UNIVERSITY of WASHINGTON

Tranexamic acid for prevention and treatment of postpartum hemorrhage

Obstetric Consensus Conference

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OVERVIEW

DRUG INFORMATION

Postpartum hemorrhage continues to be a major cause of maternal mortality worldwide (1). In recent years, tranexamic acid (TXA), an antifibrinolytic agent, has received increased global attention from the obstetrics community in the effort to decrease maternal mortality due to postpartum hemorrhage. TXA is a synthetic analog of the amino-acid lysine that acts by reversibly binding receptor sites on plasminogen thereby preventing the proteolytic activity of plasminogen and the degradation of fibrin. TXA has a half-life of ranging from 2-11 hours and is renally cleared. For pregnancy, it has a US Food and Drug Administration category B designation, is known to cross the placenta, and is excreted in small amounts in breastmilk. (2, 3)

EVIDENCE FROM NON-OBSTETRIC LITERATURE

A large portion of information about TXA comes from non-obstetric literature. One of the largest and best-known studies is the CRASH-2 trial which explored the use of TXA in trauma patients (4). CRASH-2 was a randomized control trial (RCT) that was conducted in 40 countries in which 10,096 trauma patients were randomly allocated to receive TXA and 10,115 patients were allocated to receive placebo. The major finding of this study was that all-cause mortality was significantly reduced in the TXA group (1463 [14.5%] TXA vs 1613 [16.0%] placebo; RR 0.91, 95% CI 0.85–0.97; p=0.0035). In addition, risk of death due to bleeding was significantly reduced if TXA was given within 3 hours of injury (489 [4.9%] TXA vs 574 [5.7%] placebo; RR 0.85, 95% CI 0.76–0.96; p=0.0077). Roberts et al conducted an exploratory analysis of the CRASH-2 data and found that the time-dependent effect of TXA in bleeding trauma patients was not explained by the type of injury, whether head injury was present or by systolic blood pressure. TXA was found to decrease risk of death due to bleeding if given within 3 hours of injury, regardless of type of injury, Glasgow Coma Scale (GCS) score or blood pressure.

Other fields that utilize TXA include cardiothoracic surgery for extra-corporeal membrane oxygenation (ECMO) patients (5). In addition, studies in the field of orthopedic surgery have shown decreased blood loss, higher postoperative hemoglobin levels and decreased blood transfusion rates with TXA use in total hip and knee arthroplasties (6, 7). Early activation of fibrinolysis is common after trauma, with evidence that this fibrinolytic process contributes to mortality (8). Similar changes in fibrinolysis after childbirth have been noted, thus driving interest in research regarding TXA in the obstetric population (9).

OBJECTIVE OF THIS CONSENSUS STATEMENT

The objective of this consensus conference and statement is to evaluate the use of TXA for prevention and treatment of postpartum hemorrhage (PPH) in the obstetric setting based on a literature review and existing recommendations from professional organizations. We will not be discussing use of TXA for obstetric patients with hemophilias or other bleeding disorders.

LITERATURE REVIEW

PROPHYLACTIC USE

There are multiple smaller studies of mixed design quality regarding TXA for prevention of postpartum hemorrhage. We have focused here on the largest published reviews. There are three major reviews on prophylactic use of TXA for prevention of PPH and one abstract that was presented in January 2018:

- Novilova et al conducted a systematic review, "Tranexamic acid for preventing postpartum haemorrhage (Review)", published in the *Cochrane Database for Systematic Reviews* in 2015 (10). The objective of this study was to review all published, unpublished, and ongoing RCTs to determine if TXA was effective and safe for preventing PPH compared to placebo, or no treatment, or to uterotonic agents. They found 12 trials involving 3285 healthy women at low risk for bleeding undergoing cesarean delivery (CD) (9 trials) or spontaneous vaginal delivery (VD) (3 trials). All patients received routine uterotonics as well as TXA versus placebo versus no intervention. In these trials, TXA was administered intravenously (IV) before CD or after VD in varying doses, including one gram of TXA diluted in 20 mL of 5% glucose over five minutes (5 trials), one gram of TXA diluted in 20 mL of 5% glucose over 10 minutes (2 trials), one gram of TXA by slow IV injection (1 trial), 10 mg/kg TXA IV in 200 mL of normal saline over 10 minutes (2 trials), 10 mg/kg in 20 mL of 5% dextrose compared to 15 mg/kg diluted in 20 mL of 5% glucose over 20 minutes (1 trial), and 0.5 gram compared to 1 gram TXA given IV over 2-3 minutes (1 trial). Findings demonstrated that for patients who had received TXA, estimated blood loss (EBL) of >400mL or 500mL, and >1000 mL was less common (RR 0.52, 95% CI 0.42-0.63 for EBL >400mL or 500mL; and RR 0.40, 95% CI 0.23-0.71 for EBL >1000mL). Evaluating mode of delivery, EBL > 1000 mL had a decreased incidence in women who delivered by CD and who received TXA, but not for VD. Mean blood loss in the intervention groups was 77.8 mL less in the TXA groups as compared to placebo. With TXA, medical interventions and blood transfusions were less frequent compared to placebo. There was an uncertain effect on maternal mortality, severe morbidity and thromboembolic events (See Table 1). The authors concluded that "tranexamic acid prevents PPH and blood transfusions following vaginal birth and cesarean section in women at low risk of PPH based on studies of mixed quality."(10)

- Simonazzi G, Berghella V, et al conducted a systematic review and meta-analysis, "Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials," published in *Acta Obstetricia et Gynecologica Scandinavica* in 2016 (11). The objective of this study was to evaluate the effectiveness of TXA in reducing blood loss when given prior to routine CD. The primary outcome was postpartum (PP) blood loss (mL) in CD. Secondary outcomes included incidence of PPH (>500 mL), severe PPH (> 1000 mL), use of additional medical interventions, thromboembolic events, hemoglobin drop 24 hours after CD, blood transfusions, severe maternal morbidity (intensive care unit admission, hysterectomy, organ failure) and drug reactions. Nine trials from global settings with a total of 2365 women were included. The TXA dose used in most of the included studies was 1 gram (or 10 mg/kg) given 10-20 minutes before spinal anesthesia or before incision. Results showed that with TXA, there was moderately decreased PP blood loss (-160.27mL, p<0.00001; and -136.75mL, p=0.0009, compared to controls and placebo, respectively), a lower drop in hemoglobin, a lower incidence of PPH and severe PPH compared to controls, and a lower rate of blood transfusion (see Table 1). There was no increased incidence of thromboembolic events with TXA administration. Five studies reported on neonates and no adverse events were noted. The authors concluded that "prophylactic tranexamic acid given before cesarean skin incision in women undergoing cesarean delivery significantly decreases blood loss, including postpartum hemorrhage and severe postpartum hemorrhage."(11)

- Li et al conducted a systematic review and meta-analysis titled “Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention? A systematic review and meta-analysis” which was published in *Medicine (Baltimore*) in 2017 (12). The objective of this study was to assess the efficacy and safety of TXA in reducing blood loss and lowering transfusion needs for patients undergoing routine CD and VD. Twenty-five trials were included in this study with a total of 4747 participants. Most studies used TXA 1 gram IV 10-30 minutes before CD or at delivery of the anterior shoulder with VD. Results showed that use of TXA in CD modestly reduced intra-, post-operative and total blood loss by mean volume of 141 mL, 36 mL and 154 mL, respectively ($p<0.00001$ for all groups). Use of TXA in VD minimally reduced intra-, post-operative and total blood loss by mean volume of 23 mL ($p=0.10$), 41 mL ($p<0.0001$) and 85 mL ($p<0.0001$). No increased incidence of thromboembolic events was found with TXA use. In this study no comment was made on potential neonatal effects. The authors concluded that “although prophylactic tranexamic administration is associated with reduced PPH, current existing data are insufficient to draw definitive recommendations about its clinical significance due to the poor to moderate quality of the included literature.” (12)

- Sentilhes et al presented an oral abstract at the Society for Maternal-Fetal Medicine (SMFM) meeting in January 2018 entitled , “Tranexamic acid for the prevention of postpartum hemorrhage after vaginal delivery: the TRAAP trial.”(13). This French study was a multicenter 2 arm RCT with the objective to test the impact of 1 gram of TXA after routine VD on the incidence of PPH. In this study, women were randomized to receive 1-gram TXA IV or placebo in addition to standard prophylactic oxytocin within 2 minutes of delivery. The primary outcome was PPH ≥500mL. The secondary outcomes were other measures of PPH and potential adverse effects of TXA. 4079 women were included, of which 3891 had a VD and underwent statistical analysis. The TXA study arm demonstrated decreased PPH >500 mL and decreased clinically significant PPH according to caregivers as compared to placebo (6.6% versus 8.8%, $p=0.01$ and 7.8% versus 10.4%, $p=0.004$). There was also decreased need for additional uterotonics in the TXA group (7.3% versus 9.7%, $p=0.006$), but there was increased nausea and vomiting as compared to placebo (7.0% versus 3.2%, $p<0.0001$). There were no significant differences in thrombotic events or other adverse outcomes. In pre-specified subgroup analyses, there was decreased rate of the primary outcome with instrumental delivery (9.6% versus 14.5%, $p=0.0498$) as well as with episiotomy (12.3% versus 17.3%, $p=0.049$). In the subgroups of spontaneous vaginal delivery and deliveries without episiotomy, the primary outcome of PPH ≥500mL was no longer significant.

Table 1. Major reviews/abstract on prophylactic use of TXA for prevention of PPH

Study	Numbers	TXA dose	Findings: with TXA
Cochrane: Novikova N, Hofmeyr GJ, Cluver C. *Cochrane Database Syst Rev*. 2015.	12 trials: 3285 low risk women undergoing CS (9 trials) or SVD (3 trials).	given IV before CD or after VD in varying doses (ranging from 0.5 gram, 10 mg/kg, 1 gram, and 15 mg/kg)	-↓ **EBL >400mL** or **>500mL** RR 0.52 (95%CI 0.42-0.63) -↓ **EBL > 1000 mL** (for CD only) RR 0.40 (95% CI 0.23-0.71) -↓ **Mean blood loss 77.8 mL** CI -97.95 to -57.64 -↓ **Use of other interventions to control PPH** RR 0.48 (0.34-0.68) - Uncertain effect on mortality, morbidity, VTE
Simonazzi G, Bisulli M, Saccone G, Moro E, Marshall A, Berghella V. *Acta Obstet Gynecol Scand*. 2016.	9 trials: 2365 women	most studies 1 gram (or 10 mg/kg) 10-20 minutes before spinal anesthesia or before incision	↓ **PP blood loss** **-160 mL compared to controls** 95% CI -224.63, -95.92 **-137 mL compared to placebo** 95% CI -217.39, -56.11**)** ↓drop in hemoglobin Mean -0.61 grams, (95%CI -1.04 to -0.18) ↓**incidence of PPH** (RR 0.21; 95%CI 0.16-0.28) ↓**severe PPH** (RR 0.42; 95% CI 0.19-0.92) ↓ **rate of blood transfusion** (RR 0.33, 95%CI 0.19-0.58) - No increased VTE - 5 studies: no neonatal adverse events.
Li C, Gong Y, Dong L, Xie B, Dai Z. *Medicine (Baltimore*). 2017.	25 trials: total 4747 women	most studies 1 gram IV 10-30 minutes before CD or at delivery of the anterior shoulder with VD	**CD:** ↓intra-, post-op and total blood loss by **141 mL, 36 mL and 154 mL (all p<0.0001)** **VD:** ↓ intra-, post-op and total blood loss by **23 mL (p=0.10), 41 mL, and 85 mL (p<0.0001)** - No increased VTE - No comment on neonatal effects.
Sentilhes et al. *AJOG*. 2018 (Abstract).	3891 women with VD	1 gram IV within 2 minutes of delivery	↓ **PPH greater than or equal to 500mL** RR 0.75 (95%CI 0.61-0.94) ↓ **need for additional uterotonics** RR 0.75 (95%CI 0.61-0.92) ↑ nausea or vomiting in labor RR 2.16 (95%CI 1.61-2.89) No difference in thrombotic events **Subanalysis** ↓ **PPH with instrumented delivery** RR 0.66 (95%CI 0.44-1.00, P=0.0498) ↓ **PPH with episiotomy** RR 0.73 (95%CI 0.53-1.00, P=0.049)

THERAPEUTIC USE

Unlike the literature review of TXA for prevention of PPH, there are no published large meta-analyses on TXA for treatment of PPH. Instead, there are multiple smaller studies regarding TXA for treatment of PPH. Many of these, however, are of limited quality and performed in low-resource settings with limited generalizability to the United States. We will review 2 prospective RCTs and 1 larger retrospective trial as the best available literature regarding TXA for treatment of PPH.

- Ducloy-Bouthors et al conducted a multicenter RCT in France which was published as "High-dose tranexamic acid reduces blood loss in postpartum haemorrhage" in *Critical Care* in 2011 (14). The objective of this study was to determine whether administration of TXA at diagnosis of PPH could decrease blood loss. In this study, women with PPH >800 mL following VD were assigned to receive TXA versus no intervention. The primary outcome of this study was blood loss reduction, with secondary outcomes of PPH duration, anemia, transfusion and need for invasive procedures. 144 women were included in this study. With administration of TXA 4 grams IV over 1 hr, women who received TXA compared to placebo had lower blood loss from the time of inclusion over 6 hours (median 170 mL versus 221 mL, respectively; p=0.041), shorter bleeding duration (p=0.004), cessation of bleeding by 30 minutes after enrolment (63% in the TXA group, compared to 46%of controls; p=0.034), less frequent progression to severe PPH and blood transfusion (p=0.028), more frequent resolution of PPH with uterotonics and blood transfusion (p=0.016), but more frequent mild, transient adverse manifestations such as nausea and vomiting (p=0.03) (See Table 2). The authors concluded that "high-dose tranexamic acid can reduce blood loss and maternal morbidity in women with PPH." (14)

- Gillissen et al's study, "The effect of tranexamic acid on blood loss and maternal outcome in the treatment of persistent postpartum hemorrhage: A nationwide retrospective cohort study," was a retrospective cohort study conducted in the Netherlands with data from 61 hospitals and was published in *PLOS* in 2017 (15). The objective of this study was to compare early TXA to late TXA or no TXA in PPH in a high-income country. The primary outcome of this study was a combined endpoint of maternal mortality or severe morbidity, including hysterectomy, uterine artery ligation, B-lynch stitch, uterine artery embolization or ICU admission. Secondary endpoints were total blood loss, additional blood loss, volume and number of blood products transfused. PPH was defined as bleeding that occurred within 24 hours of delivery with persistent bleeding despite timely first line therapy. 1260 women were found to have persistent PPH with transfusion of at least 4 units red blood cells (RBC) or fresh frozen plasma (FFP) or platelets in addition to RBCs. 247 women received early TXA (within 1 hour or 1-3 hours). The mean dose of TXA administered was 1.1 grams IV (range 0.1-3 grams). Results showed no difference in the composite endpoint for early TXA versus late TXA or no TXA, with an adjusted OR of 0.92 (95% CI 0.66-1.27). No difference in additional EBL was found between the groups (-177mL, 95%CI -509.4 to +155.0mL). The authors concluded that "in a high-resource country the effect of tranexamic acid on both blood loss and the combined end point of maternal mortality and morbidity may be disappointing." (15)

- The World Maternal Antifibrinolytic (WOMAN) trial was an RCT conducted at 193 centers in 21 countries. Findings were published by WOMAN Trial Collaborators, Shakur et al as "Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomized, double-blind, placebo-controlled trial" in the *Lancet* in 2017 (16). In this RCT, 20,060 women with a clinical diagnosis of PPH (>500 VD, >1000 CD) were randomized to receive TXA 1 gram IV (+ second dose as needed) versus a placebo. The primary outcome was death from hemorrhage, while secondary outcomes were maternal thromboembolic

events, surgical interventions, complications, other medical events, quality of life, and neonatal thromboembolic events in breastfed babies. Results showed that with TXA administration compared to placebo, death from hemorrhage was reduced by approximately 20% (1.5% in the TXA group versus 1.9% in the placebo group; RR 0.81; 95% CI, 0.65-1.00; p=0.045) (See Table 2). In addition, there did not appear to be an increase in thromboembolic risk with this 1 gram dose of TXA (17 cases of thromboembolic event in TXA group, 20 cases in placebo group). The authors concluded that "tranexamic acid reduces death due to bleeding in women with postpartum hemorrhage with no adverse effects."(16)

Table 2. Major studies on use of TXA for treatment of PPH

Study	Design	TXA dose	Findings with TXA
Ducloy-Bouthors *et al. Critical Care 2011*.	Multicenter RCT France 144 women	4 grams IV over 1 hr	**↓ blood loss** median 170 mL vs 221 mL, p=0.041 **↓ bleeding duration** cessation of bleeding by 30 minutes (63% vs. 46%; p=0.034) **↓ progression to severe PPH and transfusion (p=0.016)**
Gillissen et al. *PLOS* 2017.	Retrospective cohort Netherlands (61 hospitals) 1260 women	mean dose 1.1 grams (range 0.1-3 grams) IV	**Negative study** - aOR for composite endpoint for early TXA versus no/late TXA was 0.92 (95% CI 0.66-1.27) - No difference in maternal morbidity or blood loss between groups.
WOMAN Trial Collaborators, Shakur et al. *Lancet* 2017.	RCT at 193 centers in 21 countries 20,060 women	1 gram IV (+1 additional dose prn) vs placebo	**↓ in death from hemorrhage by 20% 1.5% (TXA); 1.9% (placebo)** RR 0.81; 95% CI, 0.65-1.00; p=0.045 No increase in thromboembolic risk with low doses of TXA

ADVERSE EVENTS WITH TRANEXAMIC ACID

While TXA is generally well tolerated, several concerning adverse events have been reported. One adverse event is renal cortical thrombosis. This is documented to have occurred after continuous infusion of TXA (mean 0.5-1 gram/hour for 5.3 hours), which is significantly higher dosing than used in the obstetric studies reviewed in this consensus statement (17). Another reported adverse event was due to an anesthesia substitution error in which there was intrathecal administration of TXA instead of bupivacaine. This was due to similar visual appearance of the bottles for both medications and, unfortunately, resulted in a maternal death (18). Finally, TXA is known to be a competitive antagonist of gamma-aminobutyric acid (GABA). This reduces inhibition of neurotransmission and may result in dose-dependent seizures with an incidence of 0.9-2.5% in non-pregnant patients. Seizures have primarily been noted at doses that are higher than the typical 1gm IV doses used in many obstetric trials (19).

NEONATAL CONSIDERATIONS AND EFFECTS ON BREASTFEEDING

There is a paucity of data on effects of peripartum TXA administration on the neonate. In their review, Simonazzi et al included five studies that reported on neonatal outcomes and did not find any adverse events after administration of TXA prior to CD (11). Based on limited data, TXA is not thought to cause fetal or neonatal harm, although it is known to cross the placenta (2, 20). Similarly, very little data is available on breastfeeding after TXA administration. TXA concentrations in breastmilk are about 1/100 of maternal serum levels, however, are not thought to have significant effects on the neonate (20).

RECOMMENDATIONS FROM PROFESSIONAL HEALTH ORGANIZATIONS

In light of the findings discussed above, in particular the findings from the WOMAN trial, select organizations have issued recommendations. These include the American College of Obstetricians and Gynecologists (ACOG) who updated their Practice Bulletin on PPH in 2017 to include a revised definition of PPH as a total blood loss ≥ 1000 mL or as blood loss that is associated with signs or symptoms of hypovolemia within 24 hours after delivery regardless of mode of delivery. They also included the statement that while there is insufficient data to recommend use of TXA for prevention of PPH, TXA should be considered in the setting of PPH when initial medical therapy fails, with maximum benefit observed if given within three hours of delivery (21). The World Health Organization (WHO) updated their recommendations in 2017 to strongly recommend early use of 1gram of TXA within 3 hours of birth in all cases of PPH, used as part of standard PPH treatment regardless of whether bleeding is thought to be due to genital tract trauma or other etiologies including uterine atony (22).

CONSENSUS STATEMENT

GENERAL DISCUSSION

After completing the above literature review, TXA use should be considered in two separate clinical scenarios: as prophylaxis and as treatment.

Published data regarding TXA for prophylaxis of PPH is predominantly smaller studies of variable quality, with the above 3 meta-analyses demonstrating statistically small reductions in postpartum hemorrhage that are of uncertain clinical benefit. The American College of Obstetricians and Gynecologists reports that "data are insufficient to recommend the use of tranexamic acid as prophylaxis against postpartum hemorrhage" at this time (21). An NIH sponsored randomized, double-blinded, placebo controlled clinical trial "Tranexamic Acid in Adherent Placenta (TAP)" (ClinicalTrials.gov Identifier: NCT02329756) has been posted but is not yet recruiting patients (26).

In terms of TXA for treatment of postpartum hemorrhage, the 3 trials reviewed above vary in size, resource availability and conclusions. The Ducloy-Bouthors and Gillissen publications were smaller studies, both performed in high-resource countries, with conflicting results regarding the efficacy of TXA for treatment of PPH. The WOMAN trial was large with over 20,000 patients, impressive statistical design and follow through. While the results are meaningful and highly applicable in a low-resource setting, the generalizability to the United States is uncertain. Perhaps one of the most important benefits of the WOMAN trial is the demonstration of no increased thromboembolic risk in this large cohort of pregnant women. The question of thromboembolic risk with TXA use has been a concern raised regarding TXA for clinical use in obstetrics for many years. The American College of Obstetricians and Gynecologists currently recommends that "tranexamic acid should be considered in the setting of obstetric hemorrhage when initial medical therapy fails … [with] benefit primarily in women treated sooner than 3 hours from the time of delivery" (21).

It is also important to consider the setting in which prior studies were conducted. In high-income settings, such as those found in Washington state, maternal mortality is low at 9 deaths per year per 100,000 live births in 2014-2015 compared to global maternal mortality at 216 deaths per 100,000 live births in 2015 (23, 24). Labor and Delivery inpatient units within Washington State have access to blood transfusions, and, in many cases, have established massive transfusion protocols. In comparison, the baseline all-cause maternal mortality in the WOMAN trial, performed in predominantly low-resource countries, was 2.6% (1 in 38 women). While hemorrhage is the leading cause of maternal mortality worldwide, in high resource settings death from hemorrhage is rare (<0.1%) and is surpassed by mortality due to hypertension and cardiovascular complications of pregnancy.

While several of the reviewed publications in this consensus demonstrated a statistically significant decrease in postpartum hemorrhage and other measures of PPH morbidity, the absolute quantity of overall blood loss reduction was small. In the studies reviewed above, for those that reported a quantitative difference in EBL between TXA and placebo groups, the reduction in blood loss was less than 200mL in all publications. Small decreases in EBL at this magnitude are less likely to have a significant effect on maternal morbidity due to PPH within our high-resource state.

Finally, there is uncertainty about how TXA actually functions to decrease bleeding in obstetric hemorrhage. Postpartum hemorrhage and coagulopathy is multifactorial, and more studies are needed to examine incidence, timing and extent of hyperfibrinolysis among women with PPH (25).

In terms of cost, TXA is an inexpensive medication. At the University of Washington, TXA is estimated to cost approximately $8.75 per gram while the IV piggy back fluid costs about $10.00 per bag. The total cost therefore amounts to ~$20 for one course of TXA.

With these caveats in mind, TXA has potential to decrease morbidity from PPH with low risk of adverse effects, and our patients may benefit from its therapeutic use as a second line agent when initial medical therapy fails, and in rare cases of preventative use. The following inclusion and exclusion criteria have been set up to maximize potential benefit from TXA while minimizing potential risks to our patients.

INCLUSION CRITERIA

USE OF TRANEXAMIC ACID FOR PREVENTION OF POSTPARTUM HEMORRHAGE

Given the limited data regarding benefit of TXA as pre-delivery prophylaxis, *consider* TXA administration only in the highest risk cases, such as:

Suspected invasive placentation

USE OF TRANEXAMIC ACID FOR TREATMENT OF POSTPARTUM HEMORRHAGE

As post-delivery treatment, *consider* TXA administration in cases of diagnosed postpartum hemorrhage where there is continued bleeding from uterine atony or vascular injuries requiring further therapy in order to control the ongoing hemorrhage.

Qualifying criteria for consideration of TXA as treatment of postpartum hemorrhage:

PPH defined as a cumulative blood loss of ≥ 1000 mL for vaginal or cesarean delivery *within 3 hours of delivery*
-- AND ONE OF THE FOLLOWING--
There is continued uterine atony requiring additional uterotonics beyond routine oxytocin administration
There is continued bleeding due to perineal lacerations or intraoperative vascular injuries requiring further interventions to obtain hemostasis (ex. hysterotomy extension, uterine artery laceration, prolonged repair of bleeding hysterotomy, complex perineal or vaginal laceration with ongoing bleeding)

EXCLUSION CRITERIA

Based on known reported adverse events and potential risks, the following are contraindications to TXA use in obstetric patients:

- Underlying renal disease
- History of thromboembolic event
  (i.e. deep venous thrombosis, pulmonary embolus, cerebrovascular event)
- Underlying seizure disorder
- Eclamptic seizure
- Known thrombophilia

DOSING AND ADMINISTRATION

Based on current literature, we recommend the following dosing and timing of administration:

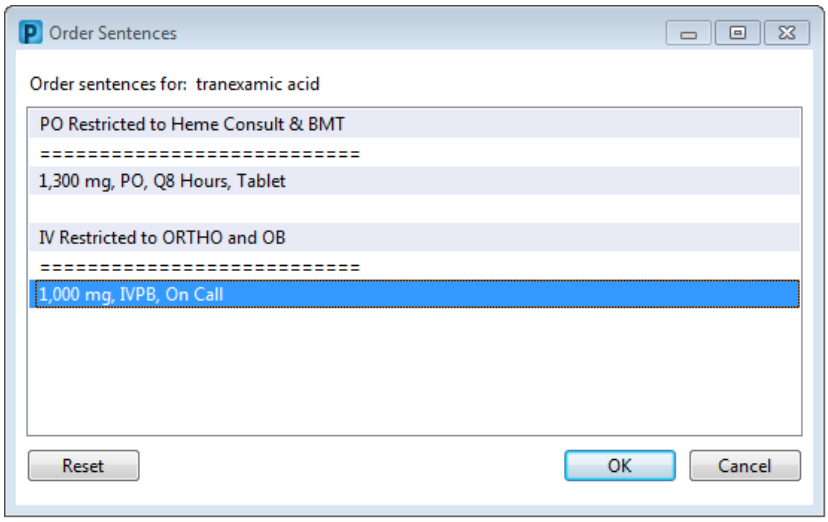
DOSING AND ADMINISTRATION
1 gram IV given over 10 minutes
May repeat once after 30 minutes if continued bleeding, but still within 3 hours of delivery

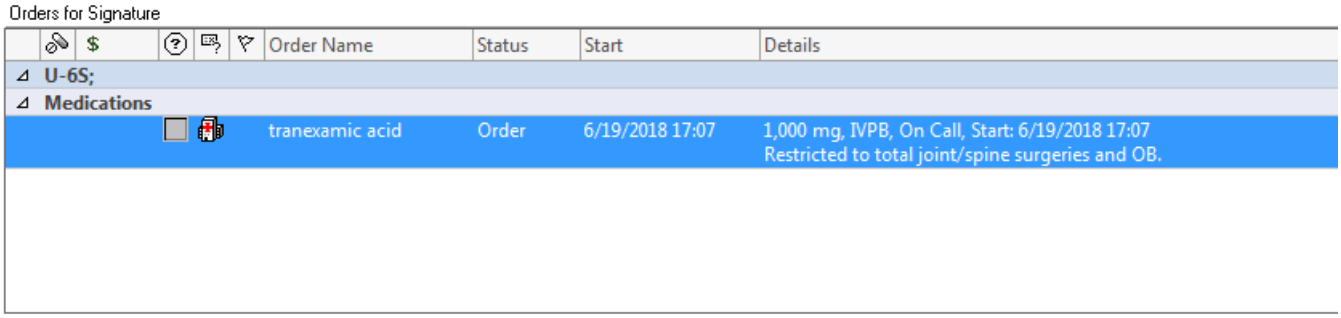
PROPHYLAXIS
In the rare *prophylactic* use scenario of suspected invasive placentation, give TXA at skin incision. A second dose may be repeated after 30 minutes if hemorrhage ensues, but within 3 hours after delivery

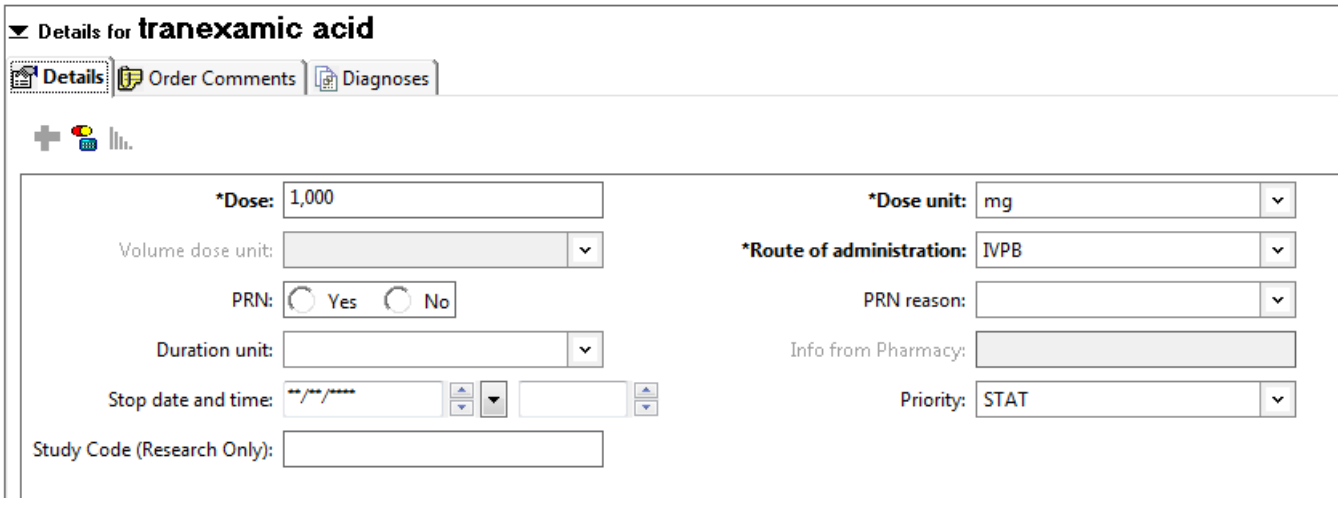
TREATMENT
For 2nd line *treatment* of PPH to treat ongoing hemorrhage due to atony or vascular injury, give TXA concurrently with additional uterotonics or surgical interventions. A second dose may be repeated if there is non-resolution of bleeding after 30 minutes, but within 3 hours of delivery

At the University of Washington, TXA will be stored in the anesthesia Pyxis on Labor and Delivery, to be mixed by the anesthesia resident or attending as a 100mL IV piggy back. Medication mixing is not within the standard of care practices for floor nursing at UWMC. Thus, if the patient is in the operating room, TXA can be administered and charted by anesthesia. For patients in a labor and delivery room, once the IV piggy back is mixed by the anesthesia staff, the 100mL IV piggy back can be administered and charted by the Labor and Delivery nursing staff. The TXA order should be included in the standard postpartum order set submitted by the OB service.

EXAMPLE UW MEDICINE ORDER SET







QUALITY IMPROVEMENT AND MONITORING

The use of TXA for prevention and treatment of PPH in obstetrics in the United States is currently not standard of care, however, recommendations by ACOG regarding TXA use for treatment of PPH have been made. Since large studies on TXA use in high-income settings and particularly in the United States are not available, we would recommend beginning collection of quality improvement metrics concurrently with initiation of TXA use in obstetrics at an individual health center. Possible data collection points could include:

- Number of obstetrics cases with TXA use
- Information on the clinical scenario and postpartum hemorrhage
- TXA administration (dose, number of doses)
- Maternal morbidity (ICU admission, transfusion of blood products)
- Adverse events and side-effects

Disclaimer

This consensus document is to be used as a guideline for practice management. It is generated by expert review from the Departments of Obstetrics and Gynecology, Hematology and Anesthesia, as well as UW Nursing.

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