WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage

31 October 2017

Recommendation

Early use of intravenous tranexamic acid (within 3 hours of birth) in addition to standard care is recommended for women with clinically diagnosed postpartum haemorrhage following vaginal birth or caesarean section.

(Strong recommendation, moderate quality of evidence)

Publication history

First published: September 2012

Updated: October 2017

Assessed as up-to-date: October 2017

Remarks

- Based on the dosing regimen used in the WOMAN trial, the GDG supports the administration of tranexamic acid (TXA) at a fixed dose of 1 g (100mg/ml) intravenously (IV) at 1 ml per minute (i.e. administered over 10 minutes), with a second dose of 1g IV if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose.
- The WOMAN Trial defined “clinically diagnosed postpartum haemorrhage” as clinically estimated blood loss of more than 500 mL after a vaginal birth or 1000 mL after caesarean section, or any blood loss sufficient to compromise haemodynamic stability.
- Based on evidence from the WOMAN trial, the reference point for the start of the 3-hour window for starting TXA administration is time of birth. If time of birth is unknown, the best estimate of time of birth should be used as the reference point. As most deaths due to postpartum haemorrhage occur within the first 2 to 3 hours after birth, it is critical that TXA is given as soon as possible to achieve clinical benefits.
- Analysis of the effects of timing of administration in the WOMAN trial, as well as an individual participant data (IPD) meta-analysis of 40,138 bleeding patients (including WOMAN trial participants), indicates that TXA administration beyond 3 hours does not confer any clinical benefit. Furthermore, the point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, the GDG does not support the use of TXA more than 3 hours after birth.
Administration of TXA should be considered as part of the standard postpartum haemorrhage treatment package. Standard care in the context of this recommendation includes routine care for PPH treatment, including fluid replacement, medical (uterotonics), monitoring of vital signs, non-surgical (e.g. bimanual compression, intrauterine balloon tamponade, non-pneumatic anti-shock garment, aortic compression) and surgical interventions (e.g. brace sutures, arterial ligation, or hysterectomy) in accordance with WHO guidelines or adapted local PPH treatment protocols.

TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma, or other causes.

The use of TXA should be avoided in women with a clear contraindication to antifibrinolytic therapy (including TXA) (eg: a known thromboembolic event during pregnancy)

This recommendation applies only to intravenous use. The evaluation of benefits and potential harms of other routes of TXA administration is a research priority.

Regardless of the level of health system resources, TXA should be recognised as a life-saving intervention and be made readily available for the management of postpartum haemorrhage in settings where emergency obstetric care is provided.

This updated recommendation supersedes the previous recommendation on tranexamic acid for PPH treatment, issued in the 2012 WHO recommendations on prevention and treatment of PPH.

Background

Postpartum haemorrhage (PPH) is defined as blood loss of 500ml or more within 24 hours after birth. PPH is the primary cause of nearly one-fifth of all maternal deaths globally. Most of these deaths occur during the first 24 hours after birth. The majority could be prevented through the use of prophylactic uterotonics during the third stage of labour, and by timely and appropriate management.

Tranexamic acid is a competitive inhibitor of plasminogen activation, and it can reduce bleeding by inhibiting the enzymatic breakdown of fibrinogen and fibrin clots. It is in routine clinical use for reduction of blood loss in surgery and trauma, and is listed on the WHO Essential Medicines List for management of anticoagulation.

In 2017, the Executive Guideline Steering Group on WHO maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendation on the use of tranexamic acid for PPH treatment, in response to important new evidence on this intervention.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach. Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of postpartum haemorrhage (2012). A further two outcomes were identified by the WHO Steering Group and the GDG as critical for this question, namely maternal death (all causes) and maternal death due to bleeding.

A Cochrane systematic review on the efficacy of antifibrinolytics for postpartum haemorrhage treatment was conducted. Randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting in August 2017. This group of independent experts used the evidence profiles to assess evidence on effects on the pre-specified outcomes.
GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to finalize the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Further information on procedures for updating this recommendation are available here.

**Recommendation question**

For this recommendation, we aimed to answer the following questions:

- For women with postpartum haemorrhage, does administration of tranexamic acid in addition to standard care compared to standard care alone improve outcomes?
- If so, when is the most appropriate period to administer tranexamic acid to improve outcomes?

**Evidence Summary**

Evidence on the use of TXA for treatment of PPH was extracted from a forthcoming Cochrane systematic review of two trials (20 212 women). This review included trials that compared the use of any fibrinolytic drug with no treatment in women with PPH. However, no evidence was identified for interventions other than TXA.

One multicentre trial was conducted in eight obstetric units in France with recruitment between 2005 and 2008. This trial randomized 152 women with PPH > 800 ml after a vaginal birth. The intervention group received a loading dose of 4 g TXA mixed with 50 ml saline, administered IV over 1 hour, followed by a maintenance dose of 1 g/hour for 6 hours. Women in the control group were given standard care only, as per the routine practice in participating facilities. The primary outcome was blood loss between randomization and 6 hours.

The second (WOMAN trial) was a multicountry, multicentre, placebo-controlled randomised trial of 20 060 women in 193 hospitals, across 21 high-, middle- and low-income countries conducted between March 2010 and April 2016. The trial randomized women with clinically diagnosed PPH, defined as clinically estimated blood loss after a vaginal birth of > 500 ml, or > 1000 ml following a caesarean section, or any blood loss sufficient to compromise haemodynamic stability and where the clinician responsible for care was uncertain as to whether or not to use TXA. In addition to usual care, women in the experimental group were initially given 1 g TXA IV in a 10 ml solution, at an approximate rate of 1 ml/minute, as soon as possible after randomization. A second dose was used if bleeding continued after 30 minutes or if it stopped and restarted within 24 hours after the first dose. The control arm received placebo (normal saline) using the same regimen. When the trial protocol was registered, the primary outcome was a composite of death from all causes or hysterectomy within 42 days. During the course of the study (but before results were available or any unblinding), the primary outcome was revised to maternal death due to bleeding, and the sample size increased.

Evidence regarding this intervention is almost entirely derived from the WOMAN trial.

*Comparison: TXA (in addition to standard care) versus standard care alone*

The effects of TXA on critical outcomes for all women with PPH, regardless of how PPH was defined, the mode of birth or timing of PPH administration, are described below.
Maternal mortality (all causes): Moderate certainty evidence suggests slightly fewer deaths in the group receiving TXA although this difference was not statistically significant (two studies, 20 172 women; 227/10 113 (2.2%) vs 256/10 059 (2.5%); RR 0.88, 95% CI 0.74 to 1.05).

Maternal mortality due to PPH: In both trials, clinicians were asked to record the primary cause of death. Moderate certainty evidence suggests that deaths that were considered to be due to bleeding were probably reduced in the TXA group (two studies, 20 172 women, 155/10 113 (1.5%) vs 191/10 059 (1.9%), RR 0.81, 95% CI 0.65 to 1.00). The number needed to treat (NNT) to prevent one maternal death due to bleeding is 258 (95% CI 133.2 to 4051.8).

Severe maternal morbidity: The French trial reported multiple organ failure; there were no events in either arm and very few admissions to intensive care (one study, 152 women, 3/77 (3.9%) vs 5/74 (6.8%), RR 0.58 (95% CI 0.14 to 2.33). The number of women suffering any severe morbidity was not reported in the WOMAN trial report, but specific morbidities were reported. Moderate certainty evidence suggested little or no difference between groups for any of morbidity outcomes reported (respiratory failure: RR 0.87, 95% CI 0.67 to 1.12; seizure: two studies; RR 0.76, 95% CI 0.49 to 1.20; hepatic failure RR 0.96, 95% CI 0.58 to 1.60; cardiac failure: RR 0.95, 95% CI 0.73 to 1.23; renal failure: two studies; RR 0.85 to 1.39).

Blood products transfusion (all): Moderate certainty evidence suggests there is very little or no difference between groups for transfusion of blood products, with more than half of the women in both arms of the WOMAN trial receiving a transfusion (two studies; RR 1.00, 95% CI 0.97 to 1.03).

Additional blood loss: The French trial reported additional blood loss > 500 ml or > 1000 ml. Low-quality evidence suggests TXA probably reduces blood loss > 500 ml (RR 0.50, 95% CI 0.27 to 0.93, 151 women). Although the direction of effect was the same for loss > 1000 ml, the study had insufficient power to demonstrate a difference between groups (4/77 women versus 8/74).

Additional uterotonic: The vast majority of women in the WOMAN trial received uterotonic (99.3% vs 99.1%, two studies; RR 1.00, 95% CI 1.0 to 1.0).

Surgical interventions: High or moderate certainty evidence suggests there is probably little difference between groups for most surgical interventions to control bleeding (hysterectomy (all): two studies; RR 1.01, 95% CI 0.88 to 1.17; ligature: RR 0.88, 95% CI 0.74 to 1.05; embolization: RR 0.82, 95% CI 0.42 to 1.62). High certainty evidence suggests laparotomy to control bleeding is reduced for women in the TXA group (0.8% vs 1.3%) (RR 0.64, 95% CI 0.49 to 0.85) while brace sutures are increased (RR 1.19, 95% CI 1.01 to 1.41).

Invasive nonsurgical interventions: High certainty evidence suggests there is probably little or no difference in intrauterine tamponade (one study; RR 0.96, 95% CI 0.87 to 1.06) or manual removal of placenta: (one study; RR 0.95, 95% CI 0.87 to 1.04).

Procedure-related complications: Moderate certainty evidence suggests there is probably little or no difference between groups for thromboembolic events (any maternal thromboembolic event: RR 0.88, 95% CI 0.54 to 1.43; deep venous thrombosis: two studies; RR 0.62 95% CI 0.20 to 1.88; pulmonary embolism RR 0.85, 95% CI 0.44 to 1.61; myocardial infarction: RR 0.66, 95% CI 0.11 to 3.97; stroke: RR 1.33, 95% CI 0.46 to 3.82).

Neonatal adverse effects: Available neonatal outcome data were limited (data from WOMAN trial only). There were no neonatal thromboembolic events and no clear differences in deaths in breastfed neonates (eight deaths with TXA vs seven deaths with placebo) in the WOMAN trial.

Longer-term outcomes: Available data on longer-term outcomes was limited (data from the WOMAN trial only). Outcomes in the WOMAN trial were measured up to hospital discharge or 42 days if still in hospital. There was no information on longer-term outcomes in women or babies.

Subgroup analysis examining treatment effect by mode of birth (vaginal or caesarean) suggests no clear difference in effect on maternal death (all causes) and maternal death due to PPH for type of birth (moderate certainty of evidence).
Comparison: TXA (in addition to standard care) versus standard care alone, by timing of TXA administration

Evidence for this subgroup comparison was derived from a pre-planned subgroup analysis of the WOMAN trial.

- **Maternal mortality due to PPH:** There are subgroup differences for the timing of drug administration. Women receiving TXA less than 1 hour after birth had reduced risk of death from bleeding, but the confidence interval crossed the line of no effect (less than 1 hour: RR 0.80, 95% CI 0.55 to 1.16). Women receiving TXA 1 to 3 hours after birth were at reduced risk of death from bleeding (1 to 3 hours: RR 0.60, 95% CI 0.41 to 0.88) compared with women where more than 3 hours had elapsed before TXA was administered (more than 3 hours: RR 1.07, 95% CI 0.76 to 1.51).

- **Maternal mortality (all cause):** Compared to the control group, women receiving TXA less than 1 hour after birth had similar risks of death (any cause) (less than 1 hour: RR 0.98, 95% CI 0.72 to 1.33), as did women receiving TXA more than 3 hours after birth (more than 3 hours: RR 1.00, 95% CI 0.75 to 1.33). However, women receiving TXA 1 to 3 hours after birth were at reduced risk of death from all causes (1 to 3 hours: RR 0.69, 95% CI 0.49 to 0.96).

- **Death or hysterectomy:** Compared to the control group, women receiving TXA less than 1 hour after birth had similar risks of death or hysterectomy (less than 1 hour: RR 1.08, 95% CI 0.91 to 1.28), as did women receiving TXA more than 3 hours after birth (more than 3 hours: RR 1.01, 95% CI 0.82 to 1.25). However, women receiving TXA 1 to 3 hours after birth were at reduced risk of death or hysterectomy (1 to 3 hours: RR 0.80, 95% CI 0.63 to 1.00).

- **Laparotomy for bleeding:** Compared to the control group, women receiving TXA less than 1 hour after birth had reduced risk of laparotomy for bleeding (less than 1 hour: RR 0.48, 95% CI 0.29 to 0.79), as did women receiving TXA at 1 to 3 hours after birth (1 to 3 hours: RR 0.54, 95% CI 0.31 to 0.95). Women receiving TXA more than 3 hours after birth were not at reduced risk of laparotomy for bleeding (more than 3 hours: RR 0.89, 95% CI 0.59 to 1.35).

Further information on evidence supporting this recommendation are available here.

Implementation considerations

- TXA should be included as part of standard package for PPH treatment. It should therefore be available in the labour room of facilities providing emergency obstetric care, at all times.
- Due consideration should be given to any specific manufacturer’s instructions on precautions and contraindications. TXA for injection may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and dextran solutions. TXA should not be mixed with blood for transfusion, solutions containing penicillin or mannitol.
- TXA should be administered as a bolus IV injection over 10 minutes, as there is a potential risk of transient lowering of blood pressure. It can be administered via the same IV cannula used for IV hydration or uterotonic administration.
- An enabling environment should be created for the use of TXA (for example, by widening its availability), in order to support changes in the behaviour of health care practitioners to enable the use of evidence-based practice. This includes technical support for local guideline implementers in the development of training manuals, flow charts and quality indicators as well as participation in stakeholders meetings. Local professional societies play important roles in this process and an inclusive and participatory process should be encouraged.
- Health facilities where emergency obstetric care is provided need to have the necessary supplies and equipment, as well as the necessary training for staff attending births, so that tranexamic acid can be administered safely by intravenous infusion. The shelf life of TXA is generally three years, and can be stored at room temperature (15 – 30 degrees Celsius) however opened product should be used...
immediately. However, the manufacturer’s instructions on storage and use should always be given precedence.

- The recommendation should be adapted into locally-appropriate guidelines and protocols that are able to meet the specific needs of each country and health service. Modifications to the recommendation should be justified in an explicit and transparent manner.

Research implications

The GDG identified that further research on the use of tranexamic acid for postpartum haemorrhage is a priority:

- What are the effects of tranexamic acid by other routes of administration (eg: oral, intramuscular, topical, buccal) when used for postpartum haemorrhage treatment?
- What is the cost-effectiveness of tranexamic acid when used for postpartum haemorrhage treatment?
- What is the optimal dosing regimen of tranexamic acid for postpartum haemorrhage treatment?
- What are the longer term effects (on women and breastfed newborns) of tranexamic acid when used for postpartum haemorrhage treatment?
- What are the effects of oral or intravenous tranexamic acid when used for postpartum haemorrhage prevention?

Related Links

WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage (2017) - full document and evidence tables

Highlights and key messages from World Health Organization’s 2017 global recommendations


Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

References


Citation