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# The evolving role of prophylactic use of tranexamic acid before cesarean section: balance between maternal benefits and unknown neonatal effects

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## Abstract

Tranexamic acid (TXA), an antifibrinolytic agent, has recently been investigated as a potentially useful drug for both prevention and treatment of Primary Postpartum Hemorrhage (PPH). This article highlights the continuing evolvement of this antifibrinolytic medication in the broad field of anesthesiology, and more specifically, obstetric anesthesiology, focusing on three important aspects of TXA administration: the continuing studies and assessment of the potential benefits of TXA administration to minimize PPH in both non high risk and high risk parturients, the possible adverse effects of TXA on the mother, and finally the unknown risks of the administration of TXA to 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 on all three of these aspects before its widespread use can be recommended safely. Until that time, it is imperative that the anesthesiologist be well informed on this delicate balance of potential benefit of TXA to the mother versus potential and unknown risk to the mother and neonate.

**Keywords**: Perioperative complications, high risk obstetric parturients, primary postpartum hemorrhage, tranexamic acid, anesthetic issues and peri-operative care, preoperative evaluation and anesthesia risk, antifibrinolytics

## 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 a 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 also been shown to reduce blood loss in elective surgery, cardiac 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, as studies are currently ongoing to assess these benefits and unknown risks, the anesthesiologist must be aware of the evolving knowledge of TXA in the obstetric setting in order to maximize the beneficial effects on the mother while concurrently minimizing any potential deleterious effects on the neonate.

## Review

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, often times 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].

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 the link between plasminogen kringle 5 and lysine site of the fibrin heavy chain at one of the sites where antiplasmin and thrombin-activatable fibrinolysis inhibitor (TAFI) have their potential action. Thus, depending on the dose and the condition of the tertiary complex elements of the patient (tPA-Native Fibrin-plasminogen) and the secretion of the natural antifibrinolytic (antiplasmin depending on the liver function and TAFI depending on the thrombin secretion), tranexamic acid can supply a deficient natural antifibrinolysis or be competitive with it. This is one of the challenges of future trials to determine the optimal dose and the best timing of administration in the course of the fibrinolytic process.

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 elective non haemorrhagic 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, 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]. In the study, it was found that 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]. The choice of this particular population of high risk obstetric parturients is of high importance. Even

if the outcome of the currently ongoing clinical trials reveals there is minimal benefit on mortality to using TXA on non high-risk patients, this particular study highlights the need for more focused studies on the targeted use of TXA in treating high risk obstetric patients. High risk obstetric patients specifically include the populations of anemic patients as well as mothers with high risk obstetric conditions including placental abruptions or abnormal placentation, including placenta accreta, increta, and percreta. 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.

There are very few studies specifically addressing the adverse effects or even the possible risks of TXA. A recent study by Kratzer et al., concluded that TXA administered at clinically relevant concentrations increases the propagation of neuronal excitation in the basolateral nucleus of the amygdala. The observed enhancement of neuronal excitation arises from reduced synaptic inhibition rather than from increased neuronal excitability [10]. TXA impairs neuronal inhibition by a postsynaptic antagonism against $GABA_A$ receptors. In contrast, TXA does not affect the excitatory glutamatergic synaptic transmission. Because inhibitors of $GABA_A$ receptors are known to act in a proconvulsant manner, this mechanism of action may explain the increased incidence of seizures in patients treated with TXA [10]. This study elucidates a potential mechanism for the neuronal excitation and subsequent seizures that have been seen with TXA administration.

Given the sparsity of studies of maternal adverse effects with TXA, it should not be surprising that there are even fewer assessing the potential risks to the neonate. A recent study by Yee et al., found the effective concentration of TXA in neonatal plasma (*in vitro*) that inhibits fibrinolysis is far lower than the concentration needed in adults [11]. These two aforementioned studies speak for caution regarding neonatal exposure: there is a potential mechanism for seizures, and in addition the neonate may be more sensitive to low drug levels. These studies point to the need for further studies to be done asssessing the serum levels associated with neonatal seizures. As a result, this places even more importance on the timing of TXA administration. Until that information is obtained, it may be imperative to continue suggesting that the drug be held until the cord is clamped. Most of the RCTs that have been completed at this time have involved the administration of the TXA well before the cord is clamped. Neonatal exposure will occur when TXA is given before the cord is clamped, as TXA is known to cross the placenta [12].

However, the unknown potential neonatal effect on a predelivery administration of TXA could have more potential clarity given the results of a very recent study by Wesley et al., on the pharmacokinetics of TXA in neonatal cardiac surgery with cardiopulmonary bypass [13]. This study was the first population pharmacokinetic analysis of TXA in neonates and young infants undergoing cardiac surgery. The most

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

| 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) [16] | 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 5min | 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) [17] | 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 5min | 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) [18] | 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 5min | 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) [19] | 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 |

**Continuation of Table 1**

| Study [ref] | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Movafegh et al., 2011 [20] | 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., [22] | 262.5 ml vs 404.7 ml | <0.001 | No thromboembolic events |
| Xu et al., 2013 [21] | 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., [22] | 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 [22] | 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 Measurement of blood loss from the time of placental delivery to end of 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 [23] | Pakistan | Randomized, single center, double-blindedplacebo-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 |

**Continuation of Table 1**

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abdel-Al-eem et al., 2013 [24] | Egypt | Random-ized, 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 10min | Blood loss 2 hr 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 [25] | 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 re-ported | No thromboembolic side effects |

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.
CS: Cesarean Section; TXA: Tranexamic acid; IV: Intravenous; EBV: Estimated blood volume=the woman's weight (kg)x85

significant finding of their analysis was the need for different and generally reduced dosing regimens from those that are commonly used at this time. Additional findings include the importance of developmental changes during the first year of life leading to very different dosing requirements in newborns when compared with children over 12 months old. The dosing schedules found as a result of their study allow clinicians to target specific plasma concentrations in children of different ages. Their study also highlights that a single dose schedule used across all age ranges to achieve a desired plasma TXA concentration is unlikely to be effective [13].

Alternatively, a study by O. Gilad et al., evaluated the outcome 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 [14]. This study compared to the prior two mentioned studies highlight the lack of concrete evidence of adverse effects of TXA on the neonate.

## Conclusions

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 and considered safe for administration. 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 [15]. The results of this study should provide more evidence about the potential benefits of TXA to the mother.

## List of abbreviations

PPH: Primary Postpartum Hemorrhage
TXA: Tranexamic Acid
RCT: Randomized Controlled Trials
CRASH-2: Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2
TAFI: Thrombin-Activatable Fibrinolysis Inhibitor

## Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

| Authors' contributions | OV | SS | HG |
|---|---|---|---|
| Research concept and design | ✓ | ✓ | ✓ |
| Collection and/or assembly of data | ✓ | ✓ | ✓ |
| Data analysis and interpretation | ✓ | ✓ | ✓ |
| Writing the article | ✓ | -- | -- |
| Critical revision of the article | ✓ | -- | ✓ |
| Final approval of article | ✓ | ✓ | ✓ |

### Publication history

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