et al. concluded that monitoring coagulation via ROTEM at the scene of a trauma would not provide any clinically significant information in the majority of trauma patients.[7] However, upon arrival to the receiving center, growing, but weak, evidence exists suggesting that point-of-care TEG or ROTEM may guide in any additional TXA dosing and blood product administration in critically ill patients.[35] At present, we feel that administering TXA empirically to those with signs of hemorrhagic shock is an effective practice until further prehospital point-of-care diagnostic techniques are available.

LIMITATIONS:

Multiple limitations exist within our study. First, this study was limited by design. The prospective, non-randomized cohort design in comparison did not allow TXA to be administered

in a blinded fashion. Prehospital providers and physicians were aware that TXA had been administered, which may have introduced a slight bias related to the level of care provided. However, we anticipate this to have minimal effect on study outcomes as standard Advanced Life Support and Advanced Trauma Life Support guidelines were followed with all trauma patients.

Second, this study relied upon prehospital providers ability to accurately recognize signs of trauma-related hemorrhagic shock in the prehospital setting, even if active external bleeding was not present. Despite thorough didactic training, high injury acuity and/or inexperience may have resulted in some providers improperly including or excluding TXA candidates. Incidences of improper exclusion were noted during the initial months after implementation and future incidences were reduced through active troubleshooting, quality control, and education sessions. EMS teams were also backed by real-time physician consultation to provide added assistance; this teamwork approach was instituted to minimize the possibility of inappropriate TXA administration.

CONCLUSION:

The current study noted reduced mortality following the administration of prehospital TXA to patients with signs of traumatic hemorrhagic shock. We further noted a decrease in blood product transfused and shorter hospital and ICU LOS, without an increase in thromboembolic events. Finally, this study demonstrated that TXA can be effectively and feasibly administered by civilian prehospital providers and in accordance with North American emergency medicine protocols and standards. Our findings support the use of prehospital TXA in adult civilian trauma in the setting of traumatic injury with signs of hemorrhagic shock.

Author contribution: MMN and JP conceived the study. MMN, FD, JP, R Vaezazizi, DW, RB, EK, contributed to the designed of the study and development of study protocols. For each region involved, those individuals from that county further contributed to the design of study protocol and data collection within that region; these individuals include MMN, R Vara, R Vaezazizi, JP, SK, XLO, SB, KRO, DL, KS. MMN, FD, R.Vara, JT, R.Vaezazizi, AJ, NN, MR, were involved in data collection and database compilation. FD performed statistical analyses. MMN, FD, JT, MM, drafted the initial manuscript and all authors contributed significantly during the revision process. MMN managed all aspects of the study.

Acknowledgements: We acknowledge the efforts of Joy Peters, RN, Sonny Alforja, RN, Charles W. Hendra, RN, BSN, Sharon Brown, RN, MSN, and Tyler Jaques for their help with data collection and database compilation. We thank Daved Van Stralen, MD, for his work in designing the first responder TXA education module. We thank Carlos Peace, RN, BSN for his help with editing of the manuscript. We thank Sandra Kolodzik, EMT-P for compiling the report for the Emergency Medical Directors Association of California meeting. We further thank Kenji Inaba MD for his advisory role and editing of the manuscript. We are grateful to Emergency Medical Services Authority (EMSA) their guidance to prepare for this study. Additionally, we would like to send a special thank you to the men and women of all the air and ground emergency medical service agencies in the San Bernardino, Riverside, Alameda, and Napa County regions who are currently participating in the Cal-PAT study.

Table 1: Inclusion and exclusion criteria provided to first responders in the field and clinicians at receiving trauma centers.

Inclusion Criteria	**Exclusion Criteria**
The prehospital and hospital use of TXA should be considered for all trauma patients that meet **any** of the following criteria: • Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock within three hours of injury. o Systolic blood pressure of less than 90 mmHg at scene of injury, during air and/or ground medical transport, or upon arrival to designated trauma centers. o Heart rate >120. o Estimated blood loss of 500 milliliters in the field o Bleeding not controlled by direct pressure or tourniquet. Major amputation of any extremity above the wrists and above the ankles.	• Any patient <18 years of age • Any patient more than three hours post-injury • Any patient with an active thromboembolic event (within the last 24 hours) – i.e. active stroke, myocardial infarction or pulmonary embolism • Any patient with a hypersensitivity or anaphylactic reaction to TXA • Traumatic arrest with more than five minutes of cardiopulmonary resuscitation without return of vital signs • Penetrating cranial injury • Traumatic brain injury with brain matter exposed • Isolated drowning or hanging victims • Documented cervical cord injury with motor deficits

*TXA = tranexamic acid

Table 2: Patient outcomes for the control and TXA intervention groups.

	Control Group (n=362)	Intervention Group (n=362)	P-value
Mortality at 24 hours			0.1737
Dead	13 (3.6%)	7 (1.9%)	
Mortality at 48 hours			0.2308
Dead	16 (4.4%)	10 (2.8%)	
Mortality at 28 days			0.0075
Dead	30 (8.3%)	13 (3.6%)	
Total blood products transfused (in units), Median (Q1, Q3)	3 (2, 8)	1 (0, 6)	<0.0001
Hospital LOS (in days), Median (Q1, Q3)	8 (5, 15)	4 (1, 12)	<0.0001
ICU LOS (in days), Median (Q1, Q3)	5 (3, 8)	4 (2, 8)	0.0047
Mechanism of Injury			1
Blunt trauma	134 (37%)	134 (37%)	
Penetrating trauma	228 (63%)	228 (63%)	
Gender			1
Female	69 (19.1%)	69 (19.1%)	
Male	293 (80.9%)	293 (80.9%)	
Age, years, mean ± SD	37.64 ± 16.33	37.96 ± 16.11	0.7904
Injury severity score, mean ± SD	17.15 ± 11.71	16.08 ± 10.69	0.2009

*TXA = tranexamic acid; LOS = length of stay; ICU = intensive care unit

Table 3: Subgroup analysis of the TXA intervention group.

	Pre-hospital 1 Dose of TXA (n=235)	1 Pre-hospital + 1 hospital dose of TXA (n=127)	P-value
Mortality at 24 hours			0.7155
Dead	5 (2.1%)	2 (1.6%)	
Mortality at 48 hours			0.3108
Dead	8 (3.4%)	2 (1.6%)	
Mortality at 28 days			0.74
Dead	9 (3.8%)	4 (3.2%)	
Total blood products transfused (in units), Median (Q1, Q3)	0 (0, 3)	3 (0, 13)	<0.0001
Hospital LOS (in days), Median (Q1, Q3)	4 (1, 10)	6 (2, 15)	0.0564
ICU LOS (in days), Median (Q1, Q3)	3 (2, 5)	4 (2, 12)	0.0759
Mechanism of Injury			0.4954
Blunt trauma	84 (35.7%)	50 (39.4%)	
Penetrating trauma	151 (64.3%)	77 (60.6%)	
Gender			0.473
Female	47 (20%)	22 (17.3%)	
Male	188 (80%)	105 (82.7%)	
Age, years, mean ± SD	37.53 ± 16.57	38.76 ± 15.25	0.4866
Injury severity score, mean ± SD	15.69 ± 10.77	16.81 ± 10.53	0.3412

*TXA = tranexamic acid; LOS = length of stay; ICU = intensive care unit

Table 4: Subgroup analysis of patients receiving ≥10 units of blood product.

	Massive Transfusion (n=140)		
	Control Group (n=69)	TXA Group (n=71)	P-value
Mortality at 24 hours			0.4819
Dead	6 (8.7%)	4 (5.6%)	
Mortality at 48 hours			0.2367
Dead	9 (13%)	5 (7%)	
Mortality at 28 days			0.0166
Dead	16 (23.2%)	6 (8.5%)	
Total blood products transfused (in units), Median (Q1, Q3)	20 (14, 31)	18 (14, 32)	0.8662
Hospital LOS (in days), Median (Q1, Q3)	10 (6, 14)	13 (5, 22)	0.3181
ICU LOS (in days), Median (Q1, Q3)	6 (4, 8)	5 (3, 14)	0.4544
Mechanism of Injury			0.0013
Blunt trauma	16 (23.2%)	35 (49.3%)	
Penetrating trauma	53 (76.8%)	36 (50.7%)	
Gender			0.0624
Female	6 (8.7%)	14 (19.7%)	
Male	63 (91.3%)	57 (80.3%)	
Age, years, mean ± SD	35 ± 14.68	37.87 ± 15.49	0.2622
Injury severity score, mean ± SD	23.46 ± 14.96	21.39 ± 10.51	0.344

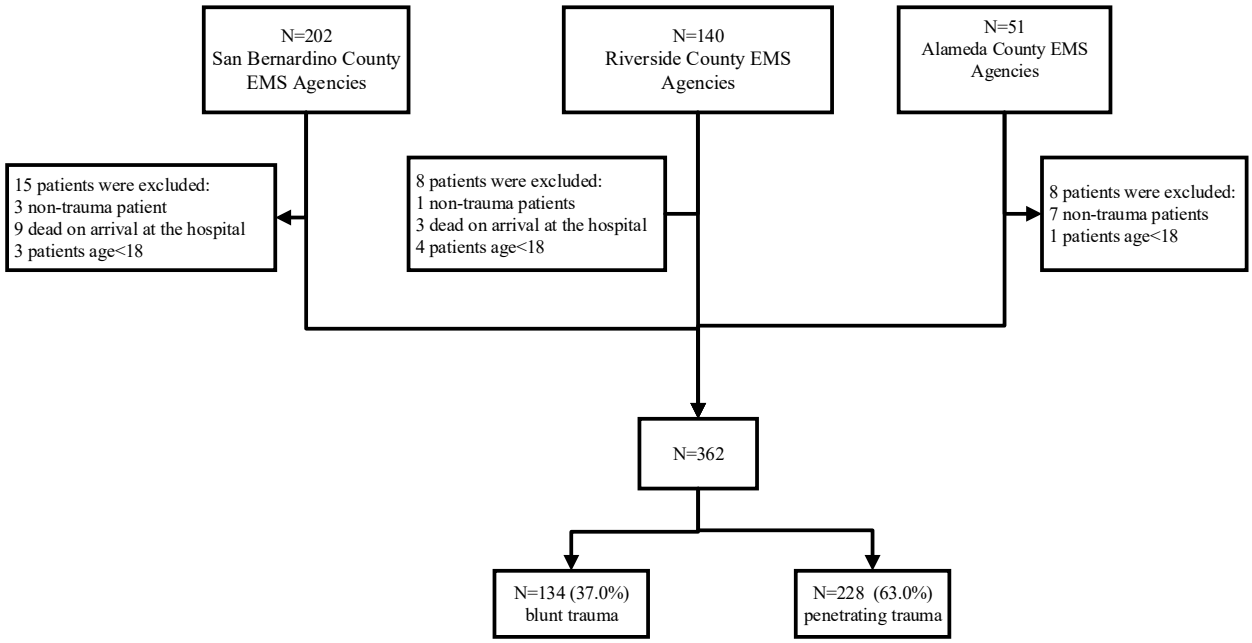
*TXA = tranexamic acid; LOS = length of stay; ICU = intensive care unit

Table 5: Subgroup analysis of patients with injury severity score ≥16.

	Patients with ISS≥16		
	Control Group (n=172)	TXA Group (n=168)	P-value
Mortality at 24 hours			0.8278
Dead	8 (4.7%)	7 (4.2%)	
Mortality at 48 hours			0.6842
Dead	11 (6.4%)	9 (5.4%)	
Mortality at 28 days			0.0092
Dead	25 (14.5%)	10 (6%)	
Total blood products transfused (in units), Median (Q1, Q3)	4 (2, 12)	4 (0, 15)	0.6053
Hospital LOS (in days), Median (Q1, Q3)	10 (6, 17)	8 (2, 16)	0.4368
ICU LOS (in days), Median (Q1, Q3)	5 (3, 8)	5 (2, 13)	0.9933
Mechanism of Injury			0.5253
Blunt trauma	76 (44.2%)	80 (47.6%)	
Penetrating trauma	96 (55.8%)	88 (52.4%)	
Gender			0.808
Female	31 (18%)	32 (19.1%)	
Male	141 (82%)	136 (81%)	
Age, years, mean ± SD	36.97 ± 15.07	36.72 ± 15.42	0.887
Injury severity score, mean ± SD	26.65 ± 11.73	26.28 ± 9.97	0.7661

*TXA = tranexamic acid; ISS = injury severity score; LOS = length of stay; ICU = intensive care unit

Figure 1: Patient sample size flow chart



*EMS = emergency medical services

References

1. WISQARS - Leading Causes of Death Reports, National and Regional, 1999 - 2014. Centers for Disease Control and Prevention; 2015. http://www.cdc.gov/injury/wisqars/. Accessed Feb 23, 2016.
2. Sauaia A, Moore F, Moore E, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma Acute Care Surg.* 1995;38(2):185-193.
3. Kauvar D, Lefering R, Wade C. Impact of Hemorrhage on Trauma Outcome: An Overview of Epidemiology, Clinical Presentations, and Therapeutic Considerations. *J Trauma Acute Care Surg.* 2006;60(6 Suppl):S3-11.
4. Ausset S, Glassberg E, Nadler R, et al. Tranexamic acid as part of remote damage-control resuscitation in the prehospital setting: A critical appraisal of the medical literature and available alternatives. *J Trauma Acute Care Surg.* Jun 2015;78(6 Suppl 1):S70-75.
5. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. *J Trauma Acute Care Surg.* Jun 2003;54(6):1127-1130.
6. Niles SE, McLaughlin DF, Perkins JG, et al. Increased mortality associated with the early coagulopathy of trauma in combat casualties. *J Trauma Acute Care Surg.* Jun 2008;64(6):1459-1463; 1463-1455.
7. Theusinger OM, Baulig W, Seifert B, et al. Changes in coagulation in standard laboratory tests and ROTEM in trauma patients between on-scene and arrival in the emergency department. *Anesth Analg.* Mar 2015;120(3):627-635.
8. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg.* 2014;77.

9. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost.* Feb 2013;11(2):307-314.

10. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg.* Dec 2014;77(6):811-817.

11. Kashuk JL, Moore EE, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. *Ann Surg.* Sep 2010;252(3):434-442; discussion 443-434.

12. Kunze-Szikszay N, Krack LA, Wildenauer P, et al. The pre-hospital administration of tranexamic acid to patients with multiple injuries and its effects on rotational thrombelastometry: a prospective observational study in pre-hospital emergency medicine. *Scand J Trauma Resusc Emerg Med.* Oct 10 2016;24(1):122.

13. Shakur H, Roberts I, Bautista R, 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.

14. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet.* 2011;377(9771):1101.e1101-1101.e1102.

15. Lipsky AM, Abracmovich A, Nadler R, et al. Transexamic acid in the prehospital setting: Israel Defense Forces' initial experience. *Injury.* 2014;45(1):66-70.

16. Vu EN, Schlamp RS, Wand RT, et al. Prehospital use of transexamic acid for hemorrhagic shock in primary and secondary air medical evacuation. *Air Med Journal.* 2013;32(5):289-292.

17. Paudyal P, Smith J, Robinson M, et al. Tranexamic acid in major trauma: implementation and evaluation across South West England. *Eur J Emerg Med.* Aug 26 2015.

18. Strosberg DS, Nguyen MC, Mostafavifar L, et al. Development of a Prehospital Tranexamic Acid Administration Protocol. *Prehospital Emergency Care.* 2016/07/03 2016;20(4):462-466.

19. Wafaisade A, Lefering R, Bouillon B, et al. Prehospital administration of tranexamic acid in trauma patients. *Crit Care.* May 12 2016;20(1):143.

20. Shiraishi A, Kushimoto S, Otomo Y, et al. Effectiveness of early administration of tranexamic acid in patients with severe trauma. *Br J Surg.* May 2017;104(6):710-717.

21. Neeki MM, Dong F, Toy J, et al. Efficacy and Safety of Tranexamic Acid in Prehospital Traumatic Hemorrhagic Shock: Outcomes of the Cal-PAT Study. *West J Emerg Med.* Jun 2017;18(4):673-683.

22. Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet.* 2011;377.

23. Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? *J Trauma Acute Care Surg.* Jun 2013;74(6):1575-1586.

24. Syrovets T, Lunov O, Simmet T. Plasmin as a proinflammatory cell activator. *J Leukoc Biol.* Sep 2012;92(3):509-519.

25. Jimenez JJ, Iribarren JL, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care.* 2007;11(6):R117.

26. Schochl H, Frietsch T, Pavelka M, et al. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. *J Trauma Acute Care Surg.* Jul 2009;67(1):125-131.

27. Cole E, Davenport R, Willett K, et al. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg.* 2015;261.

28. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg.* 2012;147.

29. Eckert MJ, Wertin TM, Tyner SD, et al. 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.* Dec 2014;77(6):852-858; discussion 858.

30. Casati V, Romano A, Novelli E, et al. Tranexamic acid for trauma. *Lancet.*376(9746):1049-1050.

31. Pilbrant A, Schannong M, Vessman J. Pharmacokinetics and bioavailability of tranexamic acid. *Eur J Clin Pharmacol.* 1981;20(1):65-72.

32. O. Eriksson H, Kjellman Å, Pilbrant MS. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. *Eur J Clin Pharmacol.* 1974;7(375).

33. Benoni G, Björkman S, Fredin H. Application of Pharmacokinetic Data from Healthy Volunteers for the Prediction of Plasma Concentrations of Tranexamic Acid in Surgical Patients. *Clin. Drug Invest.* 1995;10(5):280–287.

34. Toner RW, Pizzi L, Leas B, et al. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Appl Health Econ Health Policy.* 2011;9(1):29-37.

35. Wikkelso A, Wetterslev J, Moller AM, et al. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev.* Aug 22 2016(8):Cd007871.