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The Effect of Intravenous Tranexamic Acid on Postoperative Blood Loss in Patients Undergoing a Total Knee Arthroplasty

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PERMISSION

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ABSTRACT

Title: The effect of intravenous tranexamic acid on postoperative blood loss in patient's undergoing a total knee arthroplasty

Background: Total knee arthroplasty is a commonly performed surgery, which can result in extensive blood loss. The use of a tourniquet is a standard of practice to help decrease intra-operative blood loss and improve surgical field visualization. However, the hemodynamic changes caused by the tourniquet can exacerbate postoperative blood loss in the hours immediately following surgery. Postoperative blood loss can have negative effects on the patient including: prolonged hospital stay, increased time between surgery and rehabilitation, impaired hemodynamics, need for blood transfusion, and decreased patient satisfaction.

Purpose: The purpose of this independent project is to understand the mechanism of action of tranexamic acid (TXA) and its impact on postoperative blood loss.

Process: A review of the literature was performed using both the Harley E. French Library of the Health Sciences and the Chester Fritz Library from the University of North Dakota. Under the Harley E. French Library of the Health Sciences, the databases PubMed and CINAHL were utilized. Each reference found was extensively reviewed for validity and applied as necessary.

Results: The administration of TXA in patients undergoing total knee arthroplasty has shown to significantly decrease postoperative blood loss. Tranexamic acid is more cost effective and more potent than other fibrinolytic drugs available today. With the decrease in postoperative blood loss, there are better patient outcomes and improved patient satisfaction.

Implications: Unless contraindications are identified, all patients undergoing a total knee arthroplasty should be given TXA.

Key words: Tranexamic acid, TXA, total knee arthroplasty, postoperative blood loss

The Effect of Tranexamic Acid on Postoperative Blood Loss in Patients Undergoing a Total Knee Arthroplasty

Total knee arthroplasty is a commonly performed orthopedic surgery and is often successful in decreasing or eliminating pain due to osteoarthritis. However, as with any surgery, it comes with the risk of complications. The most common complication associated with this surgery is blood loss which can increase morbidity and mortality (Pachauri, Acharya, & Tiwari, 2014). Other complications of total knee arthroplasty include pain and swelling at the joint which impairs postoperative mobilization and decreases patient satisfaction (Ishida, et al., 2011).

Total knee arthroplasty can result in significant blood loss of up to 1790 ml and may result in the patient needing a blood transfusion. However, blood transfusions have been known to be an independent risk factor for several adverse outcomes including myocardial infarction, stroke, infection, renal failure, and even death (van Erve & Wiekenkamp, 2012). Aside from the need for a blood transfusion, excessive blood loss can also impair healing, thus prolonging hospital stay, increasing cost, and jeopardizing patient satisfaction.

Blood loss that occurs intraoperatively and postoperatively is due to blood draining from damaged soft tissue and injury to the bone during surgery (Sepah et al., 2011). Blood loss resulting from surgical trauma will cause an increase in platelet activity, an increase in coagulant factors, and a decrease in coagulation inhibitors (Dahuja, Dahuja, Jaswal & Sandhu, 2014).

There are currently several techniques utilized to reduce the bleeding and prevent the need for a blood transfusion. The techniques utilized are spinal anesthesia, tourniquet use,

hypotensive anesthesia, acute normovolemic hemodilution, minimally invasive surgery, or the use of pre-donated autologous blood (Gao et al., 2016).

A tourniquet is almost always used for this type of surgery to decrease intraoperative blood loss and create a clearer surgical field for the surgeon. The use of a tourniquet does not have any effect in decreasing the amount of blood lost postoperatively (Dahuja, et al., 2014). For this type of surgery, a tourniquet can affect the coagulation cascade and exacerbate postoperative blood loss and hemorrhage. Once the clotting cascade is initiated, it is difficult to stop the process. Tourniquet use causes an increase in fibrinolysis in the area and therefore, patients can lose a large amount of blood in the days following surgery which can delay healing and prolong hospitalization (Sepah et al., 2011).

Tranexamic acid is a synthetic drug that inhibits fibrinolysis by blocking one of the binding sites of plasminogen and can also act as an inhibitor of plasmin if given at higher concentrations (Dahuja et al., 2014). This drug has been around for a long time, and its use in total knee arthroplasty has been studied over the last ten years to determine the significance of the drug. It is utilized in surgery, both intravenously and intraarticularly, to prevent postoperative blood loss and to decrease the need for blood transfusions (Danninger & Memtsoudis, 2015).

Purpose

The purpose of this evidence based independent project is to examine the effects of TXA on postoperative blood loss in patients undergoing a total knee arthroplasty. Anesthesia providers are responsible for administering medications in the perioperative period and should be aware of interventions available to decrease postoperative blood loss and improve patient outcomes.

Case Report

A 54-year-old, 139kg, 180cm Caucasian male presented for a right total knee arthroplasty due to arthritis. The patient had no known allergies. Medical history included hyperlipidemia, gastroesophageal reflux disease (GERD), type 2 diabetes, nephrolithiasis, eczema, attention-deficit hyperactivity disorder (ADHD), arthritis of the knee, depression, gout, obesity, anxiety, narcissistic personality disorder, and mood disorder. Current medications included: metformin, omeprazole, potassium, atorvastatin, allopurinol, aspirin, lamotrigine, cholecalciferol, and amphetamine/dextroamphetamine. Previous surgical history included a knee arthroscopy, strabismus surgery, left knee arthroplasty, and colonoscopy. The patient denied any previous anesthetic complications. However, it was noted that the patient experienced a deep vein thrombosis (DVT) in 2003 after an anterior cruciate ligament (ACL) repair.

The patient was classified as an American Society of Anesthesiologists (ASA) physical status level three. Airway evaluation revealed a Mallampati score of two with a Thyromental distance of less than three fingerbreadths. The patient had full range of motion in his neck and a normal dental exam. All pre-operative lab results were within normal limits, and patient's preoperative hemoglobin and hematocrit levels were 15.9 g/dL and 45.6%, respectively. Preoperative electrocardiogram (EKG) revealed the patient was in normal sinus rhythm with a right bundle branch block. Preoperative vital signs were blood pressure 136/84 mmHg, heart rate 96/min, respirations 16/min, temperature 97.7 degrees Fahrenheit and room air oxygen saturation (Sp02) 95%.

The patient was transported to the operating room and remained on the bed for placement of the spinal anesthetic. Standard monitors which included non-invasive blood pressure cuff (NIBP), a pulse oximeter, and three lead EKG were simultaneously applied to the patient. Prior to the spinal anesthetic, he was administered midazolam 2 milligrams (mg) intravenously (IV) and fentanyl 100 micrograms (mcg) IV. The patient was assisted into a sitting position per operating room (OR) staff. His back was prepped in a sterile fashion and a sterile drape was applied. The spinal was placed with some difficultly and ultimately a 22-gauge, 5inch Pencan needle was used with success. Positive cerebral spinal fluid was obtained and negative for blood and/or paresthesias. Bupivacaine 0.5% 4 milliliters (mL) was injected into the subarachnoid space. The spinal needle was removed, and the patient was placed in the supine position. He was assisted onto the surgical table per OR staff and prepped and draped for surgery. The patient's vital signs remained near baseline after spinal placement and, a propofol drip was started at 50 mcg/kg/min IV for sedation. An end-tidal carbon dioxide (ETC02) monitoring nasal cannula was placed on the patient and oxygen was delivered at four liters per min for the duration of the surgery.

Since the patient had a history of a DVT, the CRNA spoke with the surgeon before the administration of tranexamic acid to ensure it was safe to administer to the patient and there would be no increased risk of postoperative complications. With the surgeon's acknowledgement and permission, one gram of tranexamic acid was administered IV prior to inflation of tourniquet. The patient remained stable throughout the procedure and did not require the administration of any vasopressors. Propofol was titrated from 25 mcg/kg/min to 75 mcg/kg/min based on patient's comfort level, sedation level, and hemodynamics. Once the tourniquet was deflated, an additional one gram of tranexamic acid was administered IV. Zofran 4 mg IV was

administered for postoperative nausea and vomiting prophylaxis. At the conclusion of surgery, the propofol infusion was discontinued, an auto transfuse drain was placed, and it was estimated that the patient had 600 mL blood loss. Throughout the procedure, the patient received a total of 2,600 mL of Lactated Ringers (LR) solution, plus an additional 200 mL of tranexamic acid. The patient remained stable upon transfer to the post-anesthesia care unit (PACU), report was given, and care was transferred to the PACU nurse.

On the same surgical day, there was 620 ml output from the auto transfuse drain. On postoperative day one, his hemoglobin was 12.7 g/dL and drain output was 50 ml. The autotransfuser drain was removed on postoperative day one with a total of 670 ml output. The patient did experience a decline in his hemoglobin level, but it was not significant enough to require a blood transfusion, nor did the patient exhibit compromised hemodynamics that would indicate the need for one.

Literature Search

A literature search was conducted online utilizing both the Chester Fritz Library and the Harley French library through the University of North Dakota website. Each article found was carefully reviewed for the strength of research, validity, and applicability to the use of tranexamic acid in total knee arthroplasty and its effect on postoperative blood loss.

The Chester Fritz Library was utilized first, and two searches were completed. The search words “tranexamic acid in knee surgery AND postoperative blood loss” were typed into the search bar, which resulted in 35 articles. Seven of the 35 articles were reviewed in great detail due to applicability and type of study that was conducted. Any articles that did not involve the administration of intravenous tranexamic acid were not reviewed. Four of the seven were found to be relevant and applicable to this independent project. The text in the search bar was then

changed to “intravenous tranexamic acid in knee surgery AND postoperative blood loss.” This search returned five results. However, only one addressed the administration of tranexamic acid intravenously and was found to be relevant to the discussion.

It was also of interest to research articles relevant to the mechanism of action of the drug. Therefore, “mechanism of action for tranexamic acid AND total knee arthroplasty” was typed in the search box. That search resulted in two articles, but only one of them was relevant to the topic.

The Harley French Library was then utilized through the University of North Dakota website, and the search was conducted through PubMed. “Tranexamic acid total knee AND postoperative blood loss” was typed into the search bar which returned 29 results. Those 29 articles were reviewed, and seven were found to be relevant.

The next search was conducted through the database CINAHL with the words “tranexamic acid AND total knee” which returned 40 articles that were carefully reviewed. Of the 40 articles that resulted, six of them were relevant to the topic. However, two coincided with articles that were found in previous searches. More literature was needed regarding how to how TXA affects the clotting cascade and coagulation factors in patients undergoing total knee arthroplasty, therefore “tranexamic acid AND clotting AND total knee arthroplasty” was typed into the search box. This search returned 26 articles, and seven were reviewed in further detail. Of those seven, four were saved for the use in this paper, and one was found in a previous search.

All articles were found utilizing the libraries available through the University of North Dakota website. Several articles were reviewed regarding their relevance to the purpose of this project. After this search was complete, a total of 20 articles were saved. A summary of the articles will be presented in the subsequent sections of the paper.

Review of Literature

Pathophysiology and the Clotting Cascade

The body has a delicate system to maintain hemostasis between clotting and bleeding. When there is a disturbance in the inner layer of the blood vessel wall, the body begins a series of reactions to stop the bleeding, form a clot and allow the intima layer to heal. After the healing process has occurred, other physiological changes occur to dissolve the clot and maintain the fine balance of hemostasis. If there is any disruption in this process, the patient may experience hemorrhage or thrombosis (Nagelhout & Plaus, 2014).

There are three layers of endothelial cells that make up a blood vessel. The inner-most layer of the blood vessel is called the intima. It is responsible for keeping the moving blood separate from the vessel itself. These endothelial cells that make up the intima have a large role in maintaining hemostasis by creating and excreting procoagulants, anticoagulants, and fibrinolytics. They also have the ability to suppress coagulation by secreting coagulation inhibitors. Another important function of this layer is to keep the fluid contents of the blood separate from the thrombogenic factors. By doing so, this keeps the thrombogenic factors away from the vessel wall otherwise, they can activate the process of clotting. When this endothelial wall becomes damaged, it can no longer keep the blood components away from the wall of the vessel, therefore causing coagulation. (Nagelhout & Plaus, 2014).

The second layer is called the subendotheilial layer. It is rich with collagen which helps anchor platelets to repair an injury to the vessel wall. The third layer is called the adventitia and

it produces factors that have a role in both platelet function and vasodilation of the vessel itself (Nagelhout & Plaus, 2014).

When there is an injury to the vessel wall, it is detected by the intima layer. The tissue factor in this intima layer then activates the clotting cascade. Immediately after the injury occurs, the vessel wall will contract to decrease the blood flow to the area. The vasoconstriction causes the autonomic nervous system to respond by releasing factors to dilate the surrounding tissue to ensure adequate blood distribution. When the injured area of the blood vessel wall contracts, it initiates a series of events to form the clot in order to stop the bleeding. These events are separated into stages: adhesion, activation, and aggregation (Nagelhout & Plaus, 2014).

During the adhesion stage, von Willebrand Factor appears on the endothelial lining. Glycoprotein Ib appears from the platelet surface and attaches to the vWF, which makes the platelets "sticky" and able to attach to the vessel wall at the injury site. Two other glycoproteins, IIb and IIIa also appear from the platelet surface. They are responsible for linking the platelets together and forming the major platelet plug, which seals the injury and allows the site to heal. If the injury is small, this primary platelet plug is adequate to seal the injury and stop the bleeding. If the injury is large, the primary platelet plug is not adequate, and activation of the clotting cascade will occur (Nagelhout & Plaus, 2014).

The coagulation factors associated with the clotting cascade are always present in the circulation blood system. They remain inactive until activated as a result of a hemorrhagic state due to damage to the tissues or an organ. There are two different clotting pathways called the intrinsic and extrinsic pathway. Even though they work independently of each other, they both involve the common clotting pathway and involve platelet activity. The extrinsic pathway is activated by tissue factor when there is injury outside the vessel wall. The intrinsic pathway is

activated when there is damage to the blood vessel itself by prekallikrein and also from the activation of Hageman factor, or factor XII. In both pathways, once a factor is activated it creates a domino effect by activating subsequent factors. Calcium (factor IV) plays a large role and helps create this domino effect in the intrinsic pathway. The conversion of thrombin to prothrombin is extremely important in both pathways and allows the platelets to move to the area of injury. There must be enough thrombin available to activate a sufficient amount of fibrin to the injury and form an adequate clot (Nagelhout & Plaus, 2014)

Whether the injury has activated the intrinsic or extrinsic pathway, fibrin is created to seal and allow the injury to heal. Once this process is complete, the body has a mechanism in place to prevent an excess buildup of fibrin that could cause blockages and disruption in blood supply. The fibrinolytic system helps to degrade fibrin and is regulated heavily by plasma proteins. At the time of injury, there is increase blood flow which helps wash away procoagulant factors to reduce the size of the clot and help maintain hemostasis. Thrombin now behaves as an anticoagulant and can activate other anticoagulant factors, one of which is antithrombin III. Antithrombin III is one mediator responsible for the movement of factors in the clotting cascade. When it is activated, it removes these factors from the clotting cascade, which stops the formation of the clot. Plasminogen, plasmin, fibrin, and fibrin degradation products are what makes up a clot. Plasminogen, which is made in the liver, is continually stored in the body in an inactivated form. When the clotting cascade is activated and a clot is forming, plasminogen incorporates itself into the clot and is activated into plasmin by tPA and urokinase. Once plasmin is activated, it causes fibrin to breakdown into fibrin degeneration products and the body's circulatory system is responsible for removing the waste products of the clot. Once the healing

process is complete and the clot has been digested, alpha-Antiplasmin and tissue plasminogen activator inhibitor are responsible for stopping fibrinolysis (Nagelhout & Plaus, 2014)

Tranexamic Acid Mechanism of Action

In patient's undergoing a total knee arthroplasty, there is activation of both the intrinsic and the extrinsic pathways. The clotting cascade is activated to produce clots to seal the injury and promote healing. The fibrinolytic system is activated due to the presence of fibrin and is responsible for breaking down the clots to allow the vessel to maintain patency. When plasminogen is trapped inside a clot, it binds with lysine residues present on the fibrin surface and creates plasmin. The plasmin is responsible for degrading fibrin into large fragments, which continue to be degraded into fibrin degradation products and essentially eliminated through the circulatory system. This entire process is the called fibrinolysis (McCormack, 2012).

If this fibrinolytic system is activated and works in excess amounts, it will result in excess bleeding. By administering medications that work on the fibrinolytic system, it can prevent excess fibrinolysis and improve patient outcomes. Excessive fibrinolysis can result in hemorrhage, subarachnoid hemorrhage, and the need for blood transfusions. There are currently several medications available that work on the fibrinolytic system and are commonly administered, one of the medications is TXA (McCormack, 2012).

Tranexamic acid is a synthetic drug derived from the amino acid lysine. Once administered, it reversibly binds with high affinity to one of the lysine binding sites on plasminogen and also binds to four or five other sites with low affinity. Once TXA has bound to plasminogen, the plasminogen is unable to bind with fibrin to complete fibrinolysis. Since TXA only binds to few sites, there may still be some conversion of plasminogen to plasmin. However,

once plasminogen is in the presence of TXA, it is no longer able to interact with fibrin and exhibit its effects. When plasminogen is unable to exert its action on fibrin, the fibrin is unable to create fibrin degradation products and the clot remains intact which prevents re-bleeding. (McCormack, 2012; Sepah et al., 2011). Since the clot remains intact, there is no activation of the clotting cascade, and excessive bleeding following surgery is significantly decreased (Sadigursky et al., 2016).

The administration of TXA has been compared with aminocaproic acid, which was historically used for the same indications. There have been studies conducted to examine the efficacy and differences between the two. While studies have shown there are no differences, TXA has been found to have a much higher binding potency than aminocaproic acid. Tranexamic acid has also been found to have a dose-dependent effect on fibrinolysis, however, this has only been proven in animal studies (McCormack, 2012).

The altered laboratory studies associated with the administration of TXA include prolonged prothrombin time and reduced D-dimer concentration when given at dosages greater than 10 mg/mL. After administration of TXA, the drug is found to have the highest concentrations in the liver, kidneys, and lungs. It is metabolized a small amount and is excreted mostly unchanged via the kidneys. Therefore, there does not need to be any dosage adjustments for patients with hepatic failure. There are limited studies on the clearance of TXA in patients with renal disease. However, it has been found that as plasma creatinine levels increase, the excretion of TXA decreases. Therefore, dosage changes may be needed in patients with renal insufficiency. Tranexamic acid crosses the placenta and creates concentrations in the newborn similar to those in the mother and was also found in breast milk after administration. It also crosses the blood brain barrier and was discovered in the cerebral spinal fluid after

administration. The drug itself is rapidly absorbed and has an elimination half-life of two to three hours while preserving therapeutic levels for six to eight hours (McCormack, 2012; Sadigursky et al., 2016).

Since TXA is excreted mostly unchanged, there is little concern for drug to drug interactions, but there are some pharmacodynamical interactions that a practitioner should be cognizant about. The patient may be at an increased risk for thrombotic events if administered with oral contraceptives or other drugs that interfere with the fibrinolytic system such as haemocoagulase, factor IX complex concentrates, batroxobin or thrombin. If TXA is administered with tissue plasminogen activators, there may be a reduced efficacy in both of the drugs (McCormack, 2012).

Tranexamic acid is associated with very few side effects and is well tolerated for the majority of patients. The most commonly reported side effects were associated with oral administration and include a headache, dizziness, anemia, dysmenorrhea, and GI symptoms such as nausea, vomiting, and dyspepsia. Since TXA is an inhibitor of fibrinolysis, there are recommendations to avoid the drugs in patients with an increased risk of thrombotic events. There have been rare occurrences of DVT, pulmonary embolism (PE), acute renal cortical necrosis, central retinal artery and vein obstruction, and cerebral thrombosis in patients that receive the drug. The indication of the drug in the patients receiving it and the incidence of adverse effects are varied. However, there have been numerous trials of TXA completed, all have found that the administration of TXA does not increase the risk of myocardial ischemia or infarction, DVT, renal insufficiency, PE, mortality or any other thrombotic complications (McCormack, 2012).

The effective dosage of TXA has yet to be determined, but several sources have come to the conclusion that 10-15 mg/kg IV is a sufficient dose to produce therapeutic levels and provide an adequate reduction in plasminogen activity (Blaine et al., 2013; Dahuja et al., 2014). However, a commonly used dose and one that has found to be effective is 2000 mg IV, typically given both before and after tourniquet inflation. (Poeran et al., 2014). Since the clotting cascade and fibrinolytic system occur in a domino effect, it is most successfully inhibited early in the activation process. For this reason, it has been found that TXA administration should be started prior to inflation of the tourniquet to obtain early therapeutic levels (Pachauri et al., 2014).

Tourniquet Use

The use of a tourniquet is common practice for total knee arthroplasty to help decrease intraoperative blood loss and aid the surgeon with a clear surgical field. However, the use of a tourniquet can increase fibrinolysis to the area and cause an increase in postoperative bleeding, especially in the first six hours following the procedure (McCormack, 2012). Before the tourniquet is inflated, an Esmarch bandage is used to exsanguinate the limb. The tissue damage experienced by the exsanguination activates platelet aggregation (Kam, Kavanaugh & Yoong, 2001).

There are other complications that can be associated with tourniquet use due to ischemia experienced distal to the cuff and is associated with both inflation and deflation (Kam et al., 2001). When the tourniquet is inflated, there are physiological changes that occur to produce a hypercoagulable state and increase bleeding. When the tourniquet is inflated for greater than 45-60 minutes, the patient may experience “tourniquet pain,” which is associated with increased heart rate and blood pressure. Although the vital signs should return to normal after deflation of

the tourniquet, the increase in pressure could contribute to and increase blood loss. This pain also stimulates the release of catecholamines into the circulatory system that causes platelet aggregation and thereby placing the patient in a hypercoagulable state (Burleson et. al, 2016).

When the tourniquet is released the tissue damage, and inflammation cause the release of tissue plasminogen activator which activates antithrombin III and thrombomodulin that causes thrombolysis post-traumatic fibrinolysis (Pachauri et al., 2014). There is also an increase in the peripheral blood thrombolytic activity. Although this increase typically lasts for 30 mins, it can have a great impact on the amount of blood lost in the immediate postoperative period (Kam et al., 2001). However, Blanié et al., (2013) state that fibrinolysis is the highest with the use of tourniquet and peaks six hours after surgery. This fibrinolysis can last up to two days following total knee replacement. Furthermore, the anoxia and tissue acidosis has thought to have a role in promoting the release of tissue plasminogen activator. However, the degree of ischemia experienced and the extent of fibrinolysis is not completely understood (Kam et al., 2001).

Effect of Tranexamic Acid

After reviewing the evidence, several studies consistently show that TXA reduces the amount of blood loss postoperatively and thus reduces the need for blood transfusions. (Alvarez et al., 2008; Benoni, Lethagen & Fredin, 1997; Blanié et al., 2012; Burleson et al., 2016; Dahuja et al., 2014; Danninger & Memtsoudis, 2015; Formby, Pickett, Van Blarcum, Mack, & Newman, 2015; Gao et al., 2016; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016; Sepah et al., 2011). Several studies have found statistically significant variances of patients' hemoglobin levels after the administration of TXA compared to control groups. The results show that after the administration of TXA, patients experience less of a hemoglobin decrease and maintain higher hemoglobin levels postoperatively (Alvarez et al., 2008; Dahuja et al., 2014;

Formby et al., 2015; Gao et al., 2016; Sadigursky et al., 2016). Formby et al., (2015) found that the patients receiving TXA had increased hemoglobin levels on postoperative day two compared to the control group. It has also been found that the administration of TXA prevents bleeding and it is significant in the reduction in postoperative blood loss that a cell salvage drain is no longer necessary in patients that receive TXA (Alvarez et al., 2008; Poeran et al., 2014; Sadigursky et al., 2016).

There is a lack of evidence on the safety index for administering TXA to patients that are at risk for thrombotic events or patients with a previous history of MI or stroke. Although several studies have found that the administration of TXA did not have any increased risk for adverse events, there is a limited amount of evidence on the research specific to at-risk patients (Danninger & Memtsoudis, 2015; Gao et al., 2016; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016). Hiippala et al., (1995) looked at patients who were treated for several weeks following the administration of TXA due to various postoperative complications. It was found that the administration of TXA had no effect on the fibrinolytic activity in the walls of the vein. This could be in part the reason why these patients did not experience any adverse thrombotic events and why the administration of TXA has not been associated with an increased risk of thrombotic events.

Danninger & Memtsoudis (2015) addressed the issue of increased risk for adverse myocardial events and presented a valid point. The research has found TXA to be safe and efficacious without increasing the risk of any adverse events including thrombotic events. To argue that TXA increases the risk for myocardial infarction, the underlying pathophysiology of it must be presented. The pathophysiology includes decreased blood supply to the coronary arteries; plaque formation, and breakage to form a disruption in blood supply; or platelet

activation. Tranexamic acid works by blocking a receptor to help prevent the breakdown of already formed clots, thus decreasing bleeding. It does not cause platelet activation, which is a cause for thrombotic adverse events and why it has been found to have no increased risk for thrombotic events (Blanié et al., 2012; Gao et al., 2016). Hemoglobin is responsible for carrying oxygen molecules and delivering them to the tissues. Since TXA decreases blood loss and thus maintains normal a hemoglobin, the patient will be less likely to experience ischemic events due to decreased blood flow and oxygen delivery. Also, when patients experience blood loss, the body responds by increasing the heart rate. An increased heart rate can decrease blood supplied to the coronary arteries by decreasing diastole time. The authors even went further to say that due to these physiological changes experienced by patients during acute blood loss, TXA could prevent myocardial infarctions and ischemic events by decreasing blood loss. However, more evidence is needed to support this theory (Danninger & Memtsoudis, 2015).

Many studies and trials have been conducted on TXA and its use in cardiac surgery. The results of these studies have shown that in cardiac surgery when the patient is at an increased risk of myocardial infarction, the administration of TXA does not increase the incidence of myocardial infarction (McCormack, 2012).

Benoni et al. (1997) completed and utilized laboratory studies to determine the effects of TXA on fibrinolysis and D-dimer levels in peripheral blood and blood sampled from the wound. D-dimer blood levels were drawn pre-operatively and were used for comparison. Patients were either given a dose of TXA IV or the placebo, which consisted of saline. Lab values were drawn when the tourniquet was released and again three hours after the surgery was complete. The lab values showed that fibrinolysis remained increased throughout the entire period. It was found that the administration of TXA decreased the D-dimer levels from both the blood sampled from

the wound and peripheral blood drawn but had no effect on the tPA or PAI-1 levels. The findings specific to the wound show TXA creates local fibrinolysis that continues after administration to help decrease postoperative bleeding. The blood loss in the TXA group was half that of the placebo group, which is statistically significant. However, the peripheral blood samples were compared with those of the control group, and it was found that there were no statistically significant differences in D-dimer levels between the two. This suggests that the TXA group continued to have local fibrinolysis specific to the wound, rather than systemically. Based on these findings it is hypothesized that the administration of TXA remains specific to the wound and does not produce a systemic prothrombotic state, which would indicate why all studies conducted thus far have found the administration of TXA does not increase the risk for thrombotic events.

Cost Effectiveness

Studies compared TXA to alternative drugs previously used to decrease postoperative blood loss such as aminocaproic acid and fibrin sealants. Gao et al. 2016 compared TXA to fibrin sealants, it not only found that TXA had decreased postoperative blood loss and improved hemoglobin levels compared to fibrin sealants, but TXA was also more cost effective. Aminocaproic acid is a medication that is commonly used during surgery for the same reasons as tranexamic acid because they have the same mechanism of action. However, when comparing the two, TXA is 7-10 times more potent than aminocaproic acid and is cheaper which makes it more cost effective. (Danninger & Memtsoudis, 2015; Gao et al., 2016).

The administration of TXA decreases postoperative blood loss and reduces the need for blood transfusions, this can also significantly decrease the costs associated with complications related to blood transfusions (Gao et al., 2016; Pachauri et al., 2014; Poeran et al., 2014; Sepah et

al., 2011). Studies have indicated that patients who received TXA not only had a decrease in the length of hospital stay, but also had a decrease in the cost of their hospital stay if length remained the same (Danninger & Memtsoudis, 2015; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016). Patients benefited from earlier rehabilitation with the administration of TXA, which can improve patient satisfaction and increase hospital reimbursement (Sadigursky et al., 2016).

Discussion

The patient in this independent project was undergoing a total knee arthroplasty for the treatment of right knee pain due to arthritis of the knee. As presented above, the patient did exhibit some risk factors for increased blood loss including increased BMI and increased blood glucose levels. The patient had a history of DVT after an ACL repair in 2003, which places him at an increased risk for a subsequent DVT. Tourniquet use during the surgery also places the patient at an increased risk for DVT. The patient's preoperative hemoglobin and hematocrit were within normal range.

Tranexamic acid was ordered by the surgeon to be given intravenously both before inflation and after deflation of the tourniquet. This dosing regimen is commonly used and has been found to be acceptable to achieve effective therapeutic levels of the drug. Due to the patient's history of a DVT, it was verified with the surgeon that the administration of tranexamic acid continued to be his recommendation. Tranexamic acid is an inhibitor of fibrinolysis therefore, there are some recommendations to avoid the medication in patients who are at an increased risk for thrombotic events. However, several studies have shown that the administration of TXA does not increase the risk of thrombotic events including DVT. As stated above, laboratory studies have found that the fibrinolysis produced by TXA is specific to the

wound and is not evident in the vessel wall itself. Due to the evidence, it was determined that administering TXA to this patient, even with a history of DVT, was safe and appropriate.

Spinal anesthesia was utilized for this patient, as this type of anesthesia has been shown to decrease blood loss with this type of surgery. An auto transfuse drain was placed to reduce the need for a blood transfusion if the patient were to exhibit symptoms of altered hemodynamics. No other interventions were utilized to decrease blood loss.

The patient experienced a total blood loss of 1,270 mL during the surgical procedure. However, the patient remained stable and did not require a blood transfusion. The patient's hemoglobin dropped from 15.9 g/dL preoperatively to 12.7 g/dL on postoperative day one. According to Grossman and Porth (2014), the normal hemoglobin range for males is 14-16.5 g/dL. Though the patient's hemoglobin level was below the normal, it did not negatively impact the patient's outcomes. Through a review of the evidence, it can be suggested that the administration of TXA for this patient helped decrease postoperative blood loss. With the reduction in postoperative blood loss, the patient did not require a blood transfusion.

Conclusion

In conclusion, there has been extensive research on the benefits of administering tranexamic acid to patients undergoing a total knee arthroplasty to reduce the amount of blood loss. This medication will help improve postoperative hemoglobin levels, enable early rehabilitation, decrease hospital costs and possibly decrease the length of hospital stay. The current research has also shown that there is little risk in administering tranexamic acid to patients, yet more research needs to be done for at-risk patients. Overall, the benefits outweigh

the risks. The administration of TXA should become standard practice in patients undergoing a total knee arthroplasty.

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Appendix A

The Effect of Intravenous Tranexamic Acid on Postoperative Blood Loss in Patients Undergoing a Total Knee Arthroplasty

Kaylene Hill, SRNA

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Introduction

- Total knee arthroplasty is a commonly performed orthopedic surgery
  - The most common complication associated with this type of surgery is blood loss and the need for a blood transfusion
- Blood transfusions have been found to be an independent risk fact for myocardial infarction, stroke, infection, renal failure, and even death

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Case Information

- Surgical Procedure
  - Right total knee arthroplasty
- Age- 54 y/o
- Weight- 139kg
- Gender- male
- ASA- 3
- No known allergies

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Pre-operative Evaluation

- Medical History
  - Hyperlipidemia, gastroesophageal reflux disease, type 2 diabetes, nephrolithiasis, eczema, attention deficit hyperactivity disorder, arthritis of the knee, depression, gout, obesity, anxiety, narcissistic personality disorder, and mood disorder. The patient also experienced a deep vein thrombosis after a previous knee surgery.
- Surgical History
  - Knee arthroscopy, strabismus surgery, left knee arthroplasty, and colonoscopy
- Pre-op VS
  - BP 136/84, HR 96, RR 16, oxygen sat 95%
- Pre-op labs
  - unremarkable (Hgb 13.9 g/dl, Hct 45.6%)
- Airway assessment
  - Mallampati II, normal TMD, full ROM in his neck and normal dental exam
- ECG
  - NSR with right bundle branch block

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Anesthetic Course

- Induction
  - Fentanyl 100mcg
  - Versed 2mg
- Technique
  - Spinal anesthesia with 22g Pencan needle
  - Bupivacaine, 0.5%, 4 mL
- EtC02 NC at 4 L/min
- Maintenance
  - Propofol 25-75mcg/kg/min
  - Tranexamic acid, 1,000mg both before and after tourniquet use
- Anti-emetics
  - Zofran 4mg

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Intraoperative Issues

- Total Anesthesia Time
  - 3 hours
- Estimated Blood loss
  - 600ml
- Volume replacement
  - Crystalloid 2600ml
- Additional medications
  - 200 mL Tranexamic acid

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Post-operative course

- Auto transfuse drain placed
- Admitted to general floor
  - Same day 620 mL output from drain
  - Postoperative day one, hgb 12.7 g/dL and 50mL output from drain
  - Drain removed on postoperative day one for total output of 670 mL

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Pathophysiology of blood loss

- Blood loss occurs both intraoperatively and postoperatively
- Blood loss from surgical trauma causes an increase in platelet activity, an increase in coagulant factors and a decrease in coagulation inhibitors

(Dahuja, Dahuja, Jaswal, & Sandhu, 2014; Sepah et al., 2001)

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Pathophysiology and clotting cascade

- Three layers make up the blood vessel wall (intima, subendotheilial, and adventitia)
- Inner most layer keeps the blood flowing and excretes procoagulants, anticoagulants, and fibrinolytics
- The second layer is rich in collagen, which helps platelets adhere to the wall to repair the injury
- The third layer produces factors in platelet function and factors that produce vasodilation and vasoconstriction

(Nagelhout & Plaus, 2014)

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Pathophysiology and clotting cascade

- When there is damage to the vessel wall, it is detected by the intima layer and the body responds to repair the injury.
- Vasoconstriction at the injury site occurs
- Different stages then occur to stop the bleeding and repair the damage

(Nagelhout & Plaus, 2014)

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Pathophysiology and clotting cascade

- Adhesion stage
  - Von Willebrand factor appears and attaches to glycoprotein Ib to make platelets "sticky"
  - Platelets are linked together to form platelet plug
- Activation stage
  - Occurs when the platelet plug is not adequate to seal the injury and thus, the clotting cascade is activated
  - Fibrin is created to seal the injury and allow it to heal

(Nagelhout & Plaus, 2014)

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Fibrinolysis

- Four factors make up a clot
  - Plasminogen, plasmin, fibrin and fibrin degradation products
- Once the injury is healed, fibrinolysis occurs to prevent excess buildup of fibrin

(Nagelhout & Plaus, 2014)

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Fibrinolysis

- Alpha-Antiplasmin and tissue plasminogen activator inhibitor are responsible for stopping fibrinolysis
- Antithrombin III is activated to remove factors from the clotting cascade
  - Stops the formation of clots

(Nagelhout & Plaus, 2014)

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Factors to help decrease blood loss

- Spinal anesthesia
- Use of tourniquet
  - Does not affect blood lost postoperatively
- Hypotensive anesthesia
- Acute normovolemic hemodilution
- Minimally invasive surgery
- Use of pre-donated autologous blood

(Gao et al., 2016)

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Tourniquet use

- Tissue damage experienced by the Esmarch bandage causes an activation in platelet aggregation
- Tourniquet inflation produces hypercoagulable state
- At deflation, tissue damage and inflammation causes the release of tissue plasmin activator

(Burelson et al., 2016; Kam, Kavanaugh, & Yoong, 2001)

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Tourniquet use

- After tourniquet use, there is an increase in peripheral blood thrombotic activity
- Fibrinolysis peaks 6 hours after surgery but lasts up to two days
- Anoxia and tissue acidosis also promote the release of tissue plasminogen activator

(Blanié et al., 2013; Pachauri, Acharya, & Tiwari, 2014)

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Tranexamic Acid

- Derived from amino acid lysine
- Reversibly binds with high affinity to one of the lysine binding sites on plasminogen
- Once TXA is bound, plasminogen is unable to bind with fibrin to complete fibrinolysis
- Plasminogen can no longer interact with fibrin to create fibrin degradation products
- Clot remains intact

(McCormack, 2012, Sadigursky et al., 2016; Sepah et al., 2001)

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Tranexamic Acid Effectiveness

- Reduces amount of postoperative blood loss
- Reduces the need for blood transfusions
- Decreased hemoglobin drop in patients postoperatively

(Alvarez et al., 2008; Benoni, Lethagen & Fredin, 1997; Blanié et al., 2012; Burleson et al., 2016; Dahuja et al., 2014; Danninger & Memtsoudis, 2013; Formby, Pickett, Van Blarcum, Mack, & Newman, 2015; Gao et al., 2016; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016; Sepah et al., 2011)

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Risks and Contraindications

- Several studies have found that TXA does not increase the risk for adverse events
- McCormack, 2012 found that the administration of TXA in cardiac surgery does not increase the risk of myocardial infarction

(Danninger & Memtsoudis, 2015; Gao et al., 2016; Hiippala et al., 1995; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016)

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Current FDA Contraindications

- Colorblind patients
- Patients with:
  - Subarachnoid hemorrhage
  - Active intravascular clotting
  - Allergy or hypersensitivity to TXA

(FDA, 2017)

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Current FDA Precautions

- Renal insufficiency
- Patients with a history of thrombotic disease
- Concurrent administration with Factor IX or anti-inhibitor coagulant concentrates
- Patients in DIC

(FDA, 2017)

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Laboratory studies

- Tranexamic acid administration has no effect on fibrinolytic activity on vessel walls
- Creates local fibrinolysis specific to the wound, that lasts through the postoperative period

(Hiippala et al., 1995; Benoni et al., 1997)

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Cost Effectiveness

- Compared to aminocaproic acid
- Decreased hospital costs
  - Earlier rehabilitation
  - Decreased hospital stay
  - Improved patient satisfaction

(Danninger & Memtsoudis, 2015; Gao et al., 2016; Pachauri et al., 2014; Poeran et al., 2014; Sadigursky et al., 2016; Sepah et al., 2011)

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Recommendations

- Unless contraindications are identified, all patients undergoing a total knee arthroplasty should be given TXA.
- Further research is needed to determine safety in at risk patients

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Conclusion

- Patient given TXA despite previous history of DVT
  - No adverse events and patient did not require need for blood transfusion
- TXA should be considered in any patient undergoing total knee arthroplasty to improve patient outcomes

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Thank You
Are There Any Questions?

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