

Tranexamic acid for treatment of postpartum haemorrhage

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Abstract

Postpartum haemorrhage remains the leading cause of maternal mortality globally. Mortality and severe morbidity due to postpartum haemorrhage is highest in lower-resource settings. Tranexamic acid is an anti-fibrinolytic drug that has been in use in humans for nearly five decades. It is a structural analogue of lysine that binds irreversibly to plasminogen, thereby inhibiting the binding of plasmin to fibrin. This in turn inhibits fibrinolysis, thus stabilizing blood clots. Tranexamic acid has been shown to improve outcomes in trauma-related bleeding. New research has shown that early use of tranexamic acid (within 3 hours of birth), in addition to standard care, safely reduces deaths due to bleeding in women with clinically diagnosed postpartum haemorrhage, regardless of the mode of birth.

Keywords anti-fibrinolysis; maternal mortality; postpartum haemorrhage; tranexamic acid

The global burden of postpartum hemorrhage

Postpartum haemorrhage (PPH) is commonly defined as blood loss of 500 ml or more within 24 hours after birth, while severe PPH is defined as blood loss of 1000 ml or more within the same

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time period. Severe PPH affects approximately 2% of all births, and is the leading cause of maternal mortality globally especially in low-resource settings, accounting for an estimated 20% of all maternal deaths. Women who survive PPH (especially if the bleeding was severe) may suffer adverse health outcomes, such as organ dysfunction, prolonged hospital stay, need for additional invasive, life-saving interventions, use of intensive care unit and long-term disability.

PPH can be prevented through administration of a prophylactic uterotonic after delivery of the baby (such as 10 international units (IU) of intravenous (IV) or intramuscular (IM) oxytocin), uterine fundal massage, delayed cord clamping and, where trained competent staff are available, controlled cord traction. Since the most common cause of PPH is uterine atony, these preventive interventions aim to promote contractility of the uterus. In 2018, WHO updated its recommendations on uterotonics for PPH prevention, highlighting that oxytocin remains the uterotonic of choice.

Although prophylactic interventions are effective in the majority of women, some women will still experience PPH, necessitating additional pharmacological treatment. These include additional uterotonics, such as a further dose or infusion of oxytocin, 0.5 mg of IM ergometrine or a prostaglandin (including sublingual misoprostol 800 µg, 0.25 mg of IM carboprost every 15 minutes up to a maximum of 8 doses, or 20 mg of vaginal or rectal dinoprostone). The latest addition to the pharmacological armoury in the management of PPH is IV administration of one gram of tranexamic acid (TXA) within 3 hours of birth.

Pharmacology of tranexamic acid

Composition and pharmacokinetics

Tranexamic acid (TXA) is a trans-stereoisomer of 4-(aminomethyl)cyclohexane-carboxylic acid, a synthetic derivative and a structural analogue of the essential amino acid lysine. Although TXA can be administered orally, only IV administration has been evaluated for treatment of PPH. TXA is bound exclusively to plasminogen, with peak plasma concentration achieved immediately and the effect lasting 7–8 hours in serum and up to 17 hours in tissues. TXA has an elimination half-life of about 2–3 hours, and up to 95% is excreted unchanged in the urine within 12 hours. Dose adjustments are recommended for patients with renal impairment.

Pharmacodynamics

TXA is a haemostatic agent that binds irreversibly to the high affinity lysine-binding sites on plasminogen. Saturation of the binding site by TXA results in displacement of plasminogen from the surface of fibrin. This in turn prevents the formation of plasmin. As a result, no additional lysis of fibrin by plasmin occurs, and fibrin is therefore preserved and/or stabilized. This overall inhibition of fibrinolysis ultimately stabilizes clots. TXA may also exert its effects through inhibition of plasmin and fibrinogenolysis, anti-inflammation and improved platelet function.

Role of tranexamic acid in treating postpartum haemorrhage

Severe PPH may be a cause or a consequence of accelerated clot resolution due to hyperfibrinolysis. Women with PPH-related hyperfibrinolysis are more likely to benefit from TXA therapy.

The largest trial of TXA for PPH treatment to date, the World Maternal Antifibrinolytic (WOMAN) trial, demonstrated clinical benefit of therapeutic TXA in addition to standard care among women with clinically diagnosed PPH. The WOMAN trial was an individually randomized, double-blind, placebo-controlled trial, that randomized 20,060 women with a clinical diagnosis of PPH (regardless of mode of birth) in nearly 200 hospitals in 21 high, middle and low-income countries, to a regimen of 1-gram IV TXA or identical placebo. A second dose of 1 gram of IV TXA or placebo was given if bleeding continued after 30 minutes, or stopped and restarted within 24 hours of completing the first dose. The risk of death due to bleeding was 19% lower in women given TXA (155 [1.5%] of 10,036) compared to placebo (191 [1.9%] of 9,985), risk ratio ([RR] 0.81, 95% CI 0.65–1.00; $p = 0.045$), especially if TXA was administered within 3 hours of giving birth, (89 [1.2%] in the TXA compared to placebo group 127 [1.7%], RR 0.69, 95% CI 0.52–0.91; $p = 0.008$).

An individual patient-level data (IPD) meta-analysis of trials that assessed antifibrinolytics in acute severe bleeding (including only trials of more than 1,000 patients) showed similar findings. In this IPD meta-analysis of 40,138 bleeding patients, TXA increased overall survival by 20% (odds ratio [OR] of overall survival 1.20, 95% CI 1.08–1.33; $p = 0.001$). Immediate treatment improved survival by more than 70% (OR of survival 1.72, 95% CI 1.42–2.10; $p < 0.0001$), but the survival benefit decreased by 10% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit.

These findings were consistent with those of a Cochrane systematic review of anti-fibrinolytic agents (in addition to standard care) versus standard (or usual) care alone for PPH treatment which included the WOMAN trial, and a much smaller trial. The meta-analysis included outcomes of 20,212 women (the majority coming from the WOMAN trial and the remainder from a second trial conducted among 152 women with PPH > 800 ml in eight obstetric units in France). TXA was seen to reduce the risk of maternal death due to bleeding (RR 0.81, 95% CI 0.65 to 1.00) especially within 3 hours after giving birth.

Updated World Health Organization recommendation on tranexamic acid for treating postpartum haemorrhage

As a result of the WOMAN trial findings, WHO reviewed the evidence base and updated its recommendation on the use of tranexamic acid (TXA) in the treatment of PPH in October 2017. WHO now recommends administration of intravenous TXA (within 3 hours of birth) in addition to standard care for women with clinically diagnosed PPH, following vaginal birth or caesarean section. The standard care includes fluid replacement, medical treatment with uterotonics, monitoring of vital signs, nonsurgical interventions (e.g. bimanual compression, intra-uterine balloon tamponade, non-pneumatic antishock garment, aortic compression) and surgical interventions (e.g. brace sutures, arterial ligation or hysterectomy). TXA should be used for the treatment of PPH, regardless of the suspected cause but avoided in women with a clear contraindication to anti-fibrinolytics e.g. thromboembolism in pregnancy.

WHO recommends the administration of TXA at a fixed dose of 1 gram (100 mg/ml) intravenously (IV) at 1 ml per minute (i.e.

administered over 10 minutes). A second dose of 1 gram IV is recommended after 30 minutes if bleeding continues or restarts within 24 hours of completing the first dose. TXA should be administered as soon as PPH is clinically diagnosed (defined as more than 500 ml after a vaginal birth, or more than 1000 ml after caesarean section, or any blood loss sufficient to compromise haemodynamic stability), and in addition to other PPH prophylactic and treatment measures.

Conclusion

Postpartum haemorrhage contributes to almost a quarter of all maternal mortality globally. In women with PPH, TXA reduces maternal mortality due to bleeding if administered within 3 hours after birth as part of the standard PPH treatment package and in accordance with WHO guidelines. Further studies are needed to evaluate the safety and efficacy of alternative routes of administration and a prophylactic, rather than therapeutic, role of TXA in prevention of PPH. ◆

FURTHER READING

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Practice points

- Tranexamic acid (TXA) is an anti-fibrinolytic hemostatic agent which is a synthetic derivative and a structural analogue of the essential amino acid lysine.
- TXA should be administered at a fixed dose of 1 gram (100 mg/ml) intravenously (IV) at 1 ml per minute (i.e. administered over 10 minutes). A second dose of 1 gram IV should be administered after 30 minutes if bleeding continues or restarts within 24 hours of completing the first dose
- TXA reduces maternal mortality due to bleeding if administered within 3 hours after birth as part of the standard PPH treatment package and in accordance with World Health Organization guidelines.