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A Retrospective Study of Transfusion Requirements in Trauma Patients Receiving Tranexamic Acid

Brian Cornelius, DNP CRNA NRP [Responsible for research coordination, analysis and manuscript preparation.],

Department of Anesthesia, University Health-Shreveport, brian.cornelius@uhsystem.com

Kelsey Moody, DO [Responsible for data collection, analysis and manuscript preparation.],

Department of Emergency Medicine, Louisiana State University Health Sciences Center, Shreveport Louisiana, kkifer@lsuhsc.edu

Katelyn Hopper, MD [Responsible for data collection, analysis and manuscript preparation.],

Department of Anesthesia, Louisiana State University Health Sciences Center, Shreveport Louisiana, Khopp1@lsuhsc.edu

Phillip Kilgore [Responsible for data analysis and manuscript preparation.],

Laboratory for Advanced Biomedical Informatics, Department of Computer Science, Louisiana State University Shreveport, Louisiana, pkilgore@lsus.edu

Urska Cvek, ScD MBA [Responsible for data analysis and manuscript preparation.],

Laboratory for Advanced Biomedical Informatics, Department of Computer Science, Louisiana State University Shreveport, Louisiana, ucvek@lsus.edu

Marjan Trutschl, ScD [Responsible for data analysis and manuscript preparation.],

Laboratory for Advanced Biomedical Informatics, Department of Computer Science, Louisiana State University Shreveport, Louisiana, mtrutschl@lsus.edu

Angela P. Cornelius, MD [Responsible for data collection, analysis and manuscript preparation.]

Department of Emergency Medicine, Louisiana State University Health Sciences Center, Shreveport Louisiana, acorne@lsuhsc.edu

Abstract

Objectives—The MATTER and CRASH-2 studies demonstrate Tranexamic Acid (TXA) reduces mortality in patients with traumatic hemorrhage. However, their results, conducted in foreign countries and US military soldiers provoke concerns over generalizability to civilian trauma patients in the United States. We report the evaluation of patient outcomes and transfusion requirements following treatment with TXA by a civilian air medical program.

Methods—We conducted a retrospective chart review of trauma patients transported by air service to a level one trauma center. For the purposes of intervention evaluation patients meeting this criterion for the two years (2012-2014) prior to therapy implementation were compared to patients treated during the two-year study period (2014-2016). Goals were to evaluate morbidity, mortality, transfusion requirements and length of stay.

Results—During the review, 52 control (Non-TXA) and 43 study (TXA) patients were identified as meeting inclusion criteria. Patients in the control group were found to be less acute which correlated with shorter hospital stays. There was reduced mortality for patients receiving TXA in spite of their increased acuity and decreased likelihood of survival.

Conclusion—Trauma patients from this cohort study receiving TXA demonstrate decreased mortality in spite of increased acuity. This increased acuity is associated with increased transfusion requirements. Future research should evaluate patient selection with concern for fibrinolysis and provider bias. Randomized control trial is needed to evaluate the role of TXA administration in the United States.

Keywords

Tranexamic Acid (TXA); Transfusion; Trauma; Hemorrhage

Background

Tranexamic Acid (TXA) is a synthetic analog of the amino acid lysine. Its action is to stabilize formed clots by reversibly binding to lysine receptors on plasminogen. This prevents plasminogen from binding to fibrin, which effectively blocks fibrinolysis and degradation of the clot. The use of TXA has been studied in many areas of medicine including various types of surgeries such as orthopedics and obstetrics and gynecology, in trauma patients, and in emergency medicine. Although TXA has been studied as part of mass transfusion protocol for trauma patients with bleeding, its use has not yet been widely incorporated. Two of the most well-known studies on the utility of TXA include the CRASH-2 trial, and the MATTERS study. These studies describe the use of TXA in trauma patients with blood loss. Blood loss is a common cause of death in trauma patients and the administration of TXA has been studied to examine if it is effective in reducing blood loss, transfusion requirements, and death secondary to exsanguination. Although timing, doses, and administration routes differ, the data thus far has shown overwhelmingly positive results. The CRASH-2 trial showed not only a decrease in mortality in patients who received TXA but also highlighted the cost effectiveness of reducing transfusion requirements. The MATTERS trial determined that early administration of TXA to trauma patients, who in particular required mass transfusion protocol, has been shown to decrease mortality even more so than in patients who did not require mass transfusion. Included in many studies is the incidence of adverse events, primarily involving clot formation i.e. pulmonary embolus and DVT. The use of TXA has not been implicated in increasing the risk of developing thromboembolic complications or vascular occlusive events. The use of thromboelastogram is recommended to assist in the treatment of specific coagulopathies. The objective of this study was to evaluate the rate of transfusion for patients receiving TXA versus a control group which did not.

Literature Review

While there have been numerous smaller trials investigating tranexamic acid use in bleeding trauma patients, there are two trials that have gained the most recognition due to their large size: CRASH- 2 and MATTERS. Both of these studies have been instrumental in the newest

recommendations for TXA in trauma patients; however, they each have their own limitations.

CRASH-2

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage- 2 (CRASH-2) (Roberts et al, 2013) is a randomized placebo-controlled trial from May 2005 to March 2010 with over 20,000 patients in 274 hospitals over 40 different countries. Adult trauma patients who had significant hemorrhage, or were at risk for significant bleeding, were given loading dose of 1 gram bolus of tranexamic acid over 10 minutes then 1 gram infusion of 8 hours within 8 hours of injury. Significant hemorrhage was defined as systolic blood pressure < 90 mmHg or heart rate > 110 bpm. The TXA group had significantly lower all-cause mortality at 28 days compared to the placebo group, 14.5% compared to 16.0% respectively. The risk of death secondary to bleeding in the TXA group was significantly lower at 4.9% compared to 5.7% in the placebo group. If TXA was given < 1 hour from injury, the risk of death due to bleeding was reduced significantly at 5.3% compared to 7.7% in the placebo group. TXA given within 1–3 hours post-injury also reduced the risk of death due to bleeding. However, if TXA was given after 3 hours of injury, the risk of death secondary to hemorrhage was increased: 4.4% died in the TXA group compared to 3.1% in the placebo group. These results indicate that giving TXA to bleeding, trauma patients within 3 hours of injury reduced mortality up to 30%, saving 755 life years per 1,000 trauma patients. The cost of giving TXA to 1,000 patients was estimated at \$30,000, and \$48,000 was the incremental cost of giving TXA compared to not giving it. However, the incremental cost per life year gained of administering TXA was \$64. As with any trial, there were also limitations. One of the most important being that a majority of the hospitals enrolled lack modern day trauma/resuscitation practices. It is important to realize that CRASH focused mainly on blunt injury trauma with only half of the patients actually receiving transfusions, and even fewer requiring an operation. This suggests that not many of the patients in the study were severely injured. Also, due to the fact that traumatic hemorrhage can be difficult to diagnose, some of the included patients might not have been bleeding at time of randomization, which could have reduced the power of the trial to show an effect of TXA on mortality from bleeding. Of note, there was no finding of a reduction in blood transfusion requirements.

MATTERS

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERs) (Morrison et al., 2012) is a retrospective observational study published in 2011 of nearly 900 patients at a surgical hospital in southern Afghanistan. This study compared administration of TXA with no administration in patients receiving at least 1 unit of packed red blood cells. They found that TXA reduced mortality and also improved markers of coagulation. Patients in the TXA group were more severely injured according to the Revised Trauma Score but had lower mortality rates at 17.4% compared to 23.9% of group that did not receive TXA. There was a greater benefit in the group of patients who received massive transfusion, which is defined as more than 10 units of packed red blood cells. Of note, the TXA group had a higher rate of DVT and PE compared to the no TXA group. This could be related to the higher degree of injury in the TXA group or the TXA itself due to its evidence of correction of hypocoagulable state. The most important limitation of MATTERs is the lack

of variety in the patient population; the majority of study subjects were men under the age of 25. Because the study is retrospective, it is difficult to understand the incidence of venous thrombotic events, exact cause of death, and time of death.

Methods

Study Participants

University Health-Shreveport (UH) serves as the primary teaching hospital for the Louisiana Health Sciences Center-Shreveport. University Health is a level one trauma center, children's hospital and regional burn center serving a diverse geographical area to include Louisiana, Texas, Arkansas and Oklahoma.

Pafford Air One is a three-rotor wing, one fixed wing air medical service with bases in Louisiana, Arkansas and Mississippi. For the purposes of this project Pafford Air One served as the host agency providing the study intervention; only patients transported into University Health-Shreveport were included. Their treatment guidelines for TXA administration include the following: any patient who is deemed to have significant hemorrhage as evidenced by hypotension or tachycardia, or if the patient is considered to be at risk of significant hemorrhage, age greater than 18 years and three hours or less since the time of injury. Pafford utilizes one gram administered IVPB over 10 minutes followed by one gram infused over the next eight hours at the discretion of the treating provider.

Study Protocol

After institutional review board (IRB) approval, patients were identified through flight records generated by Pafford Air One during the 4-year period identified for the project. Subsequently, data were mined to the study collection spreadsheet from the EPIC Electronic Health Record (2016). The system is integrated throughout the facility and is utilized as the patient's primary clinical chart in addition to roles for quality improvement and research. For identification, the following inclusion criteria were utilized: Age >18 years, presented to University Health Shreveport via Pafford Air One, trauma patient with significant hemorrhage that includes hypotension (systolic blood pressure less than 90 mmHg), tachycardia (heart rate more than 110 beats per minute), ISS of 20 or greater and receiving blood transfusion. The control group of patients was identified from the 2-year period preceding the implementation of the TXA Protocol (08/2012–07/2014). During this time period, 52 patients were identified as meeting study inclusion protocol. The study group of patients (08/2014–12/2016), identified 43 patients which met the same inclusion criteria in addition to having received TXA.

Statistical Analysis and Analytics

Statistical analysis and image generation was done using the R programming language. After initial analysis of 450 patients, 95 met study inclusion criteria. Their information was combined into one Excel spreadsheet, transposed and a column was created to indicate whether the record belonged to the TXA or control group. Variables were divided into subcategories to compare the results among the two cohorts. Individual data records were then distributed into these groupings and comparisons were performed to calculate the

significance when comparing the TXA and Non-TXA groups. To calculate the given values, the mean, median, and standard deviations were calculated using the appropriate functions in R. Then t-test evaluations were performed with a confidence interval of 95% percent.

Results

Over the 52-month period, 52 patients were identified for the control group (Non-TXA) and 43 for the study group (TXA). Data were found to be complete for all study patients. All patients were recognized by an Injury Severity Score (ISS) of 20 or greater. Several different scores were utilized to attempt stratification: Revised Trauma Score, Glasgow Coma Scale, Injury Severity Score, Trauma Injury Severity Score and systolic blood pressure. Additionally, evaluation was conducted on injury patterns to body systems to determine group similarity. While attempts were made to stratify the two groups, several findings indicated the TXA group's condition was slightly worse. This included a lower initial systolic blood pressure (SBP), lower hospital arrival SBP, lower hospital arrival Glasgow Coma Score (GCS), lower Trauma Revised Injury Severity Score (TRISS) and higher International Normalization Ratio (INR). Thromboelastogram was not routinely used due to processing delay so it was not included in data analysis. Two patients in the control group were identified as minors and excluded.

Patients in the study group were identified as receiving increased volumes of all blood products reviewed (FFP, RBC, PLT, Cryo). Products are supplied in ratio fashion from the blood bank. The initial trauma pack contains two units of type O- RBC and two units of type O- FFP. Subsequent trauma packs contain four units of RBC and four units of FFP. Every other trauma pack is accompanied by a unit of PLT. Efforts are made to transition to type specific blood as soon as crossmatch is completed. Whole blood is not currently utilized in this facility.

Patient outcomes were reviewed for morbidity, mortality and several areas of specific concern related to TXA administration. All hospital mortalities were identified without breakdown of time to expiration. Patients surviving their injuries were categorized either to home or post hospital care facilities (LTAC). Two areas of frequent concern for patients receiving TXA are the incidence of Venous Thromboembolism and rate of mortality for patients with neurological injuries. Both of these populations were examined in the outcome data. The rate of blunt and penetrating injury was also included for review. Venous thromboembolism included deep vein thrombus or pulmonary embolism identified by radiographic findings. Neurological injuries included subdural or epidural hematoma and subarachnoid hemorrhage.

Discussion

The patients presented in this project represented over four years' worth of trauma patients transported by one air medical service to one trauma center. The sample is limited by lack of randomization which may have contributed to provider bias and a higher acuity among the TXA patients. This is interpreted to result in a slightly higher length of stay and rate of morbidity. However, the mortality rate was lower among patients receiving TXA. The

increased injury severity was also associated with increased transfusion requirements among the TXA group. The TRISS (Schulter, 2011) which serves as a calculator of likely mortality, indicates that all deaths in the study group were expected while two deaths in the control group were unexpected. There were ten patients in the control group with expected mortalities ranging from 60–87% that survived. However, there were also twelve patients in the study group with expected mortalities ranging from 60–85% that survived. The relatively increased number of patients surviving injuries calculated as unsurvivable indicates there is benefit to administration of TXA and additional research is needed. When compared to previous related research (CRASH-2, MATTERS) there is a noted elevation in ISS and RTS for both the study and control group on this project. Interestingly, in both of those studies the control groups (Non-TXA) were also found to be less acute than the study groups (TXA).

One of the clear-cut recommendations from proceeding TXA literature is that administration must be within 3 hours of the time of injury (Ramirez, Spinella & Bochicchio 2017). It was found administration after 3 hours correlated to a higher risk of death from hemorrhage (Farrell, Wing, Burke & Huiras, 2015). This is believed to be a result of the trauma-induced release of Tissue Plasminogen Activator (TPA) from the endothelium which results in plasmin activation, fibrinolysis and profuse bleeding. “TPA levels peak 30 minutes after injury and plasmin levels around 1 hour” (Wu, Darlington & Cap, 2015). TXA administration results in inhibition of fibrinolysis, reducing the rate of hemorrhage. All patients from the study group received their loading dose within the recommended 3-hour window. Incidentally, there was no correlation between administration earlier in the window and mortality.

Recent literature (Meizoso et al, 2018) suggests that administration of TXA has resulted in increased risk of fibrinolysis shutdown in critically injured trauma patients. Their study also found that those receiving TXA were generally sicker and required more blood products than those that did not receive TXA. Of note, TXA was administered more than an hour later (1.17 vs 2.27) in patients that suffered from shutdown as identified by Thromboelastogram (TEG). Their recommendation post-study is to utilize TXA in patients with significant hemorrhage and avoid blanket administration to major trauma patients.

Limitations

Our study did present several limitations. First, this was a retrospective cohort study of patients that were found after evaluation to not be identical. Comparison with samples from the previous studies found this is a common concern; patients receiving TXA are more acute than those that do not. Future randomized control trials should be completed to eliminate this study bias. This study resulted in a limited sample size; future prospective trials should allow for an increased number of patients. This is key with the recognition that the number needed to treat increased from previous studies. Patients in this study did not consistently receive the full scope of treatment to include administration of the follow-up infusion. Future studies should attempt to follow the protocol in its entirety for full treatment validation. This study included patients that were transported from the scene in addition to those transferred from outlying facilities. Our study did not identify male vs female, this is

known to effect outcomes in hemorrhage related deaths. This resulted in some variation in treatment standards prior to transfer, which may have impacted outcomes.

Finally, are the results of CRASH-2 and MATTERs generalizable to the civilian population receiving care in United States trauma systems? Significant concerns have been presented regarding how the findings of the subset populations utilized in these two studies can be applied to trauma systems and populations that are different from those studies (Mitra et al, 2014). The populations in these studies presented to medical facilities in countries that were primarily lower to middle income, with little pre-hospital care and emergency systems. Less than 2% of the patients were treated in a care setting similar to what is found in the United States. These settings found less benefit to patients receiving TXA with the reduction in deaths dropping from the 1:3 found in CRASH-2 to 1:50 in the general population. Massive transfusion protocols incorporating Fresh Frozen Plasma (FFP) have become commonplace in developed nations. Administration of FFP provides antifibrinolytic properties which are comparable, if not exceeding, to that of TXA (Bolliger, Grlinger & Tanaka, 2010). Thus, plasma administration, if available, is preferable or should be used in conjunction with TXA administration. This points to the benefit of early administration in the pre-hospital realm where plasma is unavailable.

Conclusion

In summary, we completed a retrospective evaluation of trauma patients transported by air medical service having received tranexamic acid for treatment of known or suspected hemorrhage. This cohort study compared outcomes with a control group consisting of injury stratified patients. Tranexamic Acid has demonstrated improvements in the care of multisystem trauma patients. Additionally, it offers benefits for patients undergoing various surgical procedures to include obstetric, gynecologic (Glymph, 2016), orthopedic (Boyle & Soric 2017) and neurosurgical (Vel et al, 2015). This study found that patients receiving TXA were likely to have more severe injuries and lower systolic blood pressures when compared to a control group. This directly resulted in longer lengths of stay and increased rates of blood transfusion. However, there were a higher percentage of patients that survived after TXA administration in spite of receiving injuries that were calculated as unsurvivable. This finding coupled with the lower rate of side effects indicates that TXA has a valuable role in the care of complex trauma patients. Future research should evaluate measures to further decrease the time from injury to TXA administration and patient selection criteria. This may include intramuscular use by lay rescuers (Wright, 2014), administration of multiple doses throughout the continuum of care and utilization of laboratory guidance for targeted resuscitation. TXA is a valuable component for the care of complex patients and efforts should be made for its integration in all levels of trauma care.

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Key Points

1. Traumatic injury is a significant cause of morbidity and mortality in the United States; massive hemorrhage is responsible for the vast majority of deaths.
2. Early administration of TXA to trauma patients shows promise for reducing mortality in traumatic injury patients, however it does not appear to reduce transfusion requirements.
3. Future research should focus on patient selection criteria, adjunct therapies and targeted resuscitation utilizing laboratory guidance.

Table 1

Stratification Statistics

	Mean	Mean	P-Value
	Control (SD)	Study (SD)	95% CI
Age	42.58 (4.38)	44.42	
GCS Initial	11.38 (4.38)	11.60	
GCS Hospital	9.78 (5.72)	6.92	
GCS Discharge	11.92 (4.87)	12.11	
RTS *	10.48 (1.77)	10.69 (1.64)	0.09
ISS *	30.44 (12.56)	33.29 (12.23)	0.75
Initial SBP	117.19 (35.98)	100.31	
Hospital SBP	116.67 (28.34)	99.89	
INR *	1.30 (0.35)	1.97 (3.45)	0.85
Injury to INR	163.84 (128.64)	149.96	
LOS *	15.56 (11.26)	18.25 (16.56)	0.27
Injury to TXA		70.47	
TRISS	68.73	56.34	

* Welch Two Sample t-test

Table 2

Transfusion Data

	Mean	Mean	p-value
	Control (SD)	Study (SD)	95% CI
RBC *	5.96 (8.61)	8.8 (7.47)	0.27
FFP *	7.3 (7.87)	9.86 (11.08)	0.09
Platelets *	2.62 (1.72)	2.9 (1.97)	0.75
Cryo *	2	2	0.85
Average *	4.61 (3.57)	4.95 (3.38)	0.92

* Welch Two Sample t-test

Table 3

Outcome Data

	Control (N=52)	%	Study (N=43)	%	p-Value 95% CI
VTE *	10	11.9	4	8.3	0.79
Expired ^	11	21.15	10	23.25	0.05
Home ^	23	44.23	14	32.55	0.05
LTAC ^	18	34.61	19	44.18	0.05
Penetrating	4	7.69	5	11.62	
Blunt	48	92.3	38	88.37	
Mortality in Neuro Patients	8	15.38	5	11.62	

* Pearson's Chi-squared test with Yates' continuity correction

^ Pearson's Chi-squared test