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TRANEXAMIC ACID UTILIZATION IN CESAREAN SECTION PATIENTS

by

Justin Heinz

An Independent Study

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of the

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In partial fulfillment of the requirements

For the degree of

Master of Science

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PERMISSION

Title Tranexamic Acid Utilization in Cesarean Section Patients
Department Nursing
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Abstract

Title: Tranexamic Acid Utilization in Cesarean Section Patients

Background: Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality and is responsible for one-quarter of all maternal deaths worldwide (Mpemba, Kampo & Zhang, 2014). The most common complications documented with cesarean sections are primary and secondary postpartum hemorrhage (Goswami, Sarangi, Gupta, & Babbar, 2013). A safe, low-cost, effective therapy is needed to help reduce the incidence of PPH and its associated morbidity and mortality. Tranexamic acid (TXA) is an antifibrinolytic agent that prevents the conversion of plasminogen to plasmin stabilizing clot formation in bleeding patients (Alam & Choi, 2015). TXA has been shown to reduce blood loss, transfusion requirements, and mortality in multiple perioperative settings including cardiac surgery, liver surgery, orthopedic surgery, spine surgery, and trauma cases (Alam & Choi, 2015). Tranexamic acid administration for the prevention of PPH in women undergoing a cesarean section is an area of practice that needs to be further investigated.

Purpose: To evaluate the current data on the effectiveness of tranexamic acid reducing blood loss in cesarean section deliveries.

Process: A systemic literature review was carried out using the University of North Dakota's Harley E. French Library. Databases used included CINAHL and PubMed. The search was conducted using keywords and restricted timeframe to include only the most current research. Databases were searched to determine the effectiveness of tranexamic acid reducing blood loss in cesarean sections.

Results: Tranexamic acid is currently being used in a wide range of surgical procedures without increased risk of thrombosis or other adverse effects. There have been several clinical trials that support its use in cesarean sections to decrease perioperative bleeding and reduce mortality.

Implications: Tranexamic acid may be beneficial to parturients undergoing cesarean section to decrease the total amount of blood loss. Further studies with greater sample size would be useful for analysis of different doses of TXA and timing of administration.

Keywords: tranexamic acid; cesarean section; hemorrhage; postpartum hemorrhage

Background

One of the most common surgical procedures encountered by women of child bearing age is a cesarean section. It was estimated in 2010 that the cesarean section rate was 32% in the United States and 42% in China, which are both considerably higher than the World Health Organization's recommended proportion of 10 to 15% (Wang, Hong, Duan, & Yin, 2015). Delivery by cesarean section has been noted to cause more complications than normal vaginal delivery. The most common complications documented are primary and secondary postpartum hemorrhage (Goswami, Sarangi, Gupta, & Babbar, 2013). Postpartum hemorrhage is related to an increased rate of blood transfusion and the occurrence of severe anemia (Wang et al., 2015).

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality and is responsible for one-quarter of all maternal deaths worldwide (Mpemba, Kampo & Zhang, 2014). PPH accounts for roughly 166,000 maternal deaths every year, with an average onset of bleeding to death of two to four hours (Ronsmans & Graham, 2006). Most maternal mortality due to PPH occurs in developing nations, where greater than one third of the mothers being affected. Maternal mortality rates in India are estimated at 560/100,000 live births and PPH accounts for 35-55% of these deaths (Goswami, Sarangi, Gupta, & Babbar, 2013). Anemia, adds to this prevalence. Approximately, 1% of women with spontaneous vaginal deliveries receive a blood transfusion, but the rate increases to roughly 5% for women undergoing lower segment cesarean section (Goswami, Sarangi, Gupta, & Babbar, 2013). In developing countries like India where the prevalence of anemia is as high as 70%, this blood loss could lead to serious morbidity and mortality (Goswami, Sarangi, Gupta, & Babbar, 2013). In developed nations, maternal mortality is rare, however, PPH may be implicated in up to 27% of cases (Sentilhes et al., 2015).

A safe, low-cost, effective therapy is needed to help reduce the incidence of PPH and its associated morbidity and mortality.

Tranexamic acid (TXA) is an antifibrinolytic agent that prevents the conversion of plasminogen to plasmin stabilizing clot formation in bleeding patients (Alam & Choi, 2015). TXA has been shown to reduce blood loss, transfusion requirements, and mortality in multiple perioperative settings including cardiac surgery, liver surgery, orthopedic surgery, spine surgery, and trauma cases (Alam & Choi, 2015). TXA administration for the prevention of PPH in women undergoing a cesarean section is an area of practice that needs to be further investigated.

Case Report

A 5'4", 113 kilogram, 24-year old parturient woman presented for an elective cesarean section. Her pregnancy had been uneventful per her OBGYN physician. She was a gravida three para two. Her first child was born vaginally while her second child was delivered via emergent cesarean section. Her medical history included gastroesophageal reflux disease and asthma. She stated that she used an albuterol inhaler as needed, but has not needed the inhaler for the last three months. The only medication she took regularly was her prenatal vitamin and occasionally acetaminophen. She denied any recent acute illnesses. Preoperatively her labs were as follows: hemoglobin was 12.0 gm/dL, hematocrit 35.8%, platelets 327,000. Her lung sounds were clear bilaterally. Her heart rate and rhythm were regular with no murmurs. Blood pressure was 118/66. She was a mallampati II. She was determined to be an ASA 3.

The patient was a candidate for a subarachnoid block, in which she elected for. She received 1.4 mL of 0.75% bupivacaine and 20 mcg of fentanyl in her subarachnoid injection. Prior to the administration of the spinal anesthetic, the patient had received approximately 800 mL of lactated ringers. She continued to receive the crystalloid fluid during the administration of

the spinal anesthetic. Six minutes after the administration of the spinal anesthetic, the patient started to complain of nausea, which was followed by her first hypotensive blood pressure reading. At this point, she was given 10 mg of Ephedrine.

During the procedure, the surgeon stated he was noticing more bleeding than usual. A discussion ensued with the surgeon and CRNA about the need to check a current hemoglobin level. It was also discussed about the potential for transfusion and other pharmacological options. The decision was made to continue the lactated ringer infusion and monitor blood loss, vital signs, and symptoms closely for the remainder of the procedure. She received 30 units of Pitocin after baby was delivered. Estimated blood loss was 1200 mL at the end of the procedure. In hindsight, this patient may have benefited from tranexamic acid before the start of the case. The patient was asymptomatic and vital signs were stable after the procedure was completed. The patient was given a total of 3200 mL of lactated ringers from the preoperative period through the intraoperative period. The following day her hemoglobin was noted to be 9.1 gm/dL with a hematocrit of 30.5%. She was not transfused with red blood cells. She was sent home on iron supplementation. She was discharged without issues.

Discussion

Physiology of Pregnancy

Pregnancy influences multiple systems of the body as physiologic changes affect the cardiac and circulatory system, respiratory system, renal system, gastrointestinal system, nervous system, and the musculoskeletal system.

Cardiovascular

The cardiovascular changes seen in a normal pregnancy are related to the increased metabolic demands, as well as hormonal and anatomic changes (Nagelhout & Plaus, 2014).

Heart rate is increased 20% to 30% when at term (Nagelhout & Plaus, 2014). The patient involved in the aforementioned case report had a resting heart rate in the 90's preoperatively. Cardiac output increases consistently throughout the pregnancy to approximately 40% from the nonpregnant cardiac output values. Total blood volume increases 25% to 40% throughout pregnancy to prepare for the normal blood loss that is associated with delivery (Nagelhout & Plaus, 2014). Plasma volume increases 40% to 50% with red blood cell volume increasing only 20%, which commonly results in dilutional anemia. As stated previously, the case study patient's preoperative hemoglobin was 12.0 gm/dL. Systemic vascular resistance is also noted to decrease around 20% by the end of term pregnancy. The decrease in systemic vascular resistance results in little overall systolic blood pressure change during normal pregnancy, despite having an increase in blood volume (McDonald, Fernando, Ashpole, & Columb, 2011).

Other cardiac changes are related to the heart shifting up due to the elevation of the diaphragm. Stroke volume increases 20-50% and heart rate increases 20-30%. Increased cardiac output leads to increased perfusion to the uterus and the kidneys (80% increase at 20 weeks and back down to 50% at term). SVR decreases around 20% at term due to vasodilation from hormones.

Respiratory

The respiratory changes that occur during pregnancy can drastically influence the manifestations of blood loss during delivery. Respiratory changes involve capillary engorgement in the upper airways leading to edema and a narrow glottic opening (Nagelhout & Plaus, 2014). Airway tissues are also friable and are at increased risk for damage and bleeding if manipulated. Minute ventilation is increased by 50% at term. Oxygen consumption is increased by 33% at rest and up to 100% during the second stage of labor (Nagelhout & Plaus, 2014). Functional residual

capacity, expiratory reserve volume, and residual volume are decreased at term due to the upward pressure of the diaphragm (Nagelhout & Plaus, 2014). The combination of increased oxygen consumption and a decreased functional residual capacity causes an apneic pregnant patient at increased risk for rapid desaturation. During the case involved, the patient's oxygen saturation remained greater than 95% throughout the entire case as she was able to breath spontaneously.

Coagulation

Significant changes occur in the coagulation and fibrinolytic systems during pregnancy and delivery. Parturient patients are considered to be hypercoagulable due to increased levels of fibrinogen, D-dimer, and factors VII, VIII, IX, and X (Gong, Shen, & Yan-Xia, 2016). At the same time, plasminogen levels are increased considerably, but levels of plasminogen activator inhibitor-1 and -2 also increase (Cunningham et al., 2018). Thus, plasmin activity usually decreases only until after delivery (Cunningham et al., 2018). The net result of these changes include increased levels of fibrinopeptide A, Beta-thromboglobulin, platelet factor 4, and fibrinogen-fibrin degradation products, which includes d-dimers (Cunningham et al., 2018). These changes help maintain placental function and decrease blood loss during delivery, but they also place the parturient at an increased risk for thrombosis. The incidence of venous thromboembolism is approximately 0.76 to 1.7 in 1,000 pregnancies (Gong et al., 2016). The patient involved did not have a fibrinogen or D-dimer level checked preoperatively as those values are not regularly analyzed.

Cesarean Section

Anesthesia for cesarean section depends on the maternal status, fetus status, urgency of the procedure, as well as the patient's desires. In the aforementioned cased study, neuraxial

anesthesia was chosen as it offers advantages over general anesthesia that include decreased mortality from failed intubation, better neonatal outcomes from the use of less depressant agents, and the ability of the mother to be awake for the delivery of the baby (Benhamou & Wong, 2009). Spinal anesthesia became the technique of choice over epidural anesthesia in the early 1990's when the pencil-point needles were introduced (Benhamou & Wong, 2009). Currently, 80 to 90% of cesarean sections are performed under spinal anesthesia (Ni, Liu, Zhang, Peng, & Ji, 2017). Spinal anesthesia, as compared to epidural anesthesia was also found to be faster to perform, surgical anesthesia was attained more rapidly, and had less break through pain (Benhamou & Wong, 2014).

In the aforementioned case study, after the spinal anesthetic was injected, the patient was placed in the supine position with left uterine displacement. This maneuver is important regardless of anesthetic technique. Left uterine displacement, or left lateral tilt, is performed to prevent aortocaval compression from the uterus compressing the inferior vena cava and abdominal aorta (Hasanin et al., 2018). Preventing aortocaval compression is important for preventing maternal hypotension and preserving fetal oxygenation (Hasanin et al., 2018).

Maternal hypotension is a complication in up to 60% to 70% of cesarean sections with spinal anesthesia (Ni et al., 2017). Maternal hypotension results mainly in nausea and vomiting but, if severe and untreated, may lead to cardiovascular collapse, a decreased level of consciousness, and uteroplacental hypotension (Nagelhout & Plaus, 2014). Spinal anesthesia often results in the blockade of the sympathetic nervous system, causing arterial vasodilation, venous pooling, and a reduced venous return (Nagelhout & Plaus, 2014). These changes then result in hypotension. Traditionally, a preload of crystalloid fluids is used to prevent the hypotensive response, but the efficacy has been long debated if that is the preferred time of

administration versus a co-load of crystalloid fluids. Ni et al. (2017) found that the co-load infusion of crystalloid reduced the incidence of hypotension as compared to a preload in parturients receiving spinal anesthesia for cesarean delivery. They determined the co-load of crystalloid fluids to be superior to a preload by the evidence of decreased need for vasopressors and a lower incidence of nausea and vomiting. If hypotension remains following the administration of crystalloid fluids, the preferred treatment is ephedrine and phenylephrine. Ephedrine is a synthetic, nonselective, noncatecholamine sympathomimetic drug (Nagelhout & Plaus, 2014). Phenylephrine is another vasopressor use to treat hypotension. Phenylephrine is a direct acting alpha-1 adrenergic agonist that results in vasoconstriction.

Blood Loss in Cesarean Sections

Spinal anesthesia has been shown to be superior to general anesthesia for intraoperative blood loss for cesarean sections (Kim et al., 2012). Average blood loss for a vaginal delivery is 500 mL, and for an uncomplicated cesarean section, the blood loss can be 800 to 1000 mL. Normal blood loss at delivery is generally tolerated well in the healthy parturient as a result of their compensatory mechanisms (Nagelhout & Plaus, 2014).

Severe perioperative or postpartum hemorrhage is not clearly defined. Hemorrhage can be considered severe or massive when blood loss is more than 1500 to 2500 mL, hemoglobin drops 4 g/dL or more, at least 4 units of red blood cells are transfused, or there is a need for embolization or operative intervention (De Lange et al., 2012). Hemorrhage may also be defined by the speed of blood loss such as a loss of more than 50% of the blood volume in less than 3 hours or more than 150 mL of blood loss per minute (Bonnet & Basso, 2012).

Complications from Blood Loss from Cesarean Sections

Severe blood loss with hypovolemic shock can result in tissue hypoxia, acidosis, hypothermia, and systemic inflammatory responses that trigger widespread intravascular activation of the coagulation system, which depletes the factors needed for effective coagulation (Su & Chong, 2012). This response is referred to as disseminated intravascular coagulation (DIC). Cardinal clinical signs of DIC are microvascular oozing at surgical, venipuncture, or intravenous cannula sites (Schorn & Phillippi, 2014).

Treatment Options for Blood Loss

Historically the degree of hemorrhage was determined by a visual estimation of the amount of blood lost, however, the higher the blood loss, the larger the underestimation tends to be, and therefore becomes more inaccurate in the case of severe hemorrhage (Gabel & Weeber, 2012). It is more clinically useful to assess the woman's physiologic response to blood loss rather than basing your intervention on the visual estimation of volume lost (Schorn & Phillippi, 2014).

Fluids

Hypovolemia can be reversed through fluid volume expansion with the rapid intravenous infusion of a crystalloid fluid such as Lactated Ringer's solution or 0.9% normal saline, at a volume approximately 3 times the estimated blood loss (Frigo, Pump, & Agro, 2012). The initial use of crystalloid fluid is necessary to replace volume following a small to moderate blood loss. The administration of large quantities of crystalloid fluid can worsen patient status due to hemodilution and decreased oxygen carrying capacity. Clotting factors and fibrinogen may also become diluted, causing coagulation to be impaired (Bonnet & Basso, 2012). Large amounts of intravenous crystalloid fluid are also associated with the movement of fluid into the interstitial

tissues, resulting in possible cerebral, cardiac, and pulmonary edema (Pacheo, Saade, Costantine, Clark, Hankins, 2013).

Blood Transfusions

Hemostatic resuscitation describes interventions designed to restore intravenous volume, maximize oxygen carrying capacity, and reverse coagulopathy during or following severe hemorrhage (Su & Chong, 2012). The American Society of Anesthesiologists recommends maintaining adequate intravascular volume and blood pressure with crystalloid fluids until there is substantial blood loss or there is indication of organ ischemia (American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies, 2006). However, they do not stipulate an amount of blood loss or a clinical indicator for when additional products should be given. Products that can be administered during or following severe PPH include packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and recombinant factor VIIa. These products restore blood volume, enhance tissue oxygenation with RBCs, and allow for clot formation through the administration of FFP, platelets, and Factor VIIa (Schorn & Phillippi, 2014).

Current Transfusion Triggers

The American Association of Blood Banks (AABB) recommends a restrictive RBC transfusion threshold of 7 g/dL in hospitalized hemodynamically stable adult patients, including critical care patients (Yazer & Triulzi, 2016). For patients undergoing orthopedic surgery and cardiac surgery and those with existing cardiovascular disease, AABB recommends a restrictive RBC transfusion threshold of 8 g/dL. The systematic review that included 12,000 patients found there were no significant differences in the findings of the trials that used a restrictive transfusion threshold of 7 g/dL compared to a restrictive transfusion threshold of 8 g/dL. These

recommendations apply to all but the following conditions, where the evidence is judged to be insufficient for any recommendation: acute coronary syndrome, severe thrombocytopenia in hematology/oncology patients at risk of bleeding, and chronic transfusion-dependent anemia. It is also recommended to use a RBC transfusion threshold of 7g/dL in a hemodynamically stable obstetric patient, unless they are actively bleeding or symptomatic.

Pharmacological Options

After the placenta has been delivered, Pitocin is administered to cause an increase in the frequency and strength of uterine contractions (Nagelhout & Plaus, 2014). Uterine contractions are important for limiting the amount of blood loss. Pitocin is the synthetic equivalent of oxytocin, a naturally occurring hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus (Nagelhout & Plaus, 2014). If oxytocin does not adequately stimulate uterine contractions, the next drug used is usually an ergot alkaloid, such as Methergine. An intramuscular dose of Methergine 0.2 mg is administered. Methergine is not administered intravenously as it can cause severe arterial and venous vasoconstriction, leading to coronary artery constriction, severe hypertension, cerebral bleeding, headache, nausea, and vomiting (Nagelhout & Plaus, 2014). If the uterus continues to not contract adequately, a prostaglandin such as Hemabate can be administered intramuscularly or directly into the uterine muscle. A Hemabate dose of 250 mcg is administered to stimulate potent uterine contraction.

Tranexamic Acid

Tranexamic acid is a fibrinolysis inhibitor that has been used to decrease bleeding during various surgical procedures. Tranexamic acid (TXA, trans-r-aminomethyl cyclohexane carboxylic acid) is a synthetic amino acid lysine analog that forms a reversible complex with both plasminogen and plasmin by binding at lysine-binding sites (Xu, Gao, & Ju, 2013). TXA

has not been shown to significantly alter blood pressure, heart rate, respiratory rate, postoperative prothrombin time, partial thromboplastin time, serum hemoglobin concentration, and platelet count 24 hours after surgery (Xu et al., 2013).

Dosing regimens tend to vary, but a common dosing regimen of tranexamic acid is 10mg/kg in 200 mL of normal saline over 20 minutes followed by 1-2 mg/kg/hour maintenance infusion into the immediate postoperative period (Nagelhout & Plaus, 2014). In some studies, the maintenance infusion was not included. The other most common dose used is 1 gram of TXA diluted in 20 mL of normal saline. TXA is recommended to be diluted and injected slowly as hypotension has been observed when it is injected too rapidly (Ahmed, Ahmed, Madny, Arafa, & Said, 2015).

The antifibrinolytic concentration of TXA remains in different tissues for about 17 hours, and in the serum up 7 to 8 hours, and is not completely eliminated from the blood until 9 to 18 hours after administration (Ahmed et al., 2015). Tranexamic acid is minimally protein bound and is cleared by the kidneys (Mayeux, Alwon, Collins, & Hewer, 2016). In patients with normal renal function, TXA's half-life is 2 to 3 hours. TXA is known to pass the placenta and appears in cord blood at concentrations approximately equal to maternal concentration, but data suggests that it has no adverse effects on the neonate (Ahmed et al., 2015). TXA also passes into breast milk in very low concentrations, roughly 1% of the concentration in the maternal blood (Gungorduk et al., 2011).

Side effects that have been noted with TXA have typically been gastrointestinal and neurological manifestations. The most severe side effect that has been noted is deep vein thrombosis, although it has not been shown to occur more frequently when compared to a control group (Xu et al., 2013). It is estimated that out of every 1,000 women, 0.3 to 0.5 of them are at

risk for acquiring symptomatic venous thrombosis during pregnancy, without the use of tranexamic acid (Shakur et al., 2010). In terms of mild transient adverse effects, manifestations such as nausea, vomiting, diarrhea, and phosphenes, have been noted to be more likely in the TXA group when compared to the control group (Xu et al., 2013). Hypersensitivity reactions have also been noted to include general itchiness, edema, and respiratory distress (Senturk, Cakmak, Yildiz, & Yildiz, 2013).

Lower dosing strategies should be considered for patients with kidney disease because of TXA being cleared by the kidneys. Impaired renal function does not constitute a contraindication, but to avoid accumulation, it should be given over longer intervals and adjusted to patient weight (Mayeux et al., 2016). Absolute contraindications include acquired defective color vision, hypersensitivity to TXA, active intravascular clotting, and subarachnoid hemorrhage (Mayeux et al., 2016). Relative contraindications include a history of vascular occlusive events, taking another procoagulant or a hormonal contraception (Mayeux et al., 2016).

TXA in Non-Obstetric Patients

Tranexamic acid is an antifibrinolytic agent that has been demonstrated to reduce blood loss and transfusion requirements in various elective surgeries. It has been used for many years for reducing blood loss in surgeries such as cardiac surgery with cardiopulmonary bypass, liver transplantation, transurethral prostatic surgery, total hip/knee arthroplasty, urinary tract surgeries, and spine surgeries (Shahid & Khan, 2013). TXA has also been shown to reduce total mortality in trauma patients who receive the drug early during their management (Shakur et al., 2010).

Currently there is no consensus regarding optimal TXA dosing in cardiac surgery. In 2008, the WHO recommended a TXA dose of 10 to 30 mg/kg followed by an infusion of 1 to 16 mg/kg/hour and 1 to 2 mg/kg added to the cardiopulmonary circuit (WHO, 2008). Indications for

its' use vary amongst professional guidelines. Some researchers have implied that cardiopulmonary bypass may influence TXA's elimination kinetics and subsequently blood concentrations of TXA (Mayeux et al., 2016). In a 2011 Cochrane Review that included 22 trials, when TXA was compared to a control group in cardiac surgical patients, there was no significant difference in mortality rate (Mayeux et al., 2016). Although there was no difference found in morbidity and mortality, postoperative bleeding was found to decrease by an average of 273 mL in the TXA group when compared to the control group (Mayeux et al., 2016).

A Cochrane Review comparing TXA with a placebo in orthopedic surgery, including total knee and total hip arthroplasties, found that intraoperative blood loss was reduced by 116 mL and postoperative blood loss by 229 mL on average (Henry, Carless, & Moxey, 2011). The best practice for dosage of TXA administration in orthopedic surgery has yet to be definitively determined. Although administration of TXA has been slow to become popular in orthopedic populations because of the perceived risk of thrombosis, there is overwhelming evidence that TXA reduces blood loss in these orthopedic procedures (Mayeux et al., 2016).

Trauma is another area where TXA has been used more frequently. Trauma patients experience many coagulopathies, including hyperfibrinolysis leading to hemorrhage and it is believed that trauma and surgery have similar hemostatic responses after severe vascular injury (Mayeux et al., 2016). TXA has been recently incorporated into resuscitation and massive transfusion protocols. A study of more than 10,000 trauma patients who received TXA, risk of bleeding and death were significantly reduced (Mayeux et al., 2016). This study dosed TXA as a bolus of 1 gram over 10 minutes and then an infusion of 1 gram over 8 hours.

TXA in Obstetric Patients

While a parturient is undergoing a cesarean section, fibrinogen and fibrin are quickly degraded following the removal of the placenta, while plasminogen activators and fibrin degradation products increase due to activation of the fibrinolytic system (Xu et al., 2013). Fibrin destruction products are increased because plasminogen activators catalyze the conversion of plasminogen to plasmin (Senturk et al., 2013). This activation can last as long as 6-10 hours postpartum, leading to more blood loss. TXA is an antifibrinolytic agent that may offset the effect of plasminogen and fibrin degradation products that are released by placental separation, as it is a plasminogen activator inhibitor (Senturk et al., 2013).

There have been multiple studies completed to determine the efficacy of TXA in reducing blood loss in obstetric patients, and more specifically, patients undergoing cesarean section. In the studies analyzed, the patients all received a uterotonic such as oxytocin after the delivery of the placenta. There was variance amongst the studies in the dosage of oxytocin administered. A total of 9 randomized controlled trials and 2 meta-analyses were analyzed to determine tranexamic acid's effect at reducing blood loss in the obstetric patient population.

Most studies involved women with a singleton pregnancy between 38 and 40 weeks gestation who were categorized as class 1 according to the American Society of Anesthesiologists and were scheduled to undergo cesarean delivery under spinal anesthesia. Exclusion criteria typically included a previous history of polyhydramnios, macrosomia, pre-eclampsia, thrombophilia, anemia, coagulopathy; cardiovascular, renal, or liver disorders; or other contraindication to tranexamic acid.

Xu et al. (2013) examined the effect of 10mg/kg of TXA administered 10 minutes before spinal anesthesia. Following the delivery of the neonate, 10 units of oxytocin and 0.4 mg of

methergine was administered. Blood was collected through weighed, saturated gauze, and suction canisters. The study included 176 parturients who were split into a control and intervention group. They determined that TXA had a statistically significant reduction in total blood loss from placental delivery until 2 hours postpartum (382 mL in TXA group and 452 mL in control group)

Ali et al. (2011) examined the effect of 10mg/kg of TXA administered 20 minutes before spinal anesthesia. Following the delivery of the placenta, patients received 10 units of oxytocin and an additional 30 units over the next 8 hours post-operatively. Blood loss was recorded as the sum of the suction canisters and the weight of the gauze pads and operation sheets. Amniotic fluid and blood from uterine incision was drained into a separate suction container and therefore not included in total. Blood loss was recorded intraoperatively and until 2 hours postoperatively. Blood loss was determined to be significantly less in the TXA group compared to the control group during both the intraoperative period (262 mL; 404 mL, respectively) and postoperative period (67 mL; 141 mL, respectively). They also found that the amount of additional oxytocin administered was significantly less in the TXA group compared to the control group.

Ahmed et al. (2014) looked at 124 parturients that were divided into an intervention and control group. The intervention group received 10mg/kg of TXA 5 minutes before the start of the cesarean section. After delivery of the neonate, they received 10 units of oxytocin and 0.2mg of methergine. Blood loss was measured by the weight of surgical gauze. Blood loss was recorded during the delivery until 2 hours postpartum. The study group showed a lower total amount of blood loss (391 mL) when compared to the control group (597 mL). Also, the study showed a significant difference in hemoglobin and hematocrit between the TXA and control group.

Preoperatively the TXA and control groups hemoglobin and hematocrit values (11.3g/dL and

38.2% versus 11.6g/dL and 38.3%, respectively) as compared to the postoperative values (10.2g/dL and 36.2% in TXA group versus 9.2g/dL and 34.5% in control group). Postoperative hemoglobin values were recorded 24 hours postpartum.

Abdel-Aleem et al. (2013) examined the effect of 1 gram of TXA administered before the start of the cesarean section. They did not specify how many minutes before the incision was made, that TXA was administered. The study included 740 parturients who were divided into a study and control group. Blood loss was recorded as the sum of the suction canisters and the weight of the saturated gauze pads. Following the delivery of the placenta, 5 units of oxytocin was administered and an additional 25 units was infused. Blood loss was analyzed during the delivery until 2 hours after the procedure. There was a statistically significant reduction in the average blood loss among the study group who received TXA (241 mL) in comparison to the control group (510 mL). Blood loss was recorded from the start of incision until 2 hours postpartum. Both hemoglobin and hematocrit values showed a statistically significant drop in the control group (-1.42g/dL and -4.3%) in comparison to the study group (-0.48g/dL and -1.42%).

Gungorduk et al. (2011) analyzed the effect of administering 1 gram of TXA at least 10 minutes before skin incision is made for cesarean section. The study included 660 parturients who were separated into an intervention and control group. After delivery of the neonate, 10 units of oxytocin was administered, followed by an infusion of an additional 30 units. The average blood loss was significantly lower in the TXA group than the control group (499 mL versus 600 mL, respectively). Postoperative hemoglobin and hematocrit values were lower in the control group when compared to their preoperative values (-2.2g/dL and -2.8% in the control group; -1.4g/dL and -2.3% in the TXA group). They also found that significantly more women needed additional uterotonics in the control group (14.5%) than those in the TXA group (8.5%).

Senturk et al. (2013) examined the effect of administering 1 gram of TXA 10 minutes prior to spinal anesthesia. The study involved 223 parturients who were separated into an intervention and control group. Blood loss was recorded as the sum of the suction canisters and the weight of the gauze pads. Amniotic fluid was suctioned separately when the uterine incision was made, therefore not included in total blood loss. After removal of the placenta, the patients received 20 units of oxytocin. A statistically significant difference was found between the two groups when comparing preoperative and postoperative hemoglobin values. The average preoperative hemoglobin values in the intervention and control groups (11.66g/dL and 11.86g/dL, respectively) and postoperatively (10.55g/dL and 10.52g/dL, respectively).

Shahid and Khan (2011) looked at 74 parturients who were divided into an intervention and control group. The intervention group received 1 gram of TXA 10 minutes before incision was made for the start of the cesarean section. After delivery of the neonate, they received 5 units of oxytocin and 0.4mg of methergine. They also received an additional 30 units of oxytocin through infusion over the next 6 hours. Blood loss was measured by the weight of surgical gauze and the contents of suction canisters. Amniotic fluid was suctioned separately when the uterine incision was made, therefore not included in total blood loss. Blood loss was recorded during the delivery until 2 hours postpartum. Hemoglobin values were re-drawn 3 days postpartum. There was a statistically significant difference in total average blood loss among the study group who received TXA (356 mL) in comparison to the control group (710 mL). There also was a significant reduction in hemoglobin and hematocrit in the control group when compared to the TXA group. Preoperatively the TXA and control groups hemoglobin and hematocrit values (9.7g/dL and 34.9% versus 9.8g/dL and 34.8%, respectively) as compared to the postoperative values (8.6g/dL and 33.0% in TXA group versus 8.0g/dL and 30.5% in control group).

The study by Goswami et al. (2013) looked at 2 different doses of TXA (10mg/kg and 15mg/kg) with a placebo to compare their efficacy and safety in anemic parturients undergoing cesarean section. The study included 90 parturients with a hemoglobin value between 7 g/dl and 10 g/dl. After delivery of the neonate, 20 units of oxytocin was administered to the patient. Blood loss was measured intraoperatively and postoperatively until 24 hours postpartum. Blood loss was measured by the weight of sponges, pads, and drapes as well as the volume in the suction canisters. Amniotic fluid was suctioned separately when the uterine incision was made, therefore not included in total blood loss. Postoperative hemoglobin and hematocrit values were recorded 24 hours postpartum. They found the total average blood loss in both study groups to be significantly less when compared to the control group. The study group who received 10mg/kg had an average of 146 mL less blood lost than the control group. The study group who received 15mg/kg had an average of 262 mL less blood lost than the control group. They also did not find a significant difference in adverse events when comparing the 2 dosages used.

The meta-analysis conducted by Wang et al. (2015) included studies that used varying doses of TXA including 10 mg/kg, 15mg/kg, and 1 gram. There were eight studies that used 1 gram, two that used 10mg/kg, and one study that used 15mg/kg. There were a total of 2531 parturients included in the meta-analysis. The studies recorded blood loss during the cesarean section until two hours postpartum. All the studies measured blood loss by weighing the saturated materials used. Of the nine randomized controlled trials, eight showed a significant reduction in total blood loss when TXA was administered compared to the control group. The average total blood loss in the TXA group was 141 mL less than the control group. When postoperative hemoglobin values were analyzed, there was a greater drop in values in the control group when compared to their preoperative values. The TXA group had an average hemoglobin

reduction postoperatively by -0.45g/dL, as compared to the control group that decreased by -1.3g/dL. The study did not find a significant difference between the 2 groups for requiring blood transfusions and length of hospital stay.

Conclusion

Currently, TXA is being used in a wide range of surgical procedures without increased risk of thrombosis or other adverse effects. There have been several large clinical trials that support its use to decrease bleeding and reduce mortality while maintaining a proven safe pharmaceutical profile. Even though numerous studies show a statistically significant difference in blood loss, that may not always translate into a clinical significance on the outcome of the operation or the patient's health (Ahmed et al., 2015). There does appear to be a clear trend of decreasing blood loss with the use of TXA which may amount to clinical significance, especially when considering patients who are anemic.

Severe anemia following postpartum hemorrhage is an important cause of maternal morbidity and is likely to make more women vulnerable to fatal PPH in future pregnancies (Shahid & Khan, 2013). Reducing perioperative blood loss would also reduce the risks and costs associated with blood transfusions. Blood is a resource that is not always available, especially when considering areas of the world with even greater limitations. In countries where blood is readily available, the use of TXA can decrease the risk of transfusion-transmitted viral infections because fewer units of blood will be transfused (Shahid & Khan, 2013).

Administration of TXA in pregnant women may raise concerns about thromboembolism, however, studies have shown the safety of its use in both pregnant and non-pregnant patients (Shahid & Khan, 2013). Further studies would be beneficial for the analysis of different doses of

TXA and timing of prophylactic administration. It would also be beneficial for further studies to analyze postpartum hemorrhage, blood loss, and transfusion requirements beyond a 24-hour period to accurately estimate the incidence of PPH. Since TXA would be given before the delivery, assessing the effect of TXA on the neonate is also an area of concern that would be advantageous to study thoroughly.

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Appendix A

Tranexamic Acid Utilization in
Cesarean Section Patients

Justin Heinz, SRNA

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Cesarean Section

- Cesarean section rate is 32%
- **Postpartum Hemorrhage (PPH) is leading cause of maternal morbidity and mortality**
 - Responsible for ¼ of all maternal death
 - **166,000 PPH cases per year in U.S.**
 - 1/3 of mothers affected in developing nations
- Anemia complication
 - Some developing countries have anemia rates as high as 70%

(Goswami et al., 2013; Wang et al., 2015)

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Pathophysiology

- **Cardiovascular changes:**
 - Heart rate increases 20-30%
 - Cardiac output increases up to 40%
 - Blood volume increases 25-40%
 - Plasma volume increases 40-50%
 - RBC volume increases 20%
 - SVR decreases 20%

(Nagelhout & Plaus, 2014)

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Pathophysiology

- **Respiratory changes:**
 - Capillary engorgement
 - Airway edema, narrow glottic opening, friable tissue
 - Minute ventilation increased 50%
 - **Oxygen consumption increased 33%**
 - Functional residual capacity decreased
 - Expiratory reserve decreased
 - Residual volume decreased

(Nagelhout & Plaus, 2014)

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Pathophysiology

- **Coagulations changes**
 - Fibrinogen, D-dimer, plasminogen & Factors VII, VIII, IX, & X are all increased
 - Plasminogen activator inhibitors increased
 - Fibrinopeptide A, Beta-thromboglobulin, & platelet factor IV are increased
- 0.7-1.7:1000 venous thromboembolism risk

(Cunningham et al., 2018; Gong et al., 2016)

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Case Information

- Surgical Procedure
 - *Repeat*, elective cesarean section
- Pertinent Patient Information
 - 24 years old
 - 5'4"
 - 113kg
 - ASA 3
 - No known allergies

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Pre-operative Evaluation

- Past Medical History
 - GERD & Asthma
 - Gravida 3, Para 2
 - Uneventful pregnancy
- Surgical History
 - Emergent cesarean section
- Pre-operative vital signs
 - BP 118/66, HR 89, RR 18, O2 saturation 100%
- Labs
 - Hgb 12.0g/dL, Hct 35.8%, Platelets 327,000
- Airway Evaluation
 - Mallampati II, thyromental distance 3 fingerbreadths, neck FROM

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Anesthetic Course

- Lactated Ringers 800 mL preload
- Subarachnoid Block
 - 1.4 mL 0.75% Bupivacaine; Fentanyl 20 mcg
 - 25 gauge Pencan needle; midline approach
- Nasal Cannula 3L
- Lactated Ringers infusion 3200 mL
- Pitocin 30units
- Ofirmev 1g
- Ondansetron 4mg
- Total Anesthesia time: 129 minutes

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Intraoperative Issues

- Nausea and Hypotension 6 minutes after SAB
 - Symptoms continued for 12 minutes
 - Treated with Ephedrine for a total of 30 mg
 - Urine output 50 ml/hr
- **Increased Blood Loss**
 - EBL @ 1200+ mL

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PACU/Postop

- Asymptomatic
 - Denied pain, dizziness, lightheadedness, & nausea/vomiting
- Vital signs stable
- Postop Day 1
 - Hgb 9.1g/dL; Hct 30.5%
- No transfusion
- Discharged day 3 on iron supplements

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Cesarean Section

- Anesthetic plan depends on maternal status, fetus status, urgency, and patient desires
- General Anesthesia
- Spinal Anesthesia
 - Advantages: decreased mortality (less failed intubations), better neonatal outcomes (less depressant drugs), less blood loss, & mom is awake
 - Became technique of choice over epidural in early 1990's when pencil-point needles were created

(Benhamou & Wang, 2009; Ni et al., 2017)

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Cesarean Section Complications

- **Hypotension**
 - Occurs in 60-70% of C-sections with SAB
 - Accompanied with Nausea/Vomiting
 - Can lead to decreased level of consciousness, uteroplacental hypotension, and cardiovascular collapse
 - Treated with fluids and vasopressors
- **Blood loss**
 - Vaginal (500 mL) vs C-Section (800-1000 mL)
 - Hemorrhage not clearly defined
 - (EBL 1500-2500 mL; Hgb drops 4 g/dL; 4 units RBCs transfused)

(De Lange et al., 2012; Nagelhout & Plaus, 2014; Ni et al., 2017)

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Blood Loss Treatment Options

- **Fluids**
 - Crystalloid (e.g. LR, 0.9% normal saline) 3x EBL
 - Useful for small to moderate blood loss
- **Transfusions**
 - Restore intravenous volume and maximize oxygen carrying capacity
 - Transfusion products: RBCs, FFP, Platelets, and Factor VII
 - Maintain adequate intravascular volume and blood pressure with crystalloid fluids until there is substantial blood loss or indication of organ ischemia (ASA)
 - Recommended to use a hemoglobin transfusion threshold of 7 g/dL in a hemodynamically stable obstetric patient
 - No significant differences in morbidity and mortality when using a hemoglobin transfusion threshold of 7 g/dL versus 8 g/dL
- **Pharmacologic Options**
 - Pitocin, Methergine, Hemabate
 - **Tranexamic Acid ??**

(ASA, 2012; Frigo et al., 2017; Yazer & Trulzi, 2016)

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Tranexamic Acid

- Synthetic derivative of the amino acid lysine that exerts its anti-fibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen and plasmin molecules
- Administered intravenously in various dosing regimens
 - Bolus: per kilogram or standard dose
 - Infusion: 1mg/kg/hr most common
- Has not been shown to alter BP, HR, RR, prothrombin time, Hgb, and platelets

(Ahmed et al., 2015; Xu et al., 2013)

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Tranexamic Acid

- Half-life 2-3 hours
- Cleared by kidneys
 - Impaired renal function is not a contraindication, but using a lower dose over longer interval should be considered
- Does pass placenta
- Side effects:
 - Mild: Gastrointestinal & Neurological
 - Severe: DVT
- Contraindications: Acquired defective color vision, hypersensitivity, active intravascular bleeding, & subarachnoid hemorrhage
 - Relative: vascular occlusive events, taking another procoagulant or hormonal contraception

(Ahmed et al., 2015; Mayeux et al., 2016)

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Tranexamic Acid in Non-Obstetric Cases

- **Cardiac Surgery:** Cochrane review found no difference in morbidity & mortality
 - Blood loss reduced by 273 ml
- **Orthopedic Surgery:** Cochrane review of TKA/THA
 - Intraoperative blood loss reduced by 116 ml & postoperative by 229 ml
- **Trauma:** TXA is being incorporated in resuscitation and massive transfusion protocols
 - Study of 10,000 trauma patients found TXA reduced bleeding and death

(Henry et al., 2011; Mayeux et al., 2016)

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Tranexamic Acid in Obstetrics

- During cesarean section, fibrinogen and fibrin are quickly degraded due to activation of the fibrinolytic system when the placenta is removed
 - Process can last 6-10 hours postpartum
- Tranexamic acid has a role in offsetting this process of increased degradation products, as it is an antifibrinolytic agent

(Senturk et al., 2013; Xu et al., 2013)

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Tranexamic Acid in Obstetrics

- Studies of TXA given prior to cesarean section to determine efficacy of reducing intraoperative blood loss
- **1 gram**
 - Study of 660 patients
 - Total blood loss: 499 ml vs 600 ml
 - Drop in Hgb: -1.4 g/dL vs -2.2 g/dL
 - Study of 740 patients
 - Total blood loss: 241 ml vs 510 ml
 - Drop in Hgb: -0.48 g/dL vs -1.42 g/dL
- **10mg/kg**
 - Study of 124 patients
 - Drop in Hgb: -1.1 g/dL vs -2.4 g/dL
 - Study of 100 patients
 - Total blood loss: 329 ml vs 545 ml

(Abdel-Aleem et al., 2013; Ahmed et al., 2014; Ali et al., 2011; Gungorduk et al., 2011)

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Tranexamic Acid in Obstetrics

- Study of anemic patients with Hgb values between 7 and 10 g/dL (90 patients) that compared doses of TXA
 - 10 mg/kg: blood loss 146 mL less than control
 - 15 mg/kg: blood loss 262 mL less than control
- Meta-Analysis that included studies that used TXA dosages of 10 mg/kg, 15 mg/kg, and 1 gm
 - Total blood loss: Average of 141 mL less than control
 - Drop in Hgb: -0.45 g/dL vs -1.3 g/dL

(Goswami et al., 2013; Wang et al., 2015)

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Tranexamic Acid in Obstetrics

- All studies reviewed did not find an increase in adverse events in patients who received TXA
 - This included events of DVT
- Some studies also found that the control groups needed to use additional uterotonics

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Recommendations

- Based on evidence found, there appears to be a role for TXA in cesarean section patients
- Thorough preoperative evaluation is important to determine if patient is at risk for increased blood loss
- Determine if patient is anemic or has a history of anemia
- Further studies would be beneficial to determine most effective dose and timing of administration
 - Study patients beyond 24 hours
 - Larger studies of effects on neonates

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Conclusion

- Case Review
- TXA has shown to decrease total blood loss and lessen the drop in hemoglobin when compared to placebo groups
- TXA has proven to have a safe pharmaceutical profile
- TXA is currently being used successfully in multiple other areas of surgery

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