Fall 12-2016

The Effects of Tranexamic Acid on Mortality Rate in Trauma Patients Compared to Trauma Patients with No Tranexamic Acid Treatment

Bradley Earl Tolar
University of Southern Mississippi

THE EFFECTS OF TRANEXAMIC ACID ON MORTALITY RATE IN TRAUMA PATIENTS COMPARED TO TRAUMA PATIENTS WITH NO TRANEXAMIC ACID TREATMENT

by

Bradley Earl Tolar

A Capstone Project
Submitted to the Graduate School
and the Department of Advanced Practice
at The University of Southern Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Nursing Practice

Approved:

_____
Dr. Marjorie Geisz-Everson, Committee Chair
Assistant Professor, Advanced Practice

_____
Dr. Melanie Gilmore, Committee Member
Associate Professor, Advanced Practice

_____
Dr. Janie Butts, Committee Member
Professor, Systems Leadership and Health Outcomes

_____
Dr. Karen S. Coats
Dean of the Graduate School

December 2016

Published by the Graduate School

ABSTRACT

THE EFFECTS OF TRANEXAMIC ACID ON MORTALITY RATE IN TRAUMA PATIENTS COMPARED TO TRAUMA PATIENTS WITH NO TRANEXAMIC ACID TREATMENT

by Bradley Earl Tolar

December 2016

Traumatic injury is the leading cause of death for many age groups. Traumatic accidents caused over 130,000 deaths in the United States in 2014. This DNP project studied the effects of Tranexamic acid on mortality rate in trauma patients. After the completion of a needs assessment at a local level II trauma center, a literature review was performed. The literature showed a decrease in mortality rate when patients were administered Tranexamic acid within 3 hours of injury with statistically significant statistics. Also, the data from the literature showed no correlation between vascular occlusive events and Tranexamic acid use in trauma patients. Second, a practice change proposal was drafted including the statistics found in the literature review. This proposal was presented to available trauma surgeons at a local level II trauma center in south Mississippi. Last, the trauma surgeons were asked to fill out a brief survey asking if they would be willing to change their practice based off the information provided. The surgeons were not willing to change their practice, but their practice was currently up to date with the recommendations included in the practice change proposal. Due to the project spanning over 2 years in time, the

previously performed needs assessment was outdated by the completion of the project.

ACKNOWLEDGMENTS

I would like to offer a special thanks to Dr. Marjorie Everson, my committee chair, for her help, support, and encouragement throughout the process of this capstone project. Also, thank you Dr. Janie Butts and Dr. Melanie Gilmore for your guidance and support throughout this process.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AACN	American Association of Colleges of Nursing
CDC	Centers for Disease Control
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage-2
DNP	Doctorate of Nursing Practice
IRB	Institutional Review Board
MATTERS	Military Application of Tranexamic acid in Trauma Emergency Resuscitation
tPA	Tissue Plasminogen Activator
USM	The University of Southern Mississippi

CHAPTER I – INTRODUCTION

Clinical Problem Statement

Traumatic injuries are unplanned, life altering events that can affect a family with no warning. Traumatic events are leading causes of mortality in many different age groups, especially young people (CDC, 2014). While comorbidities such as heart disease, respiratory disease, stroke, and cancer are responsible for the deaths of many older individuals, trauma accidents still claim the lives of many older individuals too (CDC, 2014). In a 2014 survey, the Centers for Disease Control found that traumatic accidents (or unintentional injuries) were the leading cause of death for people age 1 through age 44 in the United States (CDC, 2014). The goals of this DNP project were to find evidence of Tranexamic acid administration reducing mortality rate in trauma patients, and to present a practice change proposal to local trauma surgeons.

Needs Assessment

Upon choosing the trauma patient population to study for the DNP project, a needs assessment was completed at a local level II trauma center. At that time in April 2014, the use of Tranexamic acid in the trauma patient population was inconsistent at best. One of the trauma surgeons was an advocate for its use, two of the trauma surgeons did not ever use the drug, and the other three surgeons used it on occasion. With all available literature and statistics showing better patient outcomes, the project was started as a practice change proposal.

PICOT question

How does the administration of Tranexamic acid affect mortality rate in trauma patients compared to trauma patients receiving no Tranexamic acid or placebo? The patient population is acute trauma patients over the age of 16 being admitted to a nearby hospital for surgical intervention to minimize blood loss. The intervention is administration of Tranexamic acid in the preoperative, intraoperative, and postoperative phases of care. The control group will be the group of patients who do not receive Tranexamic acid or who receive placebo treatment (depending on the trial in which they were in). The outcome measured will be mortality rate of patients for treatment versus control groups. The timeframe the variable will be measured in will differ between the trials, but they will all be within the first 30 days after surgery.

Significance of the Project

The main goal of this DNP project was to expand the use of Tranexamic acid among trauma surgeons at a local level II trauma center. This was achieved by submitting a practice change proposal to the trauma surgeons with the results of the literature review included. The trauma patient population was studied in the available literature in an effort to see if Tranexamic acid decreases mortality rate as compared to a control group not receiving Tranexamic acid or receiving a placebo treatment.

Traumatic accidents are leading causes of death in many age groups (CDC, 2014). The reason for death from trauma is due to severe hemorrhage limiting the oxygen carrying capacity of the blood and oxygen delivery to the

tissues. Tranexamic acid is an antifibrinolytic drug that works by impeding fibrinolysis. Fibrinolysis is the body's own way of breaking down blood clots to make sure that the blood clots do not become problematic, such as those causing stroke, pulmonary embolus, deep vein thrombus, or myocardial infarction. By impeding fibrinolysis, the body would not break down clots, but would further strengthen the clots that form. This may lead to less hemorrhage and more stable trauma patients by maintaining adequate hemoglobin and hematocrit concentrations in the body.

Theoretical Framework

The nursing theory chosen to guide the research is Roy's adaptation model. "According to this model, problems in adaptation materialize when the adaptive systems of a person are unable to respond to stimuli from internal or external environments" (Butts & Rich, 2015, p. 410). This statement mimics the problems affecting the trauma patient in that the patient is unable to respond to other stimuli to survive. The major elements involved in Roy's adaptation model are adaptation, person, environment, health, and goal of nursing (Roy, 2009). The drug chosen, Tranexamic acid, will ultimately help with adaptation of the patient to the stressful traumatic injury. The environment would include the traumatic accident that the patient suffered as well as the stress of the surgery that the patient is enduring. Also, the environment of the hospital and the postoperative care unit that the patient is assigned to will affect the patient. The health of the patient would be compromised, but Tranexamic acid has been shown to improve the health in terms of mortality rate. The last major element of

Roy's adaptation model is goal of nursing. The goal of nursing through this project will be to improve trauma patient outcomes by expanding the use of Tranexamic acid among local trauma surgeons at a local level II trauma center.

The fit between the DNP project and Roy's adaptation model are near perfect. Roy's adaptation model states that there is never a perfect homeostatic state but that body systems adapt to try and meet a given need depending of the situation (Roy, 2009). In the project's population, the body's homeostasis is lost by a traumatic injury which causes great risk for significant hemorrhage. The cardiovascular stability is at risk and the body tries to adapt by causing a tachycardia to combat the hypotension associated with the hemorrhage. Tranexamic acid will look to help the homeostatic mechanisms that sometimes fail with excessive blood loss.

CHAPTER II – REVIEW OF LITERATURE

Tranexamic acid is a drug that is relatively new to the trauma patient population. Tranexamic acid is currently used with great success in patient populations at risk for excessive bleeding including: cardiac surgical patients, obstetric/gynecologic patients with heavy menstrual cycles, and orthopedic surgical patients. Some side effects that have been potentially linked to Tranexamic acid include: stroke, deep vein thrombosis and pulmonary embolus. Tranexamic acid has been used in trauma patients and during trauma surgeries, but many physicians have not incorporated this drug into their practice, as discovered from a needs assessment performed at a local level II trauma center. Also, there are no published clinical guidelines available for Tranexamic acid in the trauma patient population. The purpose of this literature review will be to provide a risk-benefit analysis of Tranexamic acid in relation to the treatment of trauma surgical patients. The topic of discussion will be centered around the effect Tranexamic acid has on mortality rate in the trauma patient population as compared to trauma patients that do not receive this treatment. Other important points that will be reviewed include the dosing of Tranexamic acid, the timing of Tranexamic acid administration in relation to injury, and incidence of blood transfusion in patients receiving treatment as compared to patients not receiving Tranexamic acid treatment.

Anatomy and Physiology of the Trauma Patient

Nagelhout and Plaus (2014) defined traumatic injury as "a result of an external force that ultimately disrupts normal structure and function of the body. In most situations, the initial cause of injury is not a result of genetics or environmental exposure, but circumstance and misfortune" (Nagelhout & Plaus, 2014, p. 914). Nagelhout and Plaus (2014) further state that traumatic injury is the leading cause of death for people under 40 years of age. Hoffman added to this point by stating that trauma can cause excessive bleeding by disruption of blood vessels and that more than one-third of trauma patients will die of exsanguination (Hoffman, 2004). This capstone project seeks to improve patient outcomes in trauma patients.

Trauma patients often present to the hospital with multiple injuries, some of which are not apparent upon initial physical assessment (Gruen et al., 2012). Patients can have spleen or liver lacerations that are not diagnosed until the patient has had adequate imaging scans to confirm internal bleeding. The patient can sustain closed head injuries with subdural or epidural hematomas, which lead to altered mental status and increased intracranial pressure. Also, numerous types of orthopedic injuries are possible in trauma patients (Barash, Cullen, Stoelting, Cahalan, & Stock, 2009). All of these injuries can possibly lead the patient to excessive blood loss. This can cause a state of hypovolemia leading to hypotension rather quickly (Gruen et al., 2012). Hypovolemia must be

treated aggressively to restore the circulating volume in order to perfuse all vital organs (Butterworth, Mackey, & Wasnick, 2013).

Often times, the trauma patient will require blood transfusion to maintain an adequate hemoglobin and hematocrit (Gruen et al., 2012). Hemoglobin is responsible for carrying oxygen from the lungs while the blood transports this oxygen to the tissues for extraction. If the concentration of hemoglobin falls too low, the tissues will not receive adequate oxygenation, even if the volume status is adequate. It is necessary to keep an even balance of not only the volume status, but also enough hemoglobin in the circulating blood to transport oxygen to the tissues (Guyton & Hall, 2006).

Clotting Cascade and Hemostasis

To understand how Tranexamic acid works, one must first have a basic understanding of the clotting cascade and hemostasis. Hemostasis simply defined is reduction or prevention of blood loss. This is initially caused by local vasoconstriction at the site of vascular trauma. The vasoconstriction is caused by the platelet's release of thromboxane A2, which is a potent vasoconstrictor. Upon vascular injury, this vasoconstriction occurs to limit the amount of blood loss while a platelet plug is formed to close the site of blood loss (Guyton & Hall, 2006).

The clotting cascade is a very complicated process consisting of more than 50 substances. Clotting takes place in three essential steps. First, a complex cascade of chemical reactions involving 12 or more coagulation factors

occurs in response to a vascular injury, and leaves an end product known as a prothrombin activator. Second, this product helps in the conversion of prothrombin to thrombin. Last, this helps turn fibrinogen into fibrin, which ultimately forms a clot. The initial clot starts a positive feedback loop that promotes more clotting (Guyton & Hall, 2006).

After the clot has slowed or stopped bleeding, fibrinolysis begins to occur. Fibrinolysis breaks down the clot so it does not become pathologic and cause a deep vein thrombus or pulmonary embolus. The plasma contains plasminogen that is converted to plasmin when activated. Plasmin's main job is to digest fibrin fibers and some other procoagulants. Therefore, when plasmin is formed, it will cause the clot to be broken down so it does not become pathologic (Guyton & Hall, 2006).

As previously discussed, there are over 50 substances that contribute to the clotting of blood. Some of these substances are procoagulants, leading the body to cause clots. Some of these substances are called anticoagulants, leading the blood to be thinner and less prone to clot (Guyton & Hall, 2006).

Hypercoagulable states

A hypercoagulable state is one in which there is an abundance of procoagulant factors. A hypercoagulable state is considered positive when there has been some type of vascular injury, such as with a trauma patient. This hypercoagulable state is partially responsible for forming the fibrin clot that eventually leads to cessation of blood loss. Hypercoagulable states other than

with vascular injury are usually unwanted and can lead to pathologic clots such as deep vein thrombus, pulmonary embolus, stroke, or myocardial infarction (Guyton & Hall, 2006). These 4 disease states can be caused by blood clots that block the normal flow of blood and eventually cause hypoxia to the tissues distal to the site of the clot.

Hypocoagulable state

A hypocoagulable state is one in which there is an abundance of anticoagulant factors (Guyton & Hall, 2006). In the presence of vascular injury, this could lead to excessive blood loss. However, there are many medical conditions that necessitate patients to remain in a pharmacologically induced hypocoagulable state (Guyton & Hall, 2006). Some of these include: history of cardiac dysrhythmias, stroke, deep vein thrombus, pulmonary embolus, and coronary artery disease. Most of these disease processes are caused from a previous hypercoagulable state which caused the patient to suffer some type of injury (Guyton & Hall, 2006). In turn, they are prescribed medications that work to inhibit different specific parts of the clotting cascade to induce a hypocoagulable state. This will help reduce the unwanted effects of pulmonary embolus, deep vein thrombus, stroke, and heart attack.

Drugs that Affect Coagulation

To cause a hypocoagulable state, a drug must inhibit a certain step in the clotting cascade. There are many classifications of these drugs based on what step in the clotting cascade they effect. One category of drugs, called

anticoagulants, work to thin the blood by inhibiting a particular step of the clotting cascade. Anticoagulants include: heparin, low-molecular-weight heparin, Coumadin, and direct thrombin inhibitors such as Argatroban and Pradaxa (dabigatran). There are also antiplatelet drugs that work to cause a hypocoagulable state. These drugs work directly on the circulating platelets to cause them not to agglutinate as easily. Antiplatelet drugs include: nonsteroidal anti-inflammatory drugs, Plavix (clopidigrel), and Ticlid (ticlodipine HCl). There are also herbal drugs which are usually not taken for the specific effect of hypocoagulation, but that also have that effect. This category of drugs is important to be aware of as patients often do not know that their herbal medications have side effects affecting coagulation. Herbal medications causing hypocoagulation of the blood include garlic, ginger, ginkgo, and fish oil. The herbal medication known as black cohosh can cause the blood to be hypercoagulable. The main procoagulant medication is Vitamin K. This drug can be used as the reversal agent for a patient with increased bleeding times due to Coumadin. Vitamin K is necessary for the production of many clotting factors in the body. Antifibrinolytics is another class of drugs that cause hypercoagulation. These drugs do not make the blood clot quicker, but they do improve the strength of the clot. Antifibrinolytics include Tranexamic acid and Aminocaproic acid (Nagelhout & Plaus, 2014).

Tranexamic Acid

Tranexamic acid was the drug reviewed for this DNP project. Tranexamic acid is an antifibrinolytic drug. As previously discussed, fibrinolysis is the internal process of breaking down the clot once it has slowed or stopped bleeding. Fibrinolysis is part of a system of checks and balances making sure hemostasis is well regulated. After a clot has formed, blood flow is increased to the area and thromboxane A2 and adenosine diphosphate (two potent vasoconstrictors) are washed away to allow for increased flow of blood. This increase in blood flow allows the body's own tissue plasminogen activator (tPA) and urokinase to arrive at the area with the intact clot. The body's tPA and urokinase are catalysts in converting plasminogen (already located in the clot) into plasmin. The plasmin is then able to degrade the fibrin into fibrin degradation products and the clot is then digested (Nagelhout & Plaus, 2014). Tranexamic acid works to prevent fibrinolysis from occurring. Its chief mechanism of action is to block the conversion of plasminogen to plasmin. With no active plasmin, the fibrin clot is not broken down (Hensley, Martin, & Gravlee, 2013). The goal in trauma patients is to stop the blood loss from occurring so that perfusion can be maintained to the vital organs. By stopping the premature breakdown of fibrin clots, trauma patients will have more adequate clotting to reduce blood loss and maintain function of vital organs (Gruen et al., 2012).

Studies

When searching the available literature for Tranexamic acid's use in trauma patients, two studies were a recurring reference in almost all articles. The first of these studies, Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage-2 (CRASH-2) trial, was conducted in 2010. The second study, the Military Application of Tranexamic Acid in Trauma Emergency Resusciation (MATTERS) trial, was conducted in 2012. Most articles found on the selected population cited one or both of these two studies and looked at them in different ways. While the MATTERS trial looked specifically at military administration of Tranexamic acid and CRASH-2 trial looked at civilian administration of the drug, both trials have data that is applicable to this project.

CRASH-2 trial

The CRASH-2 trial was conducted in 2010, and although it is greater than 5 years old, it is considered a gold standard in this patient population. Nearly all articles cite this trial and/or MATTERS trial in their reviews. CRASH-2 trial investigators studied the effects of Tranexamic acid on a total of 20,211 patients across 40 countries and 274 hospitals. CRASH-2 trial includes civilian patients suffering from traumatic injuries presenting with significant hemorrhages, as evidenced by tachycardia and hypotension (Guerriero et al., 2011).

In the CRASH-2 trial, 10,060 patients were given Tranexamic acid as a treatment following their traumatic accident, while 10,151 patients were given placebos. Of the 20,211 total patients in this study, 1,063 patients died from

hemorrhage. Of these 1,063 mortalities, 489 were from the Tranexamic acid treatment group, while 574 were from the control group that received placebos. When comparing mortality of treatment group versus control group, 4.9 percent of the treatment group died from hemorrhage and 5.7 percent of the control group died from hemorrhage. Relative risk statistics show a 15% decrease in risk of mortality due to hemorrhage when receiving Tranexamic acid when compared to patients in control group (RR 0.85, CI 0.76 to 0.96; P = 0.0077) (Perel, Ker, Morales Uribe, & Roberts, 2013). "These figures suggest that administration of Tranexamic acid can reduce the risk of death from bleeding" (Livingstone, 2013, p. 25). "The pooled data showed that antifibrinolytic drugs reduce the risk of death from any cause by 10% (RR 0.90, 95% CI 0.85 to 0.97; P = 0.003). This estimate is based primarily on data from the CRASH-2 trial of Tranexamic acid, which contributed 99% of the data" (Ker, Roberts, Shakur, & Coats, 2015, p. 2).

Timing of Administration. According to Livingstone (2013), patients in the CRASH-2 trial were placed into 1 of 3 groups in relation to timing of initial dose of Tranexamic acid: within 1 hour of injury, between 1 and 3 hours of injury, longer than 3 hours after injury. The data concluded that patients had a greater chance of survival when administration of Tranexamic acid was within 1 hour after injury, or between 1 and 3 hours after injury. When timing of administration was longer than 3 hours from time of injury, mortality rate increased (RR 1.44, 95% CI 1.12 to 1.84; P = 0.004) (Livingstone, 2013).

Researchers compared Tranexamic acid's use in trauma patients to tissue Plasminogen Activator (t-PA) use in ischemic stroke patients (Meurer, 2013). When Tranexamic acid is given within 3 hours of injury the data shows promising results of decreased mortality, but after 3 hours the results show more harm than good. Meurer (2013) states that t-PA was shown to reduce the number of patients with disabilities from stroke by 14 percent when given within 3 hours of onset of symptoms. Nearly 20 years after this finding was confirmed with research and a large trial, it is still not fully used in treatment facilities. Meurer calls for Tranexamic acid to "become standard of care for trauma patients worldwide long before the 20th anniversary of the CRASH-2 trial" (Meurer, 2013, para. 8).

Guerriero, Cairns, Perel, Shakur, and Roberts (2011) found that early treatment with Tranexamic acid is necessary to improve outcomes. They also found that when Tranexamic acid is administered within 3 hours of injury, the risk of death is reduced by 13 percent (RR 0.87, 95% CI 0.81 to 0.95). Guerriero et al. (2011) claim that it can be harmful to administer Tranexamic acid outside of a three hour window from the time of injury (Guerriero et al., 2011).

Dosing of Administration. Dosing of Tranexamic acid has been a question across other patient populations. There was no variance in the dose of Tranexamic acid in the CRASH-2 or MATTERS trials. Too large of a dose can cause a hypercoagulable state that could lead to pulmonary emobolus, stroke, or deep vein thrombus. Too small of a dose would not produce the therapeutic

effect of slowing down fibrinolysis. The only dose mentioned in regards to trauma patients was referenced from the MATTERS trial. Livingstone (2013) said the dose of Tranexamic acid in trauma patients was a 1 gram bolus given over 10 minutes followed immediately by 1 gram given slowly over the next 8 hours (Livingstone, 2013). The initial bolus is given to load all of the receptors so that fibrinolysis is slowed or stopped. The second dose is given slowly over 8 hours to keep a steady state of the active drug in circulation. With a half life of 3 hours, the active drug could be metabolized out of circulation before the need for the drug is complete (Nagelhout & Plaus, 2014).

Adverse Outcomes of Tranexamic Acid? There are concerns surrounding Tranexamic acid administration causing adverse vascular occlusive events, especially in at risk patients. Patients with specific risks to these events are those patients with a history of such events including: deep vein thrombus, pulmonary embolus, myocardial infarction, and stroke. According to one reviewer of the CRASH-2 trial "there is no evidence that antifibrinolytics have an effect on the risk of vascular occlusive events (quality of evidence: Moderate)" (Ker et al., 2015, p. 2).

There has also been much discussion as to whether Tranexamic acid has any effect on the number of patients needing blood transfusion after traumatic injury. Being that blood transfusion carries many risks, this is another topic of interest among the possible benefits of Tranexamic acid administration. According to the CRASH-2 trial "there is no evidence that antifibrinolytics have an

effect on the receipt of blood transfusion (quality of evidence: High)" (Ker et al., 2015, p. 2).

Cost Effectiveness. According to Livingstone's review of the CRASH-2 trial, Tranexamic acid is a much cheaper alternative to the numerous blood products given to patients with traumatic hemorrhage. In the United Kingdom, the four vials of Tranexamic acid needed to treat a patient was roughly 20 times cheaper than one unit of packed red blood cells (Livingstone, 2013). Meurer (2013) called Tranexamic acid "inexpensive" at less than 100 dollars and said it was cheaper than the cost of starting an IV line and administering a liter of saline. Guerriero et al. (2011) conducted a review with the single objective of studying cost effectiveness. While their explanation of cost was much more in depth, it still is considered a cost effective strategy. "Tranexamic acid is not only life saving… but also that it is a highly cost effective intervention if administered routinely to bleeding trauma patients in high, middle, and low income countries" (Guerriero et al., 2011, p. 5).

MATTERS trial

The MATTERS trial is considered a gold standard of studies among trauma patients receiving Tranexamic acid. The MATTERS trial was conducted in 2012 and is a retrospective study that examined medical records of military trauma patients over a 24-month period. In total, there were 896 patients with combat-related injuries. The study included all patients who suffered from combat injuries and had to receive at least one unit of packed red blood cells

within 24 hours of admission to the treatment facility. Many of these patients received greater than 10 units of blood products and were categorized as receiving a massive transfusion.

Two hundred ninety three of the 896 total patients received Tranexamic acid while 603 did not receive Tranexamic acid. Roughly 50 percent of patients receiving Tranexamic acid died within 30 days of receiving treatment. Sixty four percent of patients not receiving Tranexamic acid died in the same time frame (Livingstone, 2013).

Three hundred twenty one of the 896 total patients received mass transfusion. One hundred twenty five of these 321 patients received Tranexamic acid while 196 did not receive Tranexamic acid. Forty three percent of patients receiving a mass transfusion and Tranexamic acid died within 30 days of admission to hospital; compared with 64 percent of patients receiving a mass transfusion and no Tranexamic acid treatment (Livingstone, 2013).

CHAPTER III – METHODS

For this DNP project, a needs assessment was completed at a local level II trauma center at the start of the project in early 2014. Following the needs assessment, a review of the literature regarding the effects of Tranexamic acid on mortality rate in trauma patients was conducted. A comprehensive literature search was conducted to find relevant articles related to trauma patients receiving Tranexamic acid as a treatment for preventing hemorrhage. Multiple electronic databases were used during this search, but the majority of articles were found in CINAHL, MEDLINE, and PubMed. The terms *Tranexamic acid*, *trauma*, *txa*, *antifibrinolytic*, and *hemorrhage* were all used singly and in combination. Many articles were duplicated in searches across other databases. All articles found on this topic cited one of two trials that have taken place in this population: the MATTERS trial or the CRASH-2 trial. Inclusion criteria for all databases included articles written in the English language, full text articles only, publication dates between 2010 and present time, patients were victims of a traumatic injury, ages of patients were determined by the individual trials in which they were in. Exclusion criteria included studies not published in the English language, studies that did not include full text, studies conducted prior to 2010, and patients in any other category besides trauma.

Data was gathered from other studies, namely the MATTERS trial and the CRASH-2 trial, that have been previously completed. The most important data collected was the effect of Tranexamic acid on mortality. There was also

research performed on dose of administration and timing of administration in relation to injury.

Following the literature review, a practice change proposal to trauma surgeons at a local level II trauma center was developed. The practice change proposal was compiled using evidence from the literature on how to successfully use Tranexamic acid in the trauma patient population to maximize the drug's potential and decrease the mortality rate of trauma patients. This proposal also stated whether or not the use of Tranexamic acid is found to increase or decrease the amount of blood products needed postoperatively.

CHAPTER IV – DISCUSSION

After completing the review of literature and successfully completing Institutional Review Board (IRB) at The University of Southern Mississippi (USM), a practice change proposal was drafted and presented to available trauma surgeons at a level II trauma center in south Mississippi. After presentation of the proposal, a brief survey was administered to assess surgeons' willingness to change practice.

There was a total of 5 trauma surgeons currently practicing at the trauma center. An individual attempt was made to schedule a meeting time with all 5 of the surgeons for presentation of the findings and practice change proposal. Two of the 4 surgeons were unavailable or uninterested. A response was never obtained from 1 surgeon. Ultimately, two surgeons were presented the findings and practice change proposal.

After obtaining consent from both participants, the findings of the literature review were covered along with statistical evidence. The findings included statistics of Tranexamic acid's effect on mortality rate, incidence of vascular occlusive events, incidence of blood transfusion, and cost effectiveness. Next, a brief survey was administered that asked if the participant would consider a practice change based on the information presented. Both participants answered no to this question. Since initial meeting with these surgeons over two years ago, much effort has been made to improve their use of the drug through research of their own. This group of surgeons has access to literature that was

not available through USM libraries database. Their use of Tranexamic acid in trauma patients in on par with the recommendations made based off the literature review.

Further Research

This project could be expanded upon in the future in the form of a retrospective chart review on trauma patients that have received Tranexamic acid to examine its effects on mortality rate in the local hospital. Also, further research with more equipped databases could assess the effect of Tranexamic acid on patients with a history of vascular occlusive events. One topic that was never debated in the literature was the dose of Tranexamic acid. It was a set dose of 1000 mg IV bolus followed by 1000 mg IV slowly over the next 8 hours. All other variables were debated but this was not and the dose of administration could be studied for further research.

DNP Essentials

The DNP essentials covered in this DNP project include numbers III, IV, VI. Essential III is clinical scholarship and analytical methods for evidence-based practice (American Association of Colleges of Nursing [AACN], 2006). This essential was met through completion of the literature review and analyzing the associated statistics. Essential IV is information systems/technology and patient care technology for the improvement and transformation of health care (AACN, 2006). This essential was met using the literature databases to search for literature related to the project. Essential VI is interprofessional collaboration for

improving patient and population health outcomes (AACN, 2006). This essential was met through collaboration with trauma surgeons to provide the highest level of quality care for trauma patients.

CHAPTER V – SUMMARY

The purpose of this capstone project was to evaluate the effects of Tranexamic acid on mortality rate in the trauma patient population and to draft a practice change proposal for local trauma surgeons. The primary outcome studied was mortality rate of trauma patients receiving Tranexamic acid, while also studying the effects on vascular occlusive events and incidence of blood transfusions. A review of the literature was performed and the results of previously performed trials were analyzed. Next, a practice change proposal was drafted and presented to available surgeons at a level II trauma center in south Mississippi. A survey was presented to the surgeons after presentation of the practice change proposal. Due to their recent overhaul of their Tranexamic acid protocol for trauma patients, none of the surgeons surveyed were willing to consider a practice change.

The review of literature found that mortality rate was decreased in trauma patients receiving Tranexamic acid and that it was statistically significant. The literature also showed no difference in vascular occlusive events for trauma patients receiving Tranexamic acid versus trauma patients with no Tranexamic acid treatment.

The literature showed a decrease in mortality rate when trauma patients are treated with Tranexamic acid. That was one of the goals of this study. While the practice change proposal did not encourage trauma surgeons to change their practice, the trauma patients in this area are receiving treatment with Tranexamic

acid that is up to date with current literature. The data and literature available to the trauma surgeons was superior to the literature available to the author. Due to the availability of the literature, the trauma patients in this area have a better chance of survival due to the use of Tranexamic acid in the local level II trauma center.

ORI | Office of Research Integrity

INSTITUTIONAL REVIEW BOARD
LONG FORM CONSENT

LONG FORM CONSENT PROCEDURES
This completed document must be signed by each consenting research participant. • The Project Information and Research Description sections of this form should be completed by the Principal Investigator before submitting this form for IRB approval. • Signed copies of the long form consent should be provided to all participants. Last Edited August 28th, 2014

Today's date: 8/14/2016		
PROJECT INFORMATION		
Project Title: The Effects of Tranexamic Acid on Mortality Rate in Trauma Patients Compared to Trauma Patients with no Tranexamic Acid Treatment		
Principal Investigator: Brad Tolar	Phone: (601) 297-0785	Email: Bradley.Tolar@eagles.usm.edu
College: The University of Southern Mississippi	Department: Nursing	
RESEARCH DESCRIPTION		

1. **Purpose:**

   The aim of this project is to perform a thorough literature review and reveal if the routine use of tranexamic acid in trauma patients reduces mortality or not. A practice change proposal will be drafted and presented to available trauma surgeons. Last, a questionnaire will be administered to assess willingness to change practice after the results have been made available.

2. **Description of Study:**

   If you agree to participate, a 15 minute presentation will be given on the effects of tranexamic acid on mortality rate in trauma patients. You will then be asked to complete a 2 question survey.

3. **Benefits:**

   The potential benefits are better patient outcomes in trauma patients, if tranexamic acid is used to its full potential. This will all be based on current literature and the statistics from previously performed MATTERS trial and CRASH-2 trial.

4. **Risks:**

   There are no risks associated with this project.

5. **Confidentiality:**

   There will be no linkages between the surveys and individual consent forms. Any personal identifying information will be de-identified.

6. **Alternative Procedures:**

There are no alternative procedures available for this project.

7. **Participant's Assurance:**

This project has been reviewed by the Institutional Review Board, which ensures that research projects involving human subjects follow federal regulations.

Any questions or concerns about rights as a research participant should be directed to the Chair of the IRB at 601-266-5997. Participation in this project is completely voluntary, and participants may withdraw from this study at any time without penalty, prejudice, or loss of benefits.

Any questions about the research should be directed to the Principal Investigator using the contact information provided in Project Information Section above.

CONSENT TO PARTICIPATE IN RESEARCH

Participant's Name: _____

Consent is hereby given to participate in this research project. All procedures and/or investigations to be followed and their purpose, including any experimental procedures, were explained to me. Information was given about all benefits, risks, inconveniences, or discomforts that might be expected.

The opportunity to ask questions regarding the research and procedures was given. Participation in the project is completely voluntary, and participants may withdraw at any time without penalty, prejudice, or loss of benefits. All personal information is strictly confidential, and no names will be disclosed. Any new information that develops during the project will be provided if that information may affect the willingness to continue participation in the project.

Questions concerning the research, at any time during or after the project, should be directed to the Principal Investigator with the contact information provided above. This project and this consent form have been reviewed by the Institutional Review Board, which ensures that research projects involving human subjects follow federal regulations. Any questions or concerns about rights as a research participant should be directed to the Chair of the Institutional Review Board, The University of Southern Mississippi, 118 College Drive #5147, Hattiesburg, MS 39406-0001, (601) 266-5997.

Include the following information only if applicable. Otherwise delete this entire paragraph before submitting for IRB approval: The University of Southern Mississippi has no mechanism to provide compensation for participants who may incur injuries as a result of participation in research projects. However, efforts will be made to make available the facilities and professional skills at the University. Participants may incur charges as a result of treatment related to research injuries. Information regarding treatment or the absence of treatment has been given above.

_____	_____
Research Participant	Person Explaining the Study
_____	_____
Date	Date

APPENDIX B – Clinical Evaluation Piece

Brad Tolar

Clinical Evaluation Piece for Capstone Project

1. Would you consider a practice change based on this information presented today? YES or NO

2. If the answer is yes, what practice change would you implement?

CAPSTONE PROJECT FINDINGS & PRACTICE CHANGE PROPOSAL

- Trauma is the leading cause of death for ages 1-44 (CDC, 2014)
  - 3rd leading cause of death for ages 45-64 (CDC, 2014)
- Tranexamic acid is an antifibrinolytic
  - Impedes fibrinolysis: blocks conversion of plasminogen to plasmin (plasmin normally breaks down clots)
  - Does not lead to more clots forming, only strengthens pre-existing clots
- CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage-2 trial), 2010
  - 20,211 civilian patients
    - 10,060 were given Tranexamic acid as treatment
    - 10,151 were given placebos as treatment
  - 1,063 deaths from hemorrhage
    - 489 of these deaths were administered Tranexamic acid; this is 4.9% of the treatment group;
    - 547 of these deaths were administered placebo; this is 5.7% of the control group
    - Relative risk stats show a 15% decrease in risk of mortality due to hemorrhage when receiving Tranexamic acid (RR 0.85, 95% CI 0.76 to 0.96) (Perel, Ker, Morales, & Roberts, 2013)
  - Mortality rate from hemorrhage decreased by 15% (0.85, 95% CI 0.76 to 0.96; P = 0.0077) when compared to patients in control group (Ker, Roberts, Shakur, & Coats, 2015)
  - Treatment with Tranexamic acid within 1 hour of injury was associated with a 32% decrease (RR 0.68, 95% CI 0.57 to 0.82; P < 0.0001) in risk of death due to hemorrhage (Ker, Roberts, Shakur, & Coats, 2015)
  - Treatment with Tranexamic acid between 1 and 3 hours after injury was associated with a 21% reduction (RR 0.79, 95% CI 0.64 to 0.97; P = 0.03) in risk of death due to hemorrhage (Ker, Roberts, Shakur, & Coats, 2015)
  - Mortality rate from hemorrhage increased when timing of administration was greater than 3 hours after injury (Livingstone, 2013). Guerriero et al. (2011) also says timing of administration must be within 3 hours of injury and data shows 44% increase in risk of death due to hemorrhage when administration of Tranexamic acid is more than 3 hours after injury (RR 1.44, 95% CI 1.12 to 1.84; P = 0.004) (Ker, Roberts, Shakur, & Coats, 2015)

    - Livingstone (2013) said CRASH-2 used a dose of 1 gram bolus over 10 minutes, followed by 1 gram slowly infused over the next 8 hours
- MATTERS trial (Military Application of Tranexamic acid in Trauma Emergency Resuscitation trial), 2012
    - 896 military patients
    - 293 received Tranexamic acid treatment
        - Roughly 50% died within 30 days of injury/treatment (Livingstone, 2013)
    - 603 did not receive Tranexamic acid treatment
        - 64% died within 30 days of injury and no treatment (Livingstone, 2013)
    - 321 received mass transfusion (greater than 10 units)
        - 125 received Tranexamic acid
            - 43% died within 30 days
        - 196 did not receive Tranexamic acid
            - 64% died within 30 days
- Pooled data from both trials suggests that Tranexamic acid decreased risk of death from any cause by 10% (RR 0.90, 95% CI 0.85 to 0.97; P = 0.003) (Ker, Roberts, Shakur, & Coats, 2015)
- Adverse Outcomes??
    - "There is no evidence that antifibrinolytics have an effect on the risk of vascular occlusive events (quality of evidence: Moderate)" (Ker, Roberts, Shakur, & Coats, p. 2, 2015)
        - Vascular occlusion (RR 0.69, 95% CI 0.44 to 1.07; P = 0.096)
        - Stroke (RR 1.60, 95% CI 0.52 to 4.89; P= 0.40
        - Pulmonary Embolism (RR 0.86, 95% CI 0.46 to 1.61; P = 0.63)
    - "There is no evidence that antifibrinolytics have an effect on the receipt of blood transfusion (RR 0.98, 95% CI 0.96 to 1.01; P = 0.21) (quality of evidence: High)" (Ker, Roberts, Shakur, & Coats, p. 2, 2015)
- Cost Effectiveness
    - Livingstone (2013) said in the United Kingdom, the Tranexamic acid treatment was 20 times cheaper than one unit of PRBCs
    - Cost of Tranexamic acid for FGH is $24.47 per 1 gram dose

PROPOSAL

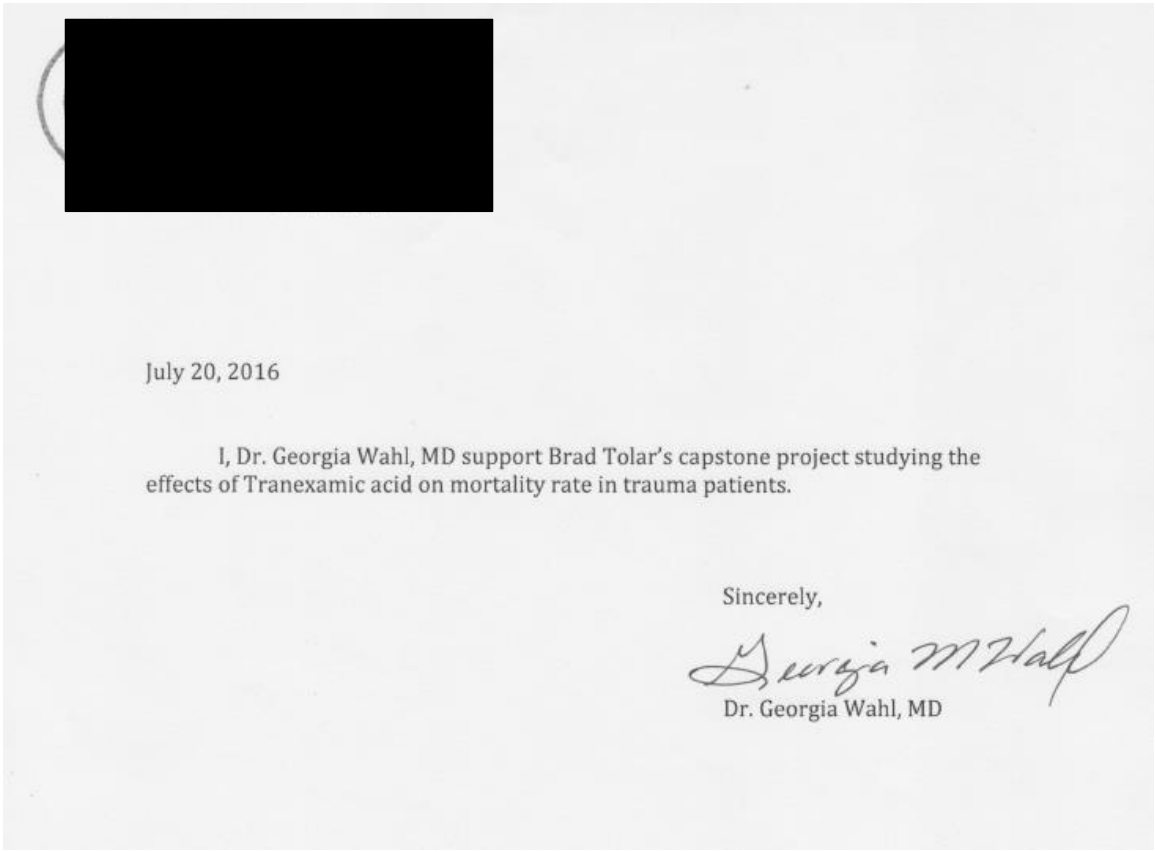
- More widespread use of Tranexamic acid in trauma patients (age 16 and over) with risk of significant bleeding
    - This does not apply to patients with traumatic brain injury with no other injuries

- 1st dose must be given within 3 hours of injury. Times longer than 3 hours are associated with increased risk of death
- Dose used in literature was 1 gram IV loading dose over 10 minutes followed by 1 gram IV given slowly over the next 8 hours
    - Dose was not researched in the literature, but this seemed to be standardized among trials

Further Research?

- Dosing of administration, as this seems to not be debated anywhere for trauma patients
- Outcomes on patients with history of vascular occlusive events
- Statistical analysis among trauma patients at FGH (cost-prohibitive for me)

APPENDIX D – Signed Support Leter



July 20, 2016

I, Dr. Georgia Wahl, MD support Brad Tolar's capstone project studying the effects of Tranexamic acid on mortality rate in trauma patients.

Sincerely,

Dr. Georgia Wahl, MD

THE UNIVERSITY OF
SOUTHERN MISSISSIPPI

INSTITUTIONAL REVIEW BOARD
118 College Drive #5147 | Hattiesburg, MS 39406-0001
Phone: 601.266.5997 | Fax: 601.266.4377 | www.usm.edu/research/institutional.review.board

NOTICE OF COMMITTEE ACTION

The project has been reviewed by The University of Southern Mississippi Institutional Review Board in accordance with Federal Drug Administration regulations (21 CFR 26, 111), Department of Health and Human Services (45 CFR Part 46), and university guidelines to ensure adherence to the following criteria:

- The risks to subjects are minimized.
- The risks to subjects are reasonable in relation to the anticipated benefits.
- The selection of subjects is equitable.
- Informed consent is adequate and appropriately documented.
- Where appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of the subjects.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of all data.
- Appropriate additional safeguards have been included to protect vulnerable subjects.
- Any unanticipated, serious, or continuing problems encountered regarding risks to subjects must be reported immediately, but not later than 10 days following the event. This should be reported to the IRB Office via the "Adverse Effect Report Form".
- If approved, the maximum period of approval is limited to twelve months.
  Projects that exceed this period must submit an application for renewal or continuation.

PROTOCOL NUMBER: 16080505
PROJECT TITLE: The Effects of Tranexamic Acid on Mortality Rate in Trauma Patients Compared to Trauma Patients with no Tranexamic Acid Treatment
PROJECT TYPE: New Project
RESEARCHER(S): Brad Tolar
COLLEGE/DIVISION: College of Nursing
DEPARTMENT: Nursing
FUNDING AGENCY/SPONSOR: N/A
IRB COMMITTEE ACTION: Exempt Review Approval
PERIOD OF APPROVAL: 08/18/2016 to 08/17/2017
Lawrence A. Hosman, Ph.D.
Institutional Review Board

REFERENCES

American Association of Colleges of Nursing. (2006). The essentials of Doctoral education for advanced nursing practice. Retrieved from American Association of Colleges of Nursing: http://www.aacn.nche.edu/dnp/Essentials.pdf

Barash, P. G., Cullen, B. F., Stoelting, R. K., Cahalan, M. K., & Stock, C. (Eds.). (2009). *Clinical Anesthesia* (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Butterworth, J. F., Mackey, D. C., & Wasnick, J. D. (2013). *Clinical Anesthesiology* (5th ed.). New York, NY: McGraw-Hill.

Butts, J., & Rich, K. (2015). *Philosophies and theories for advanced nursing practice* (2nd ed.). Burlington, MA: Jones & Bartlett Learning

Centers for Disease Control and Prevention. (2014). *10 leading causes of death by age group.* (2014). Retrieved March 15, 2016 from http://www.cdc.gov/injury/wisqars/LeadingCauses.html

Gruen, R. L., Brohi, K., Schreiber, M., Balogh, Z. J., Pitt, V., Narayan, M., & Maier, R. V. (2012). Trauma surgery 2 (pp. 999-1013). *The Lancet, 380*. Retrieved from www.thelancet.com

Guerriero, C., Cairns, J., Perel, P., Shakur, H., & Roberts, I. (2011). Cost-effective analysis of administering Tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS ONE, 6*(5), 1-6. http://dx.doi.org/10.1371/journal.pone.0018987

Guyton, A. C., & Hall, J. E. (2006). *Textbook of Medical Physiology* (11th ed.). Philadelphia, PA: Saunders, Elsevier.

Hensley, Jr., F., Martin, D., & Gravlee, G. (2013). *Cardiac Anesthesia* (5th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Hoffman, M. (2004). The cellular basis of traumatic bleeding. *Military Medicine, 169*(12), 5-7. Retrieved from http://publications.amsus.org/

Ker, K., Roberts, I., Shakur, H., & Coats, T.J. (2015). Antifibrinolytic drugs for acute injury. *Cochrane Database of Systematic Reviews 2015*, Issue 5., Art. No.: CD004896. http://dx.doi.org/10.1002/14651858.CD004896.pub4

Livingstone, C. (2013). Tranexamic acid in patients with major injuries and blood loss. *Emergency Nurse, 21*(8), 24-26. Retrieved from http://rcnpublishing.com/journal/en

Meurer, W. (2013). Tranexamic acid reduced mortality in trauma patients who were bleeding or at risk for bleeding. *American College of Physicians*, *159*(6). http://dx.doi.org/10.7326/0003-4819-159-6-201309170-02003

Nagelhout, J. J., & Plaus, K. L. (2014). *Nurse Anesthesia* (5th ed.). St. Louis, MO: Elsevier.

Perel, P., Ker, K., Morales Uribe, C. H., & Roberts, I. (2013). Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database of Systematic Reviews 2013*, Issue 1. Art. No.: CD010245. http://do.doi.org/10.1002/14651858.CD010245.pub2.

Roy, C. (2009). *The Roy adaptation model* (3rd ed.). Upper Saddle River, NJ: Prentice Hall.