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Update for Nurse Anesthetists
5

Use of Tranexamic Acid in Preventing Postpartum Hemorrhage

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Postpartum hemorrhage (PPH) continues to be a serious complication in both developed and underdeveloped countries. It remains the leading cause of maternal mortality in underdeveloped countries. Implementation of the World Health Organization guidelines of PPH treatment has reduced mortality. In addition, the prophylactic administration of tranexamic acid with uterotonic agents may contribute to the reduction of PPH. This evidence-based literature review of tranexamic acid will examine its mechanism of action as well as its effectiveness in prevention of PPH and blood loss reduction in elective surgery, obstetrics, and trauma.

Keywords: Blood loss, cesarean delivery, postpartum hemorrhage, tranexamic acid, vaginal delivery.

Objectives

At the completion of this course, the reader should be able to:

1. Describe the antifibrinolytic effect of tranexamic acid.
2. Discuss the utility of tranexamic acid in the setting of postpartum hemorrhage.
3. Cite causes and risk factors of postpartum hemorrhage.
4. Discuss trials examining the effects of tranexamic acid in postpartum hemorrhage in women scheduled for spontaneous birth and cesarean delivery.

Introduction

•***Postpartum Hemorrhage.*** Postpartum hemorrhage (PPH) is a serious complication of labor and the leading cause of maternal mortality,[1] with an estimated incidence between 6% to 11% worldwide.[2,3] The published prevalence rates vary because of numerous methods of estimating blood loss and lack of a universal definition of PPH. Most deaths are preventable with timely administration of a uterotonic agent.[1] In recent years, the implementation of preventive initiatives outlined by the World Health Organization (WHO) has reduced the mortality rate; however, in underdeveloped countries, maternal mortality ratio is still higher than in industrialized countries (Figure 1).[4] Despite a low prevalence rate in developed countries such as the United States, PPH remains a major cause of maternal morbidity and mortality in this region.

The WHO defines *PPH* as a blood loss of 500 mL or more in the first 24 hours after delivery. A blood loss of 1,000 mL or more is considered a severe form of PPH. Other methods of clinical diagnosis are presence of rapid blood loss, a decrease in hematocrit level by 10%, changes in vital signs, and the need for emergent transfusion.[1] Conventionally, PPH is diagnosed if blood loss is in excess of 500 mL and 1,000 mL after spontaneous and cesarean delivery, respectively.

The most common cause of PPH is uterine atony, accounting for 70% in reported cases.[5] Other causes include placenta abruption, placenta previa, placenta accreta, retained placenta and clots, vaginal and cervical trauma, inherited or acquired coagulopathies, and uterine inversion. Maternal risk factors include induction of labor, prolonged labor, multiple births, polyhydramnios, and fetal macrosomia.[6] However, most women have few risk factors. Since placental expulsion is crucial in the prevention of PPH, mechanical and pharmacologic methods are instituted during the third stage of labor.[7] As part of the active management of the third stage of labor (AMTSL), the WHO issued a recommendation, which included

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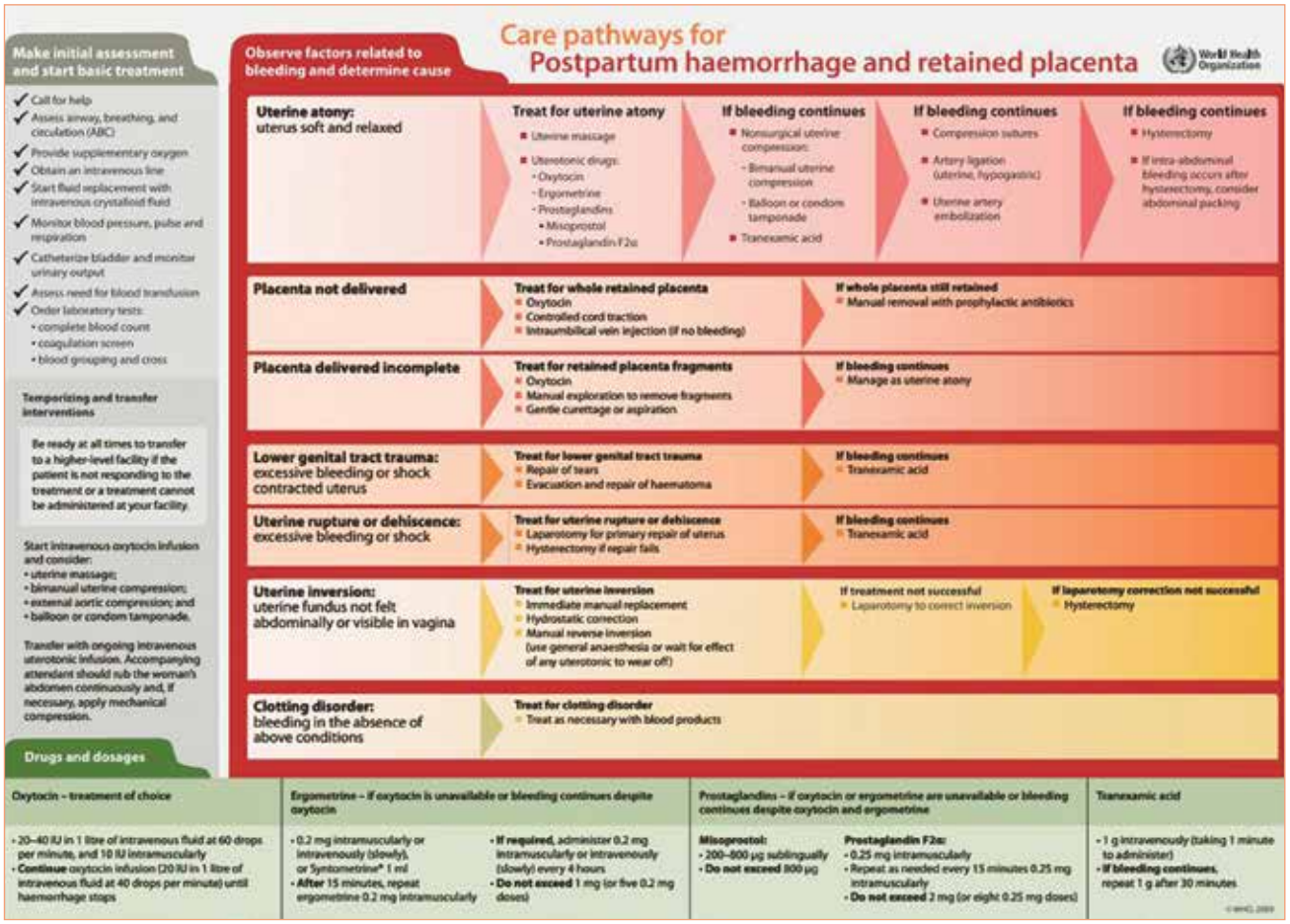

Figure 1. Care Pathways for Postpartum Hemorrhage and Retained Placenta
(Source: World Health Organization, 2009; http://apps.who.int/iris/bitstream/10665/44171/1/9789241598514_eng.pdf)

umbilical cord clamping and cutting, controlled cord contraction, and administration of uterotonic drugs.[1] Oxytocin is the recommended uterotonic drug of choice; however, other uterotonic agents can be used as alternatives if oxytocin is unavailable (Table 1).[8] Employing the preventive measures outlined in the AMTSL guideline decreases the risks of hemorrhage by 68%.[9]

The addition of prophylactic tranexamic acid (TXA), although not part of the prevention guideline proposed by the WHO, together with a prophylactic uterotonic drug, has been studied in various clinical trials in low-risk patients for the prevention of PPH.[10,11] A synthetic derivative of lysine, TXA blocks the lysine binding sites of plasminogen and thereby inhibits the conversion of plasminogen to plasmin.[10] During the third stage of labor, degradation of fibrinogen and fibrin occurs. The activation of the fibrinolytic system can last 6 to 10 hours post partum, which increases the risks of bleeding.[12] Adding TXA during the third stage of labor may contribute to the reduction of PPH.

Because maternal mortality is still high, effective prevention methods could significantly reduce death rates. In the past years, many trials examining TXA as a preventive drug in PPH have been completed. In a recent evidence-based review,[13] the authors reported that prophylactic intravenous administration of TXA significantly reduced postpartum blood loss. A similar conclusion was reported in a review published in 2009.[14] In obstetrics, TXA can be used in the management of menorrhagia and other obstetrics and gynecology–related hyperfibrinolysis. Menorrhagia is characterized by menstrual blood loss of more than 80 mL of blood per cycle.[15] In women with idiopathic menorrhagia, TXA has been shown to be superior to mefenamic acid or flurbiprofen (nonsteroidal anti-inflammatory drugs), etamsylate (hemostatic agent), or norethisterone (progestogen) at therapeutic doses.[16] In women with intrauterine contraceptive device–associated menorrhagia, TXA was superior to diclofenac sodium. In both types of menorrhagia, TXA administration significantly reduced bleeding compared with the placebo effect.[16] The utility of TXA in obstetric and gynecologic settings, its cost-effectiveness, and pharmacologic profile merit its use as a pharmacologic adjunct in preventing PPH.

- ***Mechanism of Action of Tranexamic Acid.*** Tranexamic acid is a synthetic lysine derivative that reversibly occupies the lysine-binding site of plasminogen to exert its

Generic name (brand name)	Drug class	Route	Dose	Side effects	Comments
Oxytocin (Pitocin)	Oxytocin	IV	20-40 U in 1 L of LR continuous IV	Tachycardia, hypotension, myocardial infarction	Administer slowly to avoid severe vasodilation
Methylergonovine (Methergine)	Ergot alkaloids	IM	0.2 mg	Nausea and vomiting, hypertension	Contraindicated: preeclampsia, hypertension, and CAD May be repeated 1 hour after last dose
Carboprost (Hemabate)	15-Methylprost-aglandin $F_2\alpha$	IM	0.25 mg	Pulmonary hypertension, bronchospasm	Contraindicated: pulmonary hypertension, reactive airway disease
Misoprostol (Cytotec)	Prostaglandin E_1	Rectal, sublingual	600-1,000 µg	Fever, chills	Off-label use

Table 1. Uterotonic Drugs Commonly Used in United States[8]
Abbreviations: CAD, coronary artery disease; IM, intramuscular; IV, intravenous; LR, lactated Ringer's solution.

antifibrinolytic effect. Subsequently, plasminogen-TXA complex prevents fibrinolysis by inhibiting the interaction of plasmin(ogen) and fibrin (Figures 2 and 3).[15] Inhibition of fibrin degradation can be monitored by thromboelastography and decreased blood D-dimer concentration. Furthermore, studies show that at therapeutic plasma concentrations of 5 to 10 mg/L, TXA has no effect on platelets, activated partial thromboplastin time, prothrombin time, or clotting factors. At plasma concentrations outside the therapeutic levels, TXA might prolong thrombin time. In addition, although plasminogen can still be transformed to plasmin by interacting with a plasminogen activator, presence of TXA inhibits both plasminogen and plasmin from breaking down fibrin.[15]

Tranexamic acid has a weight of 157 Da and is approximately 6 to 10 times more potent than ε-aminocaproic acid.[15,17] Tranexamic acid can be administered via oral, parenteral, and topical routes.[18] Although the drug crosses the blood-brain barrier and placenta, only 1% of the drug's serum concentration gets excreted through breast milk.[15,18] At therapeutic plasma concentrations of 5 to 10 mg/L, approximately 3% of TXA is bound to plasma protein.[16,19] Tranexamic acid is minimally metabolized and is mainly excreted unchanged by the kidneys.[15,16] Therefore, dose adjustment is indicated in renal impairment and is unnecessary in hepatic impairment. Contraindications for TXA administration include hypersensitivity to the drug or any of its components, acquired defective color vision, subarachnoid hemorrhage, active thromboembolic disease, intrinsic risk or history of thrombotic events, and concomitant use of hormonal contraception.[19]

Methods

Automatic and manual searches of major databases were the chief methods used to find evidence. Databases included PubMed, MEDLINE, *Cumulative Index to Nursing & Allied Health Literature*, and The Cochrane Library. The electronic search strategy included the following Medical Subject Headings (MeSH) and text terms: *tranexamic acid, postpartum, hemorrhage, blood loss,* and *blood transfusion* with the use of appropriate Boolean modifiers. The search was limited to full-text English-language articles. The reference lists of retrieved studies were evaluated for additional evidence. Evidence was confined to literature that met the following criteria: TXA, postpartum hemorrhage, blood loss, vaginal delivery, and cesarean delivery. The grading system proposed by Melnyk and Fineout-Overholt was used to appraise evidence.[20]

Of the 4 articles appraised in this review, 2 were systematic reviews with meta-analysis[10,11] and 2 were randomized controlled trials (RCTs).[21,22] The 2 systematic reviews are summarized in Table 2. The first systematic review[10] evaluated the efficacy and safety of intravenous TXA in preventing PPH for both vaginal and cesarean delivery. Twelve RCTs were analyzed.[23-34] Patients were at low risk of excessive bleeding and scheduled for a cesarean delivery or vaginal delivery. The authors reported an overall moderate risk of bias and moderate quality of evidence of all studies. The second systematic review[11] evaluated the use of prophylactic TXA and amount of blood loss during and after cesarean delivery. A total of 11 RCTs compared TXA with control.[23-25,28-31,34-37] Using the Jadad scoring system, the authors reported high-quality studies (Jadad score of 3 or better) except for 1 RCT[37] (Jadad score of 2) in the review.

The 2 RCTs are described in Table 2.[21,22] The primary outcomes of the RCTs included blood loss and hemoglobin levels before and 12 to 24 hours after delivery. No difference was noted in demographic characteristics between the treatment and control groups, and randomization techniques in each of the RCTs were described in detail. Authors of the 2 RCTs described blinding methods

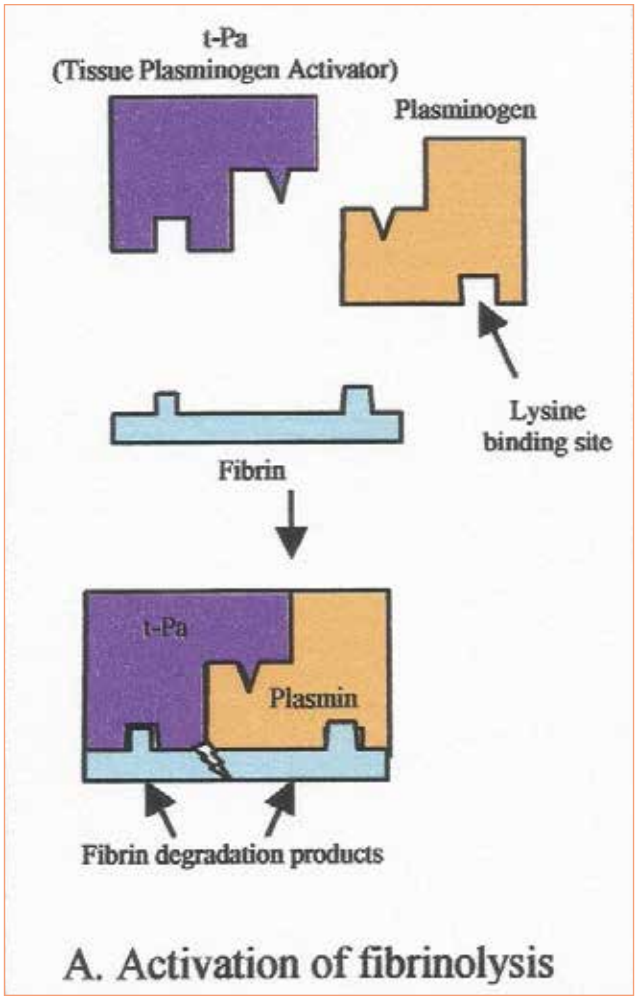

Figure 2. Activation of Fibrinolysis Showing Lysine Binding Site

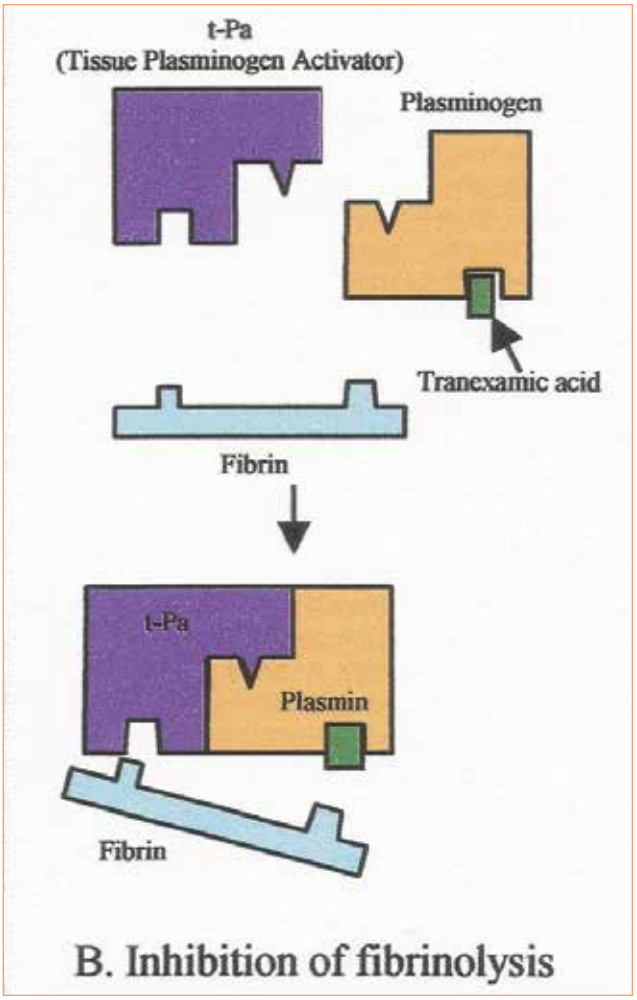

Figure 3. Plasminogen–Tranexamic Acid Complex Prevents Fibrinolysis by Inhibiting Interaction of Plasmin(ogen) and Fibrin

and conducted a power analysis to determine a sample size for outcomes measured. In these trials, TXA was administered after the delivery of the neonate or before spinal anesthesia. Oxytocin infusion was initiated after placental delivery. Cases reported in the 2 RCTs were vaginal delivery and cesarean delivery.

Results

This review examined the efficacy of TXA in preventing PPH for vaginal delivery and cesarean delivery, blood loss, and the need for blood transfusion; hemoglobin and hematocrit levels, and complications of TXA were also reviewed. In the first systematic review with meta-analysis, 9 RCTs evaluated TXA for cesarean delivery, and 3 RCTs evaluated TXA for vaginal delivery.[10] The second systematic review reviewed 11 RCTs.[11] Characteristics of the studies included in the 2 systematic reviews are described in (Tables 3 and 4).

The authors of the first systematic review postulated that blood loss would be significantly lower in women who received TXA vs placebo or no intervention. In this review, PPH was quantified as blood loss of greater than 400 mL or 500 mL, and greater than 1,000 mL. Eleven trials[23-33] adopted a standard method of blood loss calculation except 1 study,[34] which used preoperative and postoperative hematocrit values. The timing of blood collection was highly variable between studies. Pooled analysis of 4 of the studies included in this systematic review showed that TXA decreased the incidence of blood loss greater than 1,000 mL by 57% (relative risk [RR] = 0.43, CI = 0.23-0.78) in women undergoing a cesarean delivery. For women who had a vaginal delivery, the effect of TXA on blood loss of greater than 400 mL or 500 mL was more pronounced. Three TXA dosing regimens were used across all trials. Use of additional medical interventions such as the use of other uterotonic agents aside from oxytocin was reduced in women who received TXA. Blood transfusion was reduced by 76% in the TXA group, especially in women who had a cesarean delivery.

In the second systematic review,[11] 9 studies[23,24, 28-31, 34,35,37] showed a significant reduction in total blood

Evidence source, type of evidence and level[a]	Total No. of subjects	Type of delivery	Outcome	Comments
Novikova et al,[10] 2015 SR Level I	3,285 low-risk women Vaginal delivery = 832; cesarean delivery = 2,453	Vaginal (3 RCTs), cesarean (9 RCTs)	Blood loss > 400 mL or > 500 mL less in TXA group (RR = 0.52, 95% CI = 0.42 to 0.63), I^2 = 0%[b] and more evident in women having vaginal birth (RR = 0.42, 95% CI = 0.28 to 0.63), I^2 = 0% Blood loss > 1,000 mL less likely in TXA group (RR = 0.40, 95% CI = 0.23 to 0.71), I^2 = 0% Side effects[c] common in TXA group (RR = 2.48, 95% CI = 1.36 to 4.50), I^2 = 83% No significant difference in thromboembolic events in both groups	Rigorous methods Variable risks of bias of all studies Substantial amount of heterogeneity across 8 studies on side effects of TXA
Wang et al,[11] 2015 SR Level I	2,531 low-risk women TXA group = 1,276; controls = 1,255	Cesarean (11 RCTs)	Overall blood loss during and after cesarean delivery is lower in TXA group (P < .01), I^2 = 98% PPH rate lower in TXA group (RR = 0.57, 95% CI = 0.37 to 0.89), I^2 = 0%	Considerable heterogeneity was detected across 9 studies on total blood loss Indiscriminate blood collection periods Several means of calculating blood loss
Mirghafourvand et al,[21] 2015 RCT Level II	120 low-risk women	Vaginal	Blood loss from placental delivery to 2 hours post partum was lower in TXA group (P < .001) Blood loss > 1,000 mL was lower in TXA group (P = .048)	All women received oxytocin infusion after placental delivery Measurement of blood loss was from delivery of the fetus to placental expulsion and from placental expulsion to the end of the second hour after childbirth Blood loss calculated using the equation proposed in Gai et al[24]: Quantity of blood (mL) = (Weight of used materials – Weight of materials before use)/1.05
Sahhaf et al,[22] 2014 RCT Level II	200 low-risk women TXA group = 100; misoprostol group = 100	Vaginal and cesarean	Blood loss in TXA group was slightly higher than in misoprostol group (P = .79) Hemoglobin levels after 6-12 hours of labor was higher in TXA group than in misoprostol group (P = .22)	All women received oxytocin infusion after placental delivery No clear indication of the blood loss collection time and methods of measuring blood loss No distinction between quantity of blood loss from cesarean or vaginal delivery

Table 2. Summary of Evidence Sources Examining Use of Tranexamic Acid for Prevention of Postpartum Hemorrhage

Abbreviations: PPH, postpartum hemorrhage; RCT, randomized controlled trial; RR, risk ratio; SR, systematic review; TXA, tranexamic acid.

[a]From Melynk and Fineout-Overholt[20]: Level I, systematic reviews with or without a meta-analysis; Level II, well-designed randomized controlled trials; Level III, well-designed controlled trials without randomization; Level IV, well-designed case-control and cohort studies; Level V, systematic review of descriptive and qualitative studies; Level VI, single descriptive or qualitative study; Level VII, opinion of authorities and/or reports of expert committees.

[b]Authors of systematic review considered an I^2 of greater than 30% as high heterogeneity.

[c]Nausea, vomiting, headache, and skin reactions.

Evidence source	N (subjects per group)	Intervention and timing of administration	Time of blood collection and method of calculating blood loss	Primary/secondary end points	Outcomes
Abdel-Aleem et al,[23] 2013	740 (TXA = 373, control = 367)	TXA, 1 g IV 10 minutes before surgery All patients received oxytocin, 5-IU IV bolus and 20-IU IV infusion	From skin incision to 2 hours post partum Blood loss = (Weight of wet towel – Weight of dry towel) × 0.9 + Volume of blood in suction container	Mean blood loss measured during and 2 hours after operation Incidence of mild side effects, PPH, mean change in H&H, serious adverse events (thromboembolism), and admission to ICU	Mean total blood loss was 241.6 mL in TXA group vs 510 mL in control group (P = .0001) Drop in H&H lower in study group (P = .0001) Minor side effects (HA, nausea and vomiting) more in TXA group (P = .0001) No serious adverse events or admission to IC
Gai et al,[24] 2004	180 (TXA = 91, control = 89)	TXA, 1 g slow infusion 10 minutes before incision All patients received oxytocin, 10-U IV, and 20 U into intrauterine wall	From placental delivery to end of CD and until 2 hours post partum Blood loss = Weight of used materials + Unused materials – Weight of all materials before surgery)/1:05 + Volume in suction container after placental delivery	Blood loss and incidence of PPH (blood loss > 400 mL)	Reduced blood loss from the end of CD to 2 hours post partum (P = .001) and from placental delivery to 2 hours post partum (P = .002)
Goswami et al,[25] 2013	90[a] (TXA1 = 30, TXA2 = 30, control = 30)	TXA1: TXA, 10 mg/kg IV 20 minutes before surgical incision TXA2: TXA, 15 mg/kg, IV 20 minutes before surgical incision All patients received oxytocin, 20-U infusion	Intraoperatively and up to 24 hours postoperatively Blood loss = (Weight of the abdominal swabs and drapes after CD – Weight of materials before CD) + Volume in suction bottle after placental delivery	Blood loss and incidence of PPH	Mean blood loss lower in study groups compared with control Intraoperative blood loss lower in TXA groups (P = .0001) Postoperative blood loss was insignificant in all 3 groups No incidence of PPH
Movafegh et al,[28] 2011	100 (TXA = 50, control = 50)	TXA, 10 mg/kg 20 minutes before induction of spinal anesthesia All patients received oxytocin, 10-U infusion and 30 U during first 8 hours postoperatively	Intraoperatively and 2 hours after delivery Blood loss = Weight of used materials + Unused materials – Weight of all materials before surgery)/1:05 + Volume in suction container after placental delivery	Blood loss, postoperative hemorrhage 2 hours after surgery, and oxytocin administration	Quantity of blood loss was lesser in study group for intraoperative and postoperative (P < .001) Oxytocin administration less in TXA group (P = .001).
Sentürk et al,[29] 2013	223 (TXA = 101, control = 122)	TXA, 1 g IV 10 minutes before spinal anesthesia All patients received oxytocin, 20-IU bolus	Skin incision to entrance of uterine cavity and uterine repair to skin closure Blood loss = Wet weight of the patient's pad or tampon – Dry weight of the pad or tampon/1.05	Blood loss and H&H levels	Intraoperative and postoperative blood loss lower in study group (P < .01) Large decrease in H&H in control group

Shahid & Khan,[30] 2013	74 (TXA = 38, control = 36)	TXA, 1 g IV 10 minutes before skin incision All patients received oxytocin, 5-IU IV bolus; methylergometrine, 0.4 mg; and oxytocin, 30 IU over 6 hours	From the time of placental delivery to end of CD and from the end of CD to 2 hours post partum Blood loss = Weight of the used materials in both the periods subtracted weight of the materials before surgery + Volume of blood in suction canister. Pads used in CD and 2 hours post partum weighed separately.	Blood loss and H&H levels	Reduced blood loss from placental delivery to the end of CD ($P < .001$) and from the end of CD to 2 hours post partum in study group ($P = .188$) H&H much lower in placebo group ($P < .0001$)
Xu et al,[31] 2013	174 (TXA = 88, control = 86)	TXA, 10 mg/kg 20 minutes before spinal anesthesia All patients received oxytocin, 10-U infusion, and methylergometrine, 0.4 mg	From placental delivery to the end of CD and from the end of CD to 2 hours post partum Blood loss = (Weight of used materials + Unused materials – Weight of all materials before surgery)/1.05 + Volume included in suction container after placental delivery	Blood loss and incidence of PPH	Blood loss at the end of CD and 2 hours post partum was significantly lower in study group ($P < .01$) Quantity of total blood from placental delivery to 2 hours post partum was reduced in study group ($P = .02$) Number of PPH cases is lower in study group ($P < .01$)
Yehia et al,[33] 2014	212 (TXA = 106, control = 106)	TXA, 1 g with induction of anesthesia All patients received oxytocin, 10 IU IV	After delivery of the placenta to end of CD Blood loss = Estimates of soaked towels and amount of blood in suction bottle	Blood loss during CD after delivery of placenta, H&H values, and incidence of PPH	H&H 24 hours post partum higher in study group Total blood loss from placental delivery to end of CD was less in study group Incidence of PPH was significantly less in study group
Gungorduk et al,[34] 2011	660 (TXA = 330, control = 330)	TXA, 1 g IV 10 minutes before skin incision All patients received oxytocin, 5-IU IV bolus and 30-IU infusion	Before CD and 48 hours after surgery EBV × (Preoperative hematocrit – 48-Hour postpartum hematocrit)/ Preoperative hematocrit, where EBV (mL) = Woman's weight (kg) × 85	Blood loss after CD, PPH, and additional uterotonic drugs	Mean blood loss lower in women treated with TXA ($P < .001$) Women in TXA group who had an estimated blood loss > 1,000 mL was lower than the placebo group; RR = 2.7; 95% CI = 1.1 to 6.3 ($P < .03$) Women in placebo group required additional uterotonic agents; RR = 1.7; 95% CI = 1.1 to 2.6, ($P = .02$)
Gohel et al,[35] 2007	100 (TXA = 50, control = 50)	TXA, 1 g 20 minutes before skin incision All patients received oxytocin, 10-U infusion, and methylergometrine, 0.4 mg	From placental delivery to the end of the surgery, and from the end of the operation to 2 hours after birth Blood loss = (Weight of the used materials in both the periods – Weight of the materials before the surgery) + Volume sucked in the suction bottle after placental delivery + Pads used after CD to 2 hours post partum	Amount of blood loss from end of CD to 2 hours post partum and from the delivery of placenta to 2 hours post partum	Reduced amount of blood loss from the end of CD to 2 hours post partum in TXA group ($P = .001$) Significant reduction in amount of blood loss from placental delivery to 2 hours post partum ($P = .003$)

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Evidence source	N (subjects per group)	Intervention and timing of administration	Time of blood collection and method of calculating blood loss	Primary/secondary end points	Outcomes
Sekhavat et al,[36] 2009	90 (TXA = 45, control 45)	TXA immediately before surgery	From the end of CD to 2 hours post partum Blood loss = (Weight of used materials – Weight of materials before use)/1.05	Blood loss and H&H	Significant reduction in the amount of blood loss from the end of CD to 2 hours post partum (P = .000) Hemoglobin level 24 hours after CD higher in study group (P = .002)
Halder et al,[37] 2013	100 (TXA = 50, control = 50)	TXA immediately before surgery	From placental delivery to end of CD, and from the end of CD to 2 days post partum Blood loss = (Weight of used materials in both the periods – Weight of the materials before CD) + Volume in suction container after placental delivery + Pads used from the end of CD to 2 hours post partum	Blood loss and hemoglobin level	Reduced blood loss from placental delivery to 2 days post partum: 990 mL in study group vs 1,004 mL in control group Drop in hemoglobin level was significantly less in study group (P < .0001)

Table 3. Summary of Randomized Controlled Trials Examining Tranexamic Acid for Cesarean Delivery Included in Systematic Reviews With Meta-Analysis[10,11]

Abbreviations: CD, cesarean delivery; H&H, hemoglobin and hematocrit; ICU, intensive care unit; IV, intravenous; PPH, postpartum hemorrhage; RR, relative risk; TXA, tranexamic acid.
[a]Women with hemoglobin concentrations of 7 to 10 g were included.

loss with the use of TXA compared with control. Similarly, calculation of the quantity of blood loss and blood collection period varied between all trials. In this review, doses were 1 g, 10 mg/kg, and 15 mg/kg. The authors of the systematic review reported a significant reduction of blood loss when 1 g of TXA was used compared with a dose of 10 mg/kg. A decrease in hemoglobin level was reported; however, the reduction was lower in the TXA group compared with control regardless of TXA dose. In this meta-analysis, blood transfusion was reduced by 77%.

In 1 RCT, TXA was compared with misoprostol in 200 women scheduled for vaginal delivery or cesarean delivery.[22] Either drug was superior in reducing blood loss. Hemoglobin levels 6 to 12 hours after labor were greater in the TXA group compared with the misoprostol group. The other RCT compared TXA with placebo in women with a low risk of PPH who were scheduled for vaginal delivery.[21] In this trial, blood loss of greater than 1,000 mL was lower in the study group.

All 4 articles reported minor side effects of TXA. This included nausea, vomiting, headache, and skin irritation. These side effects were more pronounced in women who received TXA. Thromboembolic events were rare. One study reported 2 episodes of deep vein thrombosis both in the study and control group.[31]

Discussion

The current evidence indicates that prophylactic TXA in the third stage of labor is a promising method for preventing PPH. Adding TXA in the active management of third-stage labor reduces the incidence of PPH, the amount of blood loss, and the need for blood transfusion after vaginal delivery and cesarean delivery. To meet the Millennium Development Goals, the WHO developed guidelines to reduce the maternal mortality ratio by 5.5% each year.[38] This can be achieved by adopting guidelines for preventing and treating PPH. In 2012, a new and revised guideline was adopted. For the prevention of PPH, the guidelines include the use of uterotonic drug (oxytocin is the first choice), application of controlled cord traction, and delayed clamping of the cord (1 to 3 minutes) after birth. Although TXA is recommended in the treatment of PPH, use of TXA in the prevention of PPH is not outlined in the WHO Guidelines. However, most trials have indicated that prophylactic TXA significantly reduces the number of PPH incidents when given with a uterotonic agent.

The findings of this review agree with those of other recent systematic reviews on the use of TXA and reduction of blood loss. The efficacy of TXA in preventing perioperative blood loss has been shown

Evidence source	N (subjects per group)	Intervention and timing of administration	Time of blood collection and method of calculating blood loss	Primary/secondary end points	Outcomes
Gungorduk et al, 2013[26]	454 (TXA = 228, control = 226)	Initiated TXA infusion at presentation of anterior aspect of shoulder Routine AMTSL protocol[a] was used in both groups	From end of delivery to 2 hours post partum Blood loss (mL) = (Weight of used materials – Weight of materials before use)/1.05	Mean blood loss during the third and fourth stages of labor Incidence of PPH	Mean estimated blood loss was significantly lower in TXA group ($P <$ .001) PPH > 500 mL was lower in TXA group (RR = 3.76, 95% CI = 1.27 to 11.15; P = .01)
Mirghafourvand et al, 2013[27]	120 (TXA = 60, control = 60)	TXA, 1 g after presentation of anterior aspect of shoulder All women received oxytocin after placental expulsion	Measurement of blood loss was from delivery of the fetus to placental expulsion and from placental expulsion to the end of the second hour after childbirth Quantity of blood (mL) = (Weight of used materials – Weight of materials before use)/1.05	H&H levels	Mean hemoglobin loss was lower in experimental group (P = .11) Mean hematocrit loss was lower in intervention group (P = .03)
Yang et al, 2001[32]	400 (group I = 94, group II = 92, group III = 92, group IV = 87)	Group I: TXA (Transamin), 1.0 g injected IV Group II: TXA (Transamin), 0.5 g IV Group III: aminomethylbenzoic acid, 0.5 g IV Group IV: no treatment All women received oxytocin after shoulder presentation	Vaginal blood was precisely collected and examined immediately after the expulsion of placenta and from placental expulsion until 2 hours after delivery Amount of blood loss was measured by both methods of weight and volume	Blood loss Incidence of PPH	No differences in blood loss immediately after the expulsion of placenta among the 4 groups ($P >$ .05) Average blood loss of groups I and II was significantly less than in groups III and IV ($P <$ .01); however, there was no significant difference between group I and group II ($P >$ .05) Occurrences of postpartum hemorrhage (blood loss ≥ 400 mL) were 6.4%, 13.3%, 20.7%, and 25.3% for group I, II, III, and IV, respectively

Table 4. Summary of Randomized Controlled Trials Examining Tranexamic Acid for Vaginal Delivery Included in Systematic Review With Meta-Analysis

Abbreviations: AMTSL, active management of the third stage of labor; H&H, hemoglobin and hematocrit; PPH, postpartum hemorrhage; RR, relative risk; TXA, tranexamic acid.

[a]Protocol includes prophylactic injection of 10 IU of oxytocin within 2 minutes of birth, early clamping of the umbilical cord, and controlled cord traction following delivery.

in other clinical studies. A systematic review of 211 RCTs (n = 20,781) in patients undergoing elective surgery (cardiac, orthopedic, hepatic, urologic, and vascular cases) reported that the use of TXA reduced blood transfusion by 39% (RR = 0.61, 95% CI = 0.54-0.69).[39] Another systematic review of 129 RCTs (n = 10,488) also reported a decrease in transfusion rate by 38% (RR = 0.62; 95% CI = 0.58-0.65).[40]

Because hemorrhage is the leading cause of death in patients who sustain trauma, prompt treatment should be initiated immediately.[41] The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2), a large randomized placebo-controlled trial, among trauma patients with, or at risk of, severe hemorrhage, evaluated the effects of TXA administration on death and transfusion requirements. Adult trauma patients (n = 20,211) within 8 hours of injury, in which the physician was uncertain of whether to treat with TXA, were allocated into the TXA group (n = 10,096) and placebo group (n = 10,115).[42] A loading dose of 1 g over 10 minutes, then infusion of 1 g over 8 hours of TXA or matching placebo was administered to the participants. Data on the effects of TXA on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients were collected within 4 weeks of injury. The trial resulted in a reduction in all-cause mortality from 16% to 14.5% in the TXA group and reduced risk of death due to bleeding (n = 489 [4.9%] vs n = 574 [5.7%]).[42] Although TXA did not significantly reduce the amount of blood transfused, it should be considered for use in trauma patients who are bleeding.[42] As a result of the CRASH-2 trial, the WHO added TXA injection for the treatment of adult patients with trauma and significant risk of ongoing hemorrhage to the Selection and Use of Essential Medicines guideline as of March 2011.[43]

Additionally, TXA is used as a part of resuscitation for combat injury in the military. Another retrospective observational study of 896 injured soldiers, which required transfusion of at least 1 U of packed red blood cells, confirmed the benefit of TXA use. Mortality rate in the TXA group (n = 293) was lower compared with the control group (17.4% vs 23.9%; *P* = .03).[44] In addition to lower mortality, less coagulopathy was observed in the TXA group. The study also analyzed occurrence of deep vein thrombosis and pulmonary embolism in all patients. Although the nature of a combat injury itself initiates the cascade of abnormal coagulation, it is plausible that TXA may result in thrombotic events.[44] Despite that, treatment with TXA should be initiated in combat injury and severe hemorrhage.

Another prospective cohort study suggested outcome benefits in the severely injured civilian group. Although TXA was not associated with any changes in outcome overall or in the group without shock, multiple organ failure and mortality rates (odds ratio = 0.27, CI = 0.10-0.73, *P* = .01; odds ratio = 0.16 CI = 0.03-0.86, *P* = .03 respectively) were reduced in the patient cohort with shock.[45]

On the other hand, the American Association for the Surgery of Trauma concluded that further studies are required to outline who will benefit and who might be harmed by administration of TXA. Although correction of hyperfibrinolysis was achieved in 94% of patients (total participants, 1,032; TXA cohort, 94; control group, 934), this correction did not transform into a reduction in mortality.[46]

In this literature review, 12 RCTs for cesarean delivery and 4 RCTs for vaginal delivery reported a reduction in blood loss and PPH incidence. However, the available evidence is of insufficient quality to reach a conclusive statement. In all the studies, the study population was composed of women with a low risk of PPH. A recent well-designed trial of TXA after vaginal delivery examined the efficacy of treating PPH in selected patients with blood loss greater than 800 mL.[47] To date, this is one study that chose high-risk patients.

There is substantial heterogeneity reported in both SRs. In part, the heterogeneity across the trials is due to a variety of definitions of PPH. The WHO defines *PPH* as either blood loss of greater than 500 mL or greater than 1,000 mL in the severe form. In some studies, PPH was considered if blood loss was greater than 400 mL. Other causes of heterogeneity of the studies are the different methods of calculating blood loss and the timing of blood loss collection. Both of these factors vary across all studies.

Minor complications were common and transient in women given TXA. Most of these complications were gastrointestinal signs and symptoms. Major complications such as maternal death, seizure, and thromboembolic events were rare. These results were similar to those of other clinical trials involving TXA.

Although these are promising data, they are insufficient to determine their efficacy to women and their infants. Large, highly powered, multicenter RCTs are needed to examine PPH in both low- and high-risk patients.

Conclusion

The evidence shows that TXA can effectively reduce blood loss in patients undergoing elective surgery and in obstetric and trauma populations. World Health Organization guidelines recommend administration of TXA in treatment of PPH and trauma. The adoption of WHO guidelines for using uterotonic agents and prophylactically administering TXA may significantly reduce the number of PPH incidents. Although the findings of systematic reviews and RCTs analyzed in this evidence-based review reflect the benefits of TXA administration in PPH, more studies are required to assess the effectiveness of administering TXA prophylactically.

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