CMQCC
California Maternal
Quality Care Collaborative

Tranexamic acid (TXA) for Obstetric Hemorrhage
July 2017

Background

Obstetric hemorrhage is most often caused by either uterine atony, retained placental fragments or trauma (perineal, vaginal, cervical or uterine laceration). The initial approach is to address the underlying cause (e.g. uterotonics for atony and surgical correction for lacerations). A low fibrinogen from loss or dilution or evidence of fibrinolysis (on either TEG® or ROTEM® testing) can predict the transition to massive hemorrhage (>1500 ml). The presence of coagulopathy can make obstetric or postpartum hemorrhage (PPH) particularly dangerous, resulting in multiple units of blood transfusion, hysterectomy or death.

Tranexamic acid (TXA) is an inhibitor of fibrinolysis and may reduce bleeding in the setting of coagulation abnormalities. Prior studies have shown minimal, if any, benefit for prophylactic use of TXA at cesarean section. The recent WOMAN international randomized controlled trial showed a 31% reduction in death from hemorrhage when 1g of TXA was administered intravenously within 3 hours after the diagnosis of PPH.[1] This trial included over 20,000 women with PPH in a mix of low and high resource countries.

Should we use TXA for obstetric hemorrhage treatment in high resource settings? First, we need to stress that TXA is NOT an initial treatment—we cannot overemphasize the importance of early diagnosis and management with uterotonics or surgical repair. If the hemorrhage continues, the risk of coagulopathy rises, at which time TXA may have an important role.

TXA Safety

TXA has a reassuring safety profile for the dosage used in the WOMAN trial (1gm intravenous over 10 minutes with a second 1 gm dose administered at 30 minutes if the bleeding persists). Venous thromboembolic events, seizures and renal complications were NOT seen at higher rates than the controls in this study (these complications have been a concern with higher TXA doses). However, there have been reports of medication errors in orthopedic cases with "look-alike" vials of local anesthetics (bupivicaine) where TXA was inadvertently administered intrathecally resulting in deaths or major neurologic injuries.[2,3] These errors were not identiifed in the WOMAN trial but there have been several such errors in obstetric cases reported to SOAP (personal communication, Alex Butwick, MD).

Where should TXA fit in a hemorrhage management protocol?

Again, we consider TXA to be an adjunctive treatment and NOT a primary treatment for PPH. The exact placement in your facility's hemorrhage protocol will depend on local resources; our preliminary recommendations suggest use of TXA if:

- Bleeding continues after higher dose oxytocin and methergine have been administered (end of CMQCC Hemorrhage Stage 1), or
- Additional interventions (e.g. Hemabate® or compression balloons) are being considered (beginning of CMQCC Hemorrhage Stage 2).

- TXA should be considered for inclusion in the unit OB Hemorrhage medication kit for rapid accessibility. Restriction to a hemorrhage medication kit may reduce the risk of look-alike drug error (specifically do not put TXA in same place as local anesthetics). Another approach is to clearly label vials of TXA as "NOT FOR NEURAXIAL ADMINISTRATION" to limit the likelihood of inadvertent wrong site administration.
- Fibrinogen replacement (e.g. cryoprecipitate) in the setting of fibrin breakdown is most effective if given AFTER administration of TXA (but don't delay blood products to administer TXA if the clinical condition calls for transfusion).

Important points of emphasis:

- A serious postpartum hemorrhage requires "many hands" and there is concern for "task saturation" (many things to be done at the same time by a limited number of people), Your hospital protocol should emphasize that 1) usual initial treatment steps need to be undertaken first (and not delayed for TXA administration), 2) as TXA is an additional step, it is important to ensure that enough staff are mobilized, and that 3) TXA should be a formal part of the PPH protocol so the staff is familiar and organized in its use.
- Dosing limits should be respected; the TXA dose that has been shown to be safe and effective for limiting OB hemorrhage is 1gm that may be repeated ONCE at 30 minutes.
- The WOMAN trial clearly demonstrated that TXA is most effective when given within 3 hours of hemorrhage diagnosis, hence the recommendation that it be considered relatively early in the hemorrhage protocol.

Intravenous Administration (from PDR)

- TXA solution for intravenous use contains 100mg per ml. can be used as slow IV injection or diluted within a 50 or 100ml IV piggyback to be given as an intravenous infusion.
- To avoid hypotension, administer at a rate not to exceed 100 mg per minute. (i.e 1gm over 10 minutes)
- Prepare the same day the solution is to be used; discard any remaining solution after single-use.
- May be mixed with most solutions for infusion such as electrolyte, carbohydrate, amino acid, and dextran solutions.
- Do not add heparin to injection or mix with blood; do not mix with solutions containing penicillin.

Renal Failure/Renal Impairment Cautions (from PDR)

Use tranexamic acid cautiously in patients with renal impairment or renal failure; elimination may be significantly delayed in these patients. Tranexamic acid is eliminated primarily via the kidneys by glomerular filtration with >95% excreted unchanged in the urine. Dosage adjustment in patients with renal impairment are required (see Dosage recommendations in the PDR). Patients with renal impairment should be observed carefully for signs and symptoms of toxicity (e.g., thromboembolism) during tranexamic acid therapy.

Note: for the low doses described for PPH (1gm IV infusion with a single repeat does of 1gm) toxicity has not been described even in the setting of renal impairment.

Experience of TXA Usage in France and United Kingdom

TXA has been used for PPH for many years in France and the United Kingdom. Discussions with colleagues leading national obstetric safety programs in those countries (UK-NPEU/MBRRACE and France-INSERM and AUDIPOG)[4] identified similar usage between the two countries and is described below (July 2017, personal communications, Elliott Main, MD):

1. TXA 1gm is usually administered after routine first line PPH drugs have not controlled the bleeding but before the need for blood products and/or additional procedures (similar to the position in the CMQCC hemorrhage treatment protocol recommended above).
2. 1gm TXA diluted into a 50ml or 100ml saline bag is usually administered by an anesthesiologist (if involved) or by a nurse and usually as an intravenous drip over 10-30 minutes. The solution is commonly made up by the anesthesiologist or nurse with a double check of the label.
3. The undiluted solution of 10ml (1 gm) TXA can also be administered by slow IV push over 10 minutes.

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[1] WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017 May 27;389(10084):2105-2116.

[2] Yeh HM, Lau HP, Lin PL, et al. Convulsion and refractory ventricular fibrillation after intrathecal administration of a massive dose of tranexamic acid. Anaesthesiology 2003;98:270–2.

[3] Garcha PS, Mohan CV, Sharma RM. Death after an inadvertent intrathecal injection of tranexamic acid. Anesth Analg. 2007 Jan;104(1):241-2.

[4] UK NPEU/MBRRACE is the UK National Perinatal Epidemiology Unit and the section that oversees the confidential enquiries into maternal deaths; INSERM is the French equivalent to the NIH; AUDIPOG is a national data-driven OB quality improvement program in France