Is There a Role for Tranexamic Acid for Trauma Patients in the Pre-Hospital Setting?

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**Introduction**

Hemorrhage is one of the highest leading causes of death in patients who have suffered a significant trauma and is responsible for nearly 40% of all trauma related deaths. These deaths are associated with acute blood loss, which can be difficult to control as a result of acute traumatic coagulopathy (ACOT) in the acute care setting (Hess et al., 2008). Coagulopathy, or impaired clotting, occurs in almost all patients status-post traumatic injury and initially the causes were focused on those which may have been a result of resuscitation efforts including acidosis, hypothermia, and hemodilution. However, recent research and data has shown ACOT is associated with primary hyperfibrinolysis and occurs early after injury mediated by the activation of widespread protein C activation. ACOT is associated with an extremely high mortality rate of nearly 70%. A diagnosis of ACOT occurs in up to 40% of individuals at the time of the trauma when the injury is significant and is associated with a decrease in life sustaining tissue perfusion, independent of causes as a result of initial resuscitation (Napolitano, Cohen, Schreiber, Moore, & Cotton, 2013). As an acute care gerontological nurse practitioner (AG-ACNP) managing the trauma population in the acute care setting one of the main focuses are on patients who are at risk of ACOT and have a higher chance of suffering from early death as a result. Patients with ACOT have a significantly higher need for blood product transfusion within the first 24 hours of injury and typically require up to ten units of packed red blood cells in comparison to the two units received by trauma patients with normal clotting factors. ACOT has been associated with longer intensive care unit length of stay and higher rates of multi organ failure (Brohi, Singh, Heron, & Coats, 2003).

Given the likelihood of the presence of hyperfibrinolysis, ACOT, and the significant mortality in which it creates in the severely injured trauma patient the recent use of antifibrinolytic agents in the treatment of ACOT in addition to the standard administration of blood products is being implemented in many trauma centers across the United States (US). The most commonly used antifibrinolytic agent is the drug tranexamic acid (TXA). TXA is an inexpensive agent which acts as a binder to plasminogen and blocks the action between plasminogen and fibrin and prevents the breakdown of the fibrin clot. This particular drug has been available for nearly 20 years and was originally utilized to control surgical and uterine bleeding. Recently TXA has been used for the treatment of ACOT and significant hemorrhage in severely injured trauma patients and has gained its popularity due to successful use in the military with severely injured soldiers. TXA is most commonly administered to those patients who meet criteria for significant risk of hemorrhage given the mechanism of injury, obvious injuries on assessment, and unstable hemodynamics. TXA has been shown to decrease the need for blood product transfusions, reduces surgical bleeding, and decrease the overall percentage of death due to post-traumatic hemorrhage in the presence of ACOT (Ruiz & Andresen, 2013).

The increased use of TXA for resuscitation efforts in the acute care setting in those patients with significant risk of hemorrhage due to ACOT as a result of severe trauma poses the question as to why this medication could not be used in the field prior to arrival to a trauma center, by either flight crews or even emergency medicine services (EMS) personnel given the significant decrease in mortality shown to be associated with its use. As previously stated the use of TXA in patients at risk for significant bleeding has shown to significantly decrease mortality in the trauma population however, data has also shown that the use of TXA provides the improved results when administered within three hours of injury with the best results when given within one hour of traumatic injury (Napolitano, Cohen, Schreiber, Moore, & Cotton, 2013).

**Discussion of the Issue**

The use of TXA is growing and quickly is becoming a standard therapy for physicians and advanced practice nurses for the prevention of mortality and morbidity in trauma patients who are at risk for hemorrhage related to traumatic injury. The main issue with the administration of TXA is related to time its constraints. Data has supported the use of TXA if a physician or advanced practice nurse can order and administer the medication to patients at the latest three hours from the time of the traumatic injury; however, TXA has even better results of decreasing mortality due to bleeding if administered within one hour. TXA also has been shown to reduce the need for massive transfusion protocol, the mass administration blood products, by nearly one-third, which are known to have their own associated pitfalls, including transfusion related lung injury (TRALI), organ failure, and an increased risk of infections (Duan,Yu, & Li, 2013).

Given the time sensitivity of the administration of TXA the best place its use may be in the pre-hospital setting. There should be consideration given to allow pre-hospital personnel, including flight advanced practice nurses, paramedics, and EMS personnel to be able to administer TXA as a part of an established protocol for patients who meet criteria for impending hemorrhagic shock or who are currently hemorrhaging due to trauma. Since the most recent published research and data supports the use of TXA in those patients with traumatic injury within no more than three hours of injury, with best results within one hour, it would be benefit the patient for pre-hospital personnel to have the option to administer this medication as data has shown air and road transport has reduced mortality but at times has an extended time to reach a hospital setting. This extended time is often related to prolonged extrication or severity of injury in an attempt to stabilize, or distance from a facility of treatment given a rural location. Other times the patient is being transferred from small outlying facility with little resources as compared to larger trauma centers (Gruen & Mitra, 2011). No matter the delay, if the patient does not meet the time constraints for the administration of TXA the risks will outweigh the benefits. If TXA is given within the three hour window data reports there is no increase in thrombosis and will decrease bleeding and associated death; however, past the three hour window status post traumatic injury TXA has been shown to cause more harm than good, resulting in formation of thrombosis. The later TXA is administered the risk increases for side effects including the formation of thrombosis as hypercoagulation occurs in the later stages post traumatic injury (Duan, Yu, & Li, 2013).

Having the ability to administer TXA to those patients who will miss the time window, whether it be because of prolonged extrication or delay in being transferred to a level one trauma center by pre-hospital personnel would increase the chance of survival in those patients at risk of significant bleeding due to the likelihood of ACOT; as previously stated, 40% of trauma patients have ACOT before resuscitation efforts are initiated (Napolitano, Cohen, Schreiber, Moore, & Cotton, 2013). Furthermore, consideration should be given to the elderly, whose given comorbidities are often taking anti-platelet agents and/or anticoagulants due to a myriad of differing disease processes making this population of patients at a much higher risk of developing hyperfibrinolysis and ACOT. The administration of TXA may decrease the likelihood of hemorrhage and decrease associated death as taking anticoagulants of any kind and the elderly population in general is at a highly increased risk (Williams, Sadjadi, Harken, & Victorino, 2008). The European guideline for the management of coagulopathy and bleeding following major trauma (2013) recommends the administration of TXA to all patients with trauma and significant bleeding. Also, the guideline recommends the development of protocols for the management of bleeding related to trauma and the use of clinical judgment for basis of consideration for administration of the first dose of TXA en route to a trauma center or acute care hospital. This is due to the above mentioned time restraints and therefore ensuring the first dose of TXA is given within the three hour time limit. Clinical judgment would be based on an established protocol for those patients at high risk of hemorrhage as based on evidence based research such as unstable hemodynamics (Spahn, et al., 2013).

**Review of Literature**

ACOT has been shown to cause death from hemorrhage related to traumatic injury. Although this is known, there had been a noticeable delay in implementing treatment with the antifibrinolytic TXA in US trauma centers until two recent research trials were completed and released data revealing the strong correlations between the use of TXA and the decrease in mortality related to significant bleeding. These studies examined TXA, which use to be solely for the use of surgical and gynecological treatment of bleeding, and revealed new significant benefits in using TXA in the trauma population. The hesitation for the implementation of TXA was related to questions concerning the administration, including who should receive the mediation, and the parameters for administration (Napolitano, Cohen, Schreiber, Moore, & Cotton, 2013).

The use of TXA was assessed in patients injured during war with the purpose of identifying the effects of TXA on blood product administration, risk of thrombosis with use, and the overall associated death due to bleeding (Morrison, Dubose, Rasmussen, & Midwinter, 2012). A retrospective observational study was completed and compared patients who received TXA to those patients who did not receive TXA. The method of analysis involved the use of univariate and multivariate regression. A of total of 896 military personnel with battle related trauma were analyzed in a hospital in Afghanistan. Of those 896 patients, 293 patients were given TXA at some point during the treatment course as identified via the United Kingdom and US trauma registries. According to the results of the data, the group of patients who received the TXA had a lower rate of mortality compared to the group of no TXA (17.4% versus 23.9%, p=0.03). Data revealed the incidence of thrombotic events, including pulmonary embolism (2.7% versus 0.3%, p= 0.0001) and deep vein thrombosis (2.4% versus 0.2%, p=0.0001), significantly increased with the TXA group. However, once the data was corrected using the severity of injury index, there was no noted association of increased development of thrombotic related adverse effects, whether PE or DVT, with the use of TXA. Additionally, TXA was shown to increase survival in the patient group who received the antifibrinolytic drug (OR, 7.228; 95%CI). This study, the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERS), was one of the first supporting the use of TXA in trauma patients and supports the implementation of TXA into practice and procedure as part of the resuscitation efforts in those patients who are risk of increased bleeding, shock related to hemorrhage, and death. Given the retrospective nature of this study, there were limitations which include the inability to provide information on the time limitations associated with the use of TXA or indications of use as these patients were severely wounded combat soldiers.

In order to evaluate whether TXA decreased mortality due to bleeding in trauma patients a large randomized control study was performed in 274 hospitals in 40 different countries (Shakur et. al., 2010). This study, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2), assessed the overall mortality, bleeding, and risk and rate of thrombosis in a large sample size of 20,211 adult trauma patients. Of the total population of subjects, 10,096 received TXA one gram intravenously over ten minutes followed by a drip of one gram over eight hours while 10,115 received a placebo. The subjects were randomly assigned to a group within eight hours of injury. The inclusion criteria included any adult trauma patient who was at risk for significant hemorrhage related to mechanism of injury, unstable hemodynamic status which was defined as a systolic blood pressure less than 90 mmhg, a heart rate greater than 110 beats per minute or both, and injury within eight hours of TXA or placebo administration. Since the one of the major risks of administering an antifibrinolytic is the development of thrombosis, this study also evaluated the development of thrombotic events. In this study the demographics, trauma factors, and trauma severity score were well-adjusted. The results of the CRASH-2 trial were significant and one the most imperative findings of this study is related to time of administration. The 28-day mortality was 14.5% for the TXA group and 16% for the placebo group (RR 0.91; CI 95%; p=0.0035), and there was no noted increase in thrombotic events when comparing the two groups (PE 0.7% for the TXA group versus 0.7% for the control, DVT 0.4% for the TXA group versus 0.4% for the control, and CVA 0.6% for the TXA group versus 0.5% for the control group). Given the benefit of decreased mortality and the absence of an increase in risk of harm, a 1.5% reduction in the overall mortality is a considerable finding. This study concluded that the use of TXA could save the lives of nearly 70-100,000 trauma patients per year across the globe. Furthermore, this study concluded that the earlier the administration of TXA the better the results and noted less likelihood of death from hemorrhage. If TXA is given less than one hour from injury the best results (CI 0.68) were noted and included a 32% reduction in deaths related to bleeding. Results also revealed improvement if given within three hours (CI 0.79) but were noted to be harmful if given three hours post traumatic injury (CI 1.44) with an increase in thrombotic events. Limitations of the CRASH-2 trial included the potential for selection biases, no coagulation studies prior to administration, and a documented 100% follow-up from patients which appears unrealistic. This study, however, is considered significant and is considered the mainstay study in the implementation of TXA use in acute care settings for time of administration as well as for the parameter guidelines for those patients requiring administration. The recommendations as a result from this study are to implement TXA use into clinical practice as a way to prevent death from hemorrhage in trauma patients and should be administered as early as possible, within one hour of injury, with late administration after three hours not recommended.

A smaller retrospective multiple cohort study was completed with a purpose of initiating a TXA guideline in traumatic injury for a level one-trauma center (Swendsen, Galante , Utter, Bateni, Scherer, & Schermer, 2013). This study compared groups of severely injured trauma patients who received TXA versus those who did not. The criteria for TXA administration at this facility was persistent hypotension with a systolic blood pressure less than 90 mmhg, activation of the massive transfusion protocol, or a direct to operating room or interventional radiology per provider discretion. Charts were reviewed randomly of 126 patients who met criteria for the adminstration of TXA and either did receive or did not receive TXA and the outcomes were compared. All patients reviewed did receive TXA within three hours of injury. The outcomes that were assessed in this study were death within 24 hours of traumatic injury, death at some point during hospitalization as a result of bleeding, the development of thrombotic complications including DVT, PE, myocardial infarction (MI), CVA, and/or acute kidney injury (AKI). Results based on the Chi-Square method were noted to be similar to previous studies including the MATTERS and CRASH-2 trial. Of the total 126 patients assessed in this study, 74 did not received TXA and 52 received TXA. When comparing the no TXA group to the TXA group the results revealed a higher rate of death within 24 hours of injury for the no TXA group (17.6% versus 5.8%), death prior to discharge out of the inpatient setting (23% versus 17.3%), MI (2.7% versus 0%), stroke (0% versus 3.19%), DVT (0% versus 11.5%), and AKI (8% versus 13%). The limitations of this study were the small sample size and the differing levels of traumatic injury, as some were noted to be more severe than others. The findings of this study were that the adminstration of TXA does decrease overall mortality in relation to bleeding. This study differed from the large studies previously completed on TXA adminstration as this study demonstrated an increase in thrombotic events, even though TXA was administered within the recommended three-hour window. The authors report this finding to remain unclear and should warrant additional evaluation; however, these results should not delay the use of TXA as the benefits far outweigh the risks involved. Based on this study and the results of the other major studies on TXA, a guideline was developed and utilized in this trauma center for the use of TXA.

**Summary Statements**

There is significant evidence to support the use of TXA in trauma centers for patients who are at risk of bleeding and death from hemorrhage as a result of trauma in the acute care setting. TXA use has been shown in major studies to decrease overall mortality with no real risk of further injury as a result of the antifibrinolytic medication. The issue remains the ability to administer TXA in a timely manner in order to obtain the best overall effect of the drug. As previously stated research has provided data which supports the use of TXA within a three hour window, however, the best results for decreasing bleeding deaths was shown to be within one hour from time of traumatic injury (Morrison, Dubose, Rasmussen, & Midwinter, 2012; Shakur et al., 2010; Swendsen, Galante , Utter, Bateni, Scherer, & Schermer, 2013).

Established evidence has shown the best results of TXA is noted when administered within one of injury, therefore there is strong evidence to support the development of a protocol allowing pre-hospital personnel the ability to provide patients who meet criteria the antifibrinolytic, TXA. This would allow the patient the best chance of survival so that when a patient reaches the acute care setting the one gram of intravenous TXA bolus has already been administered and the trauma team, including physicians and advanced practice nurses, can be ahead of the bleeding and likely decrease the risk of death related to hemorrhage, especially in those elderly patients at even higher risk of developing ACOT. Once the patient then arrives to the acute care hospital the continuous infusion of TXA can be started. There are occasions in which a patient could be injured in a rural area, or be subject to a long extrication at the scene of an accident resulting in delayed transfer to a trauma center of an hour or more, given these scenarios patients injured in traumatic events would best be served if TXA could be administered out in the field when the patient meets criteria for administration. Using criteria based on the CRASH-2 trial a patient injured in a traumatic incident with a systolic blood pressure less than 90 mmhg or a heart rate greater than 110 beats per minute, or both, would be a worthy initial starting point when developing a protocol for TXA administration (Shakur et al., 2010).

Data from the two largest studies looking at the use of TXA in the trauma population supports the use in the pre-hospital settings if the patient is at risk of hemorrhage as a result of traumatic injury given the high incidence of patients with ACOT despite having no testing giving a definitive diagnosis (Spahn et al., 2013). TXA is currently a class one recommendation with its use our US Military according to their Tactical Combat Causality Care guidelines. Additionally, the European guideline for the management of coagulopathy and bleeding following major trauma (2013) recommends the use of TXA in the pre-hospital setting and suggests research be aimed in this direction to assess the use in this setting on patient mortality due to bleeding. These recommendations are based upon the results of the two large studies completed: the MATTERS trial and the CRASH-2 trial. However, there have been no true studies evaluating the actual adminstration in the pre-hospital setting outside of military combat. There is a need for studies with a focus on the adminstration of TXA by personnel in the pre-hospital setting in order to further evaluate whether there is indeed a benefit in order to extend positive outcomes to those individuals who may not be able to make the time constraint of one hour. Advanced practice nurses, especially the AG-ACNP who has experience working with trauma patients and the use of TXA, can play a significant role in helping a team to develop a protocol for the use of TXA in the pre-hospital setting based on best evidence based practice with the goal of improving patient outcomes by decreasing mortality and morbidity related to traumatic ACOT and hemorrhage. Of course there are many variables involved when attempting to get a medication such as TXA into the pre-hospital setting, but given the significance of the data retrieved in the MATTERs and CRASH-2 trial, patients at risk of hemorrhage related to trauma could certainly benefit from the early administration of TXA. Further evaluation and research at the pre-hospital level is definitely warranted and true consideration should be given to take a closer look at this option further.

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