Updated WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Haemorrhage

Highlights and Key Messages from the World Health Organization's 2017 Global Recommendation

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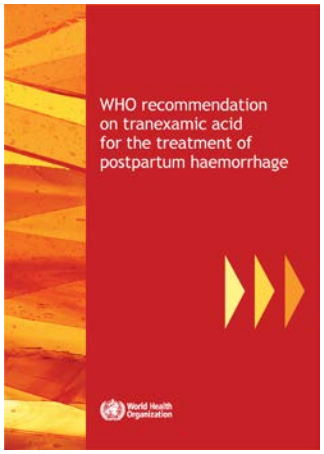
Key Messages

- The World Health Organization (WHO) recommends early use of intravenous tranexamic acid (TXA) within 3 hours of birth in addition to standard care for women with clinically diagnosed postpartum haemorrhage (PPH) following vaginal birth or caesarean section.
- Administration of TXA should be considered as part of the standard PPH treatment package and be administered as soon as possible after onset of bleeding and within 3 hours of birth. TXA for PPH treatment should not be initiated more than 3 hours after birth.
- TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.
- TXA should be administered at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes.
- TXA should be administered via an IV route only for treatment of PPH. Research on other routes of TXA administration is a priority.

Background



Globally, nearly one-quarter of all maternal deaths are associated with PPH, and, in most low-income countries, PPH is the main cause of maternal mortality. The majority of PPH-associated deaths could be avoided by the use of prophylactic uterotonics during the third stage of labour and timely, appropriate management of PPH. Efforts to prevent and reduce maternal morbidity and mortality due to PPH can reduce the profound global inequities in maternal health outcomes. Health workers, managers, and policymakers need clear, up-to-date, evidence-based recommendations to inform maternal health policies, guidelines, education platforms, and programmes to strengthen maternal care and improve maternal health outcomes.

TXA is a competitive inhibitor of plasminogen activation and can reduce bleeding by inhibiting the breakdown of fibrinogen and fibrin clots. Based on evidence for the benefit of TXA in improving trauma care outcomes, WHO's recommendations for prevention and treatment of PPH issued in 2012 included a conditional recommendation to use TXA for treatment of PPH when uterotonics fail to control the bleeding or the bleeding is thought to be due to trauma.[1]

In 2017, the results of a large, randomized controlled trial, the World Maternal Antifibrinolytic Trial,[2] were published and showed that early use of IV TXA (within 3 hours of birth and as soon as possible after onset

of bleeding) reduces death due to bleeding in women with PPH, regardless of cause, and with no adverse maternal effects. In response to this new evidence, along with evidence from the forthcoming Cochrane systematic review on the efficacy of TXA for PPH[3] and an individual participant data meta-analysis of 40,138 bleeding patients,[4] WHO updated its 2012 PPH treatment recommendations to include use of TXA for treatment of PPH. This recommendation supersedes the recommendation on TXA in the existing 2012 WHO recommendations for the prevention and treatment of PPH.[5]

This brief presents highlights of the 2017 WHO TXA recommendation (see Table 1 below), including key changes to the pre-existing 2012 WHO TXA recommendation (Table 2), and explores policy and programme considerations for adopting and implementing the recommendation at the country level. The brief is intended to support policymakers, programme managers, educators, and providers to incorporate the 2017 WHO TXA recommendation for PPH treatment into existent country maternal health policies, education platforms, and programmes.

It is important for country stakeholders to decide how to incorporate TXA into comprehensive PPH treatment algorithms and keep in mind the broader set of PPH intervention packages needed along the household-to-hospital care continuum for women who develop PPH, many of whom will not have prompt access to higher levels of care. Please see the full WHO 2017 TXA recommendation for PPH treatment for a detailed description of the methods used to develop the recommendation.

Table 1. WHO 2017 recommendation on tranexamic acid for the treatment of postpartum haemorrhage

WHO Recommendation	Service Delivery and Clinical Guidance
Early use of IV TXA (as early as possible after clinical diagnosis of PPH, and only within 3 hours of birth) in addition to standard care is recommended for women with clinically diagnosed PPH following vaginal birth or caesarean section.	• Postpartum haemorrhage (PPH) is defined as estimated blood loss of more than 500 mL after a vaginal birth or 1,000 mL after caesarean section, *or* any blood loss sufficient to compromise haemodynamic stability. • Tranexamic acid (TXA) should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes. • TXA should be considered to be part of the standard comprehensive PPH treatment package, including medical (uterotonics), nonsurgical, and surgical interventions in accordance with WHO guidelines or adapted local PPH treatment protocols. • TXA should be readily available at all times in the delivery and postpartum areas of facilities providing emergency obstetric care. • TXA is relatively cheap in most contexts, easy to administer, often available in health care settings due to its use in trauma and surgery, has a shelf life of 3 years, and can be stored at room temperature (15–30 C) in many places.[a] • 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. • Treatment delay in use of TXA appears to reduce benefit. The benefit appears to decrease by 10% for every 15-minute delay, with no benefit seen after 3 hours. • The point estimates of effect of TXA use beyond 3 hours on death for trauma[6] and for PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, WHO recommends against the use of TXA more than 3 hours after birth. • TXA should be administered at a fixed dose of 1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose.

[a] Manufacturer instructions on storage and use should always be followed.

WHO Recommendation	Service Delivery and Clinical Guidance
	• TXA should be administered slowly as an IV injection over 10 minutes, since bolus injection carries a potential risk of transient lowering of blood pressure. • TXA for injection may be mixed with most solutions for infusion, such as electrolyte solutions, carbohydrate solutions, amino acid solutions, and dextran solutions, and can be administered through the same IV cannula used for IV hydration or uterotonic administration. TXA should not be mixed with blood for transfusion, solutions containing penicillin, or mannitol.[a] • TXA should not be used in women with a clear contraindication to antifibrinolytic therapy, including TXA (e.g., a known thromboembolic event during pregnancy, history of coagulopathy, active intravascular clotting, or known hypersensitivity to TXA).

Table 2. What is new about the use of tranexamic acid (TXA) to treat postpartum haemorrhage (PPH) in the 2017 WHO recommendation on TXA for PPH treatment?

	Indication	Timing	Dosing
WHO 2012 TXA Recommendation	Use of TXA is recommended for the treatment of PPH **if oxytocin and other uterotonics fail to stop the bleeding or if it is thought that the bleeding may be partly due to trauma.**	For atonic uterus, use TXA **if oxytocin and other uterotonics fail to stop the bleeding.**	**IV (slowly): 1 g** **Repeat after 30 minutes if bleeding continues.**
WHO 2017 TXA Recommendation (updated)	Use TXA **in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes.**	Use TXA **within 3 hours and as early as possible after onset of PPH. Do not initiate TXA more than 3 hours after birth,** unless being used for bleeding that restarts within 24 hours of completing the first dose (see dosing).	Fixed dose of **1 g in 10 mL (100 mg/mL) IV at 1 mL per minute (i.e., administered over 10 minutes)** **Second dose** of 1 g IV **if bleeding continues after 30 minutes or if bleeding restarts within 24 hours of completing the first dose**

Policy and Programme Considerations

The goals of the WHO 2017 recommendation on TXA for PPH treatment are to improve the quality of care for women with PPH and prevent maternal deaths due to PPH. Successful introduction of TXA as part of a standard PPH treatment package will require action on many fronts and engagement of multiple stakeholders across system levels, including policymakers, national and subnational ministry of health managers, professional societies, facility managers, facility health care workers, community leaders, health agents, and women and families. Below are considerations for country stakeholders incorporating the WHO 2017 TXA PPH treatment recommendation into national policy and country programmes.

Photo by Jhpiego

National Policy Considerations

- Policymakers should develop or update existing national PPH prevention and treatment guidelines, including PPH treatment algorithms, to incorporate TXA into the standard PPH treatment package. National policy should specify the levels of care for administration of TXA as part of PPH treatment, as well as the provider cadres that may administer TXA.

Programme Implementation Considerations

National Programme Managers:

- Define and chart a plan for addressing the financial and programme requirements for implementing the WHO 2017 TXA PPH treatment recommendation in line with updated national policy.
- Address status and needs for procurement, distribution, and storage of TXA and other PPH treatment medicines and supplies, including uterotonics.
- National pre-service education directorates and institutions should review and update established curricula for PPH treatment (for relevant provider cadres), emphasizing competency-based approaches.
- Review and revise (or develop) provider job aids and decision support tools to help providers acquire necessary skills and incorporate TXA into routine PPH treatment (e.g., pre- and in-service education/training, onsite job aids, and clinical algorithms).
- Review national health management information system (HMIS) content and indicators relevant for PPH surveillance, prevention, and management, and prioritize PPH measures for monitoring at national, subnational, and facility levels (e.g., TXA stock-outs, PPH incidence, PPH case fatality, and PPH quality of care treatment measures, including TXA administration). The WHO standards for improving quality of maternal and newborn care in health facilities can be a useful resource and starting point for country stakeholders.[7]
- Review patient records for labour, childbirth, and postpartum care, and define areas of needed revision to capture essential clinical data points for provision of quality PPH clinical care and for calculation of quality measures to support quality improvement efforts (e.g., standardized place in record to record time of diagnosis of PPH, cause of PPH, time and dose of PPH treatments, PPH outcome, etc.).

Regional/District Managers and Facility Health Workers:

Facility Readiness to Administer TXA:

- Per national protocol, ensure all facilities have copies of updated PPH treatment protocols, job aids, and decision support tools available for immediate use in labour, delivery, and postpartum areas.