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Case Report

Tranexamic Acid for the Prevention of Primary Postpartum Hemorrhage in a High Risk Multigravida

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Abstract

We present a 31 year old chronically anemic G4P3 obstetric patient with a significant history of primary postpartum hemorrhage (PPH) requiring transfusion of blood after prior elective cesarean delivery. Given her history and risk factors for PPH along with her high risk for bleeding secondary to her anemia, the anesthesiologist administered an anti-fibrinolytic medication, tranexamic acid (TXA) after the umbilical cord was clamped, in an attempt to prevent PPH without exposing the neonate to the drug. The patient did not experience PPH nor required blood transfusion. This case report focuses on three important aspects of TXA administration: the timing of administration, the unknown potential effects of TXA on the neonate, and the utilization of the drug on high risk patients. Our case shows that TXA may have helped our high risk patient without exposing the neonate. Although there is promise in the use of TXA for prevention and treatment of PPH, large, high quality randomized controlled trials are necessary before its widespread use can be recommended.

Keywords: Perioperative complications, High risk obstetric partituents, Primary postpartum hemorrhage, Tranexamic acid, Cesarean delivery, Chronic anemia, Multiple pregnancies, Anesthetic issues and peri-operative care, Coagulopathy, Preoperative evaluation and anesthesia risk

Introduction

Primary postpartum hemorrhage (PPH) is a major cause of maternal mortality, accounting for close to one-quarter of all maternal deaths worldwide [1]. Until recently, uterotonic medications, specifically oxytocin, have been the only drugs shown to decrease PPH. Given that PPH remains a major cause of maternal mortality worldwide, there is an obvious need for additional treatments and interventions. Tranexamic acid (TXA), an antifibrinolytic agent, has recently been investigated as a potentially useful drug for both prevention and treatment of PPH [1]. It has been shown to reduce blood loss in elective surgery and trauma. It has also been used to reduce menstrual blood loss [1]. TXA appears to be a promising drug for prevention and treatment of PPH after both vaginal and cesarean deliveries. However, the timing of administration of TXA needs to be considered in the obstetric setting to maximize the beneficial effects on the mother while concurrently minimizing any potential deleterious effects on the baby.

Case Description

A 31 year old G4P3 female presents to the hospital for an elective repeat cesarean delivery. The patient's general medical history is largely negative, with the exception of asymptomatic chronic anemia, which was not treated due to patient non-compliance. The only non-obstetric surgery the patient had was a successful cholecystectomy performed in 2010.

With regards to her obstetric history, the patient has had three successful prior cesarean deliveries and now presenting for her fourth. The patient had her first cesarean delivery secondary to failed induction. Of note, the patient experienced significant PPH after the third cesarean delivery and had to be subsequently transfused with two units of packed red blood cells along with other interventions including oxytocin and methylergonovine maleate to reduce the bleeding.

The patient was admitted to the hospital with the plan for elective repeat cesarean delivery. A pre-operative complete blood count (CBC) showed a hemoglobin level of 8.3 g/dL and a hematocrit of 27.4%. Given the patients history of PPH and anemia,

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a type and cross was performed prior to the procedure. Two months prior, the patient had a CBC performed during a wellness check, with her hemoglobin of 8.7 g/dL and hematocrit of 27.7%, supporting a history of chronic anemia. In the operating room, spinal anesthesia was performed, and adequate level of anesthesia was obtained.

After delivery of the baby, and immediately after the cord was clamped, the anesthesiologist gave the patient 600 mg of TXA, based on 10mg/kg body weight. Estimated blood loss for the procedure was 500 mL. She remained hemodynamically stable throughout the procedure. The baby had APGAR scores of 9 and 9, at one and five minutes respectively. In the post anesthesia care unit, a follow up CBC showed a hemoglobin of 8.8 g/dL and a hematocrit of 28.6%. A 24 hour follow up CBC showed hemoglobin of 7.2 g/dL and a hematocrit of 23.0%. The patient did not require transfusion of packed red blood cells during her stay per her obstetrician as she remained asymptomatic and clinically stable. On day of discharge, she was started on ferrous sulfate for her chronic anemia.

Discussion

Primary postpartum hemorrhage (PPH) is classically defined as blood loss of ≥500 mL for a vaginal delivery and ≥1000 mL for a cesarean delivery in the first 24 hours after delivery [2]. It is a major cause of maternal mortality and accounts for about one-quarter of all maternal deaths worldwide [1]. The leading cause of massive obstetric hemorrhage is uterine atony [3,4], but obstetric complications such as placental abruption, placenta accreta, and amniotic fluid embolism may also precipitate obstetric hemorrhage, oftentimes complicated by consumptive coagulopathy [4]. Risk factors for PPH include previous PPH, obesity, prolonged labor, multiple pregnancies, prior caesarean delivery, primiparity, polyhydramnios, and macrosomia [5]. Our patient had risk factors of previous PPH and prior cesarean delivery and therefore was considered at risk for another presentation of PPH.

The coagulation and fibrinolytic systems are believed to be in a state of dynamic balance that maintains an intact vascular system [6]. During delivery, when the placenta separates from the uterine wall, physiologic and hemostatic changes occur sequentially to reduce bleeding: strong myometrial contractions, increased platelet activity, massive release of coagulation factors and consequently a parallel increase in fibrinolytic activity [7]. Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effects by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own hemostatic mechanisms. Consequently, clot breakdown (fibrinolysis) is inhibited and bleeding is reduced [6].

The majority of the larger studies regarding TXA have been focused on broader categories of surgical patients. The Clinical Randomisation of an Antifibrinolytic in Significant

Haemorrhage-2 (CRASH-2) trial randomized more than 20,000 adult trauma patients to receive empiric tranexamic acid within 8 hours of injury or placebo. The study not only found a significant decrease in all-cause mortality (14.5% vs 16%, relative risk: 0.91, 95% CI: 0.85–0.97, $P = 0.0035$) as well as mortality due to hemorrhage (4.9% vs 5.7%) in the tranexamic acid group, but importantly showed no significant increase in thromboembolic complications in subjects receiving tranexamic acid [8].

With regards to studies specifically addressing TXA effects on prevention of PPH, a recent article by L. Sentilhes et al published in the British Journal of Anesthesia found 10 published Randomized Controlled Trials (RCT) evaluating the efficacy of TXA in preventing PPH after caesarean delivery [1]. Their characteristics are summarized in a table created by L. Sentilhes and can be seen here in Table 1. The 10 published RCTs that have assessed the effects of TXA in preventing PPH during caesarean deliveries showed a significant reduction in blood loss in patients who received TXA and no increase in the incidence of adverse events [1] (Table 1). Although these results are promising and support the use of TXA in our particular patient, it must be noted that majority of these RCTs included small sample sizes with inadequate power to fully assess the risk of adverse effects.

Of these 10 RCTs, one in particular, Goswami *et al,.* demonstrated a decrease in estimated blood loss when tranexamic acid was used prophylactically before elective caesarean section in anemic patients [9], which is of particular interest to our patient, as she was significantly anemic prior to her elective cesarean delivery. The choice of this particular population of anemic patients increased the clinical pertinence of the study. Even minimal blood loss reduction, probably helped to avoid packed red blood cell transfusion in the two TXA groups compared to the placebo group [9].

There are very few studies specifically addressing the adverse effects or even the possible risks to the neonate with the use of TXA. As a result, these places even more importance on the timing of TXA administration. Most of the RCTs that have been completed at this time have involved the administration of the TXA well before the cord is clamped. One important exception involves the ongoing WOMAN study, where the TXA is given only after PPH was noted. Neonatal exposure will occur when TXA is given before the cord is clamped, as TXA is known to cross the placenta [10].

A recent study by O. Gilad et al evaluated the outcomes of infants exposed to tranexamic acid during lactation. The results of their study found no increase in adverse long-term outcomes in infants exposed through breastfeeding to tranexamic acid. Their data, in conjunction with previous estimates of very low drug exposure, support continuation of breastfeeding in women treated with tranexamic acid [11].

The two aforementioned studies highlight the lack of concrete evidence of adverse effects on the neonate. Nevertheless, because the safety of the drug regarding the neonate is still unproven, the anesthesiologist in our case administered the TXA after the cord was clamped.

Our case shows that TXA may have helped our high risk patient without exposing the neonate. Although there is promise in the use of TXA for prevention and treatment of PPH, large, high quality RCTs are necessary before widespread usage can be supported. Of note, The World Maternal Antifibrinolytic Trial (WOMAN) trial, which is a large, international randomized placebo controlled study, is currently ongoing at this time to compare the impact of a 1 g dose of TXA at the onset of post-partum bleeding on mortality [12]. The results of this study should provide more evidence to

Study [réf]	Country	Study design	Sample size	Study groups	Prophylactic uterotonics	Intervention	TXA Dosage/route/duration	Primary outcome/calculated sample size/Flow chart	Method for assessing estimated blood loss	Result	P value	Adverse effects
Gai et al, (2004) [62]	China	Prospective single center, randomized, controlled	N=180, primiparas, elective CS under epidural analgesia	N=91 (experimental) N=89 (no placebo)	10 IU oxytocin IV simultaneously with 20 IU oxytocin into the intra-uterine wall	Infusion of TXA 10 min before CS	1 g IV for 5 min	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of materials used + materials not used -weight of all materials before surgery)/1.05, + volume included in the suction container from placental delivery to 2 h postpartum	359.3 ml vs 439.3 ml	0.002	No thromboembolic or other side effects reported
Gohel et al, (2007) [63]	India	Prospective, single center, randomized, controlled	N=100, primiparas and multiparas, elective CS under spinal anesthesia	N=50 (experimental) N=50 (no placebo)	10 IU oxytocin IV for 30 min with 0.4 mg methylergometrine IV	Infusion of TXA 20 min before CS	1 g IV for 5 min	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of materials used - weight of material before use) + volume included in the suction container from placental delivery to 2 h postpartum	374.9 ml vs 472.8 ml	0.003	No thromboembolic or other side effects reported
Sekhavat et al, (2009) [64]	Iran	Prospective, single center, randomized, controlled	N=90, primiparas, elective CS under general analgesia	N=45 (experimental) N=45 (placebo)	10 IU oxytocin IV for 30 min	Infusion of TXA 10 min before CS	1 g IV for 5 min	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of materials used -weight of material before use))/1.05 from the end of CS to 2 h postpartum	28.0 ml vs 37.1 ml	0.001	No thromboembolic or other side effects reported
Gungorkuk et al, (2011) [65]	Turkey	Prospective, single center, double-blinded, randomized, controlled	N=666, primiparas and multiparas, elective CS*	N=330 (experimental) N=330 (placebo)	5 IU IV bolus oxytocin, then 30 IU oxytocin in 500 mL solution at a rate of 125ml/h	Infusion of TXA 10 min before CS	1 g IV for 5min	Estimated blood loss during CS. Yes, 327 per group Yes	Estimated blood loss = EBV× (preop hematocrit-postop hematocrit)/preop hematocrit	600.7 ml vs 499.9 ml	<0.001	Gastrointestinal side effects (16.3%) in the experimental group Gastrointestinal side effects not mentioned for the placebo group. No thromboembolic events
Movafegh et al, 2011 [66]	Iran	Prospective, single center, double-blinded, randomized controlled study	N=100, Primiparas and multiparas, elective CS under spinal anesthesia	N=50 (experimental) N=50 (placebo)	10 IU oxytocin IV over 20 min, then 30 IU oxytocin over 8 h	Infusion of TXA 20 min before CS	10 mg/kg IV for 10 min	Postpartum blood loss not clearly mentioned Yes, 50 per group Not reported	Method of Gai et al [67]	262.5 ml vs 404.7 ml	<0.001	No thromboembolic events
Xu et al, 2013 [67]	China	Randomized, single center, double-blinded, controlled study	N=174 primiparas, elective CS under spinal anesthesia	N=88 (experimental) N=86 (placebo)	10 IU oxytocin IV for 30 min with 0.4 mg methylergometrine IV	Infusion of TXA 10 min before CS	10 mg/kg IV for 5 min	Postpartum blood loss not clearly mentioned Yes, 76 per group Not reported	Method of Gai et al [67]	379 ml vs 441 ml	0.02	2 thromboses occurred in each group. Gastrointestinal side effects occurred in 10 TA patients versus one case placebo patient

Senturk et al, 2013 [68]	Turkey	Randomized, single center, double-blinded, controlled study	N=223, Primiparas and multiparas, elective and emergency CS under spinal anesthesia	N=101 (experimental) N=122 (placebo)	20 IU IV bolus oxytocin	Infusion of TXA 10 min before CS	10 mg/kg IV for 5 min	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of wet – dry pads or tampon)/1.05	272 ml vs 347	0.001	No thromboembolic or gastrointestinal side effects
Shahid A et al, 2013 [69]	Pakistan	Randomized, single center, double-blinded placebo-controlled study	N=74 Primiparas and multiparas, elective CS under spinal anesthesia	N=38 (experimental) N=36 (placebo)	5 IU oxytocin and 0.4 mg methylergometrine IV bolus then 30 IU oxytocin over 6 hours	Infusion of TXA 10 min before CS Measurement of blood loss from the time of placental delivery to end of CS	1 g IV.	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of materials used - weight of material before use) + volume included in the suction container from the placental delivery to the end of CS	356 ml vs 710 ml	<0.001	No thromboembolic side effects
Abdel-Aleem et al, 2013 [70]	Egypt	Randomized, single center, open, controlled study	N=740 Primiparas and multiparas, elective CS under spinal anesthesia	N=373 (experimental) N=367 (no placebo)	5 IU IV bolus and 20 IU IV infusion of oxytocin	Infusion of TXA 10 min before CS	1 g IV for 10 min	Blood loss two hours after delivery Yes, 350 per arm Yes	(weight of all towels used - weight of dry towels)× 0.9+ volume included in the suction container from the placental delivery to 2 h postpartum	241.6 ml vs 510.6 ml	<0.001	Gastrointestinal side effects (74.3% versus 53.1%; p=0.0001) No thromboembolic side effects
Goswami et al, 2013 [71]	India	Randomized, single center, double-blinded placebo controlled study	N=90 Primiparas and multiparas, elective CS under spinal anesthesia	N=30 (experimental 1) N=30 (experimental 2) N=30 (placebo)	20 IU oxytocin in 500 mL at the rate of 8 mU/min IV	Infusion of TXA 20 min before CS	Experimental 1: 10 mg/kg Experimental 2: 15 mg/kg	Postpartum blood loss not clearly mentioned Not reported Not reported	(weight of all towel used - weight of dry towels)×0.9+ volume included in the suction container from the placental delivery to 2 h postpartum	376.8 ml vs 261.2 ml vs 527.2 ml	Not reported	No thromboembolic side effects

CS, Cesarean Section; TXA, Tranexamic acid; IV, intravenous; EBV, estimated blood volume=the woman's weight (kg) x 85

* the authors did not mention the mode of anesthesia for the cesarean

Table 1: Characteristics of the randomized controlled trials that have assessed tranexamic acid for the prevention of postpartum hemorrhage after cesarean deliveries

Table created by Sentilhes et al., Tranexamic acid for postpartum haemorrhage, published in British Journal of Anaesthesia, January 2015, pages 4,5, by permission of Oxford University Press

evntually reach a definitive conclusion on this subject. Even if the outcome of this ongoing trial reveals there is no benefit on mortality to using TXA on non high-risk patients, our case report highlights the need for more focused studies on the potential benefit and effect of TXA in treating high risk obstetric patients, as even minimal blood loss in these patients can have a far more devastating outcome on the patient and even a minimal reduction in bleeding can potentially be of great benefit.

Informed Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

Competing Interest

None

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