Tranexamic acid for bleeding. Much more than a treatment for post-partum haemorrhage.

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Abstract

The evidence that early tranexamic acid treatment reduces post-partum haemorrhage deaths has major implications for obstetric care world-wide. Tranexamic acid may also have a role in the prevention of post-partum haemorrhage but more evidence is needed on the balance of risks and benefits. Most deaths from post-partum haemorrhage are in low- and middle-income countries where tranexamic acid treatment is often unavailable. Several maternal health organisations including the Reproductive Health Supplies Consortium, Clinton Health Access Initiative, Concept Foundation, FIGO and UNITAID are working to increase access. However, a wider view of the evidence on tranexamic acid and bleeding shows that it can improve maternal health in many other ways. An appreciation of these wider health benefits could facilitate efforts to increase access. By reducing heavy menstrual bleeding tranexamic acid could reduce the prevalence of maternal anaemia, a common and important risk factor for post-partum haemorrhage and other maternal and neonatal outcomes. Further clinical trials of tranexamic acid for the treatment of menstrual bleeding are needed. By reducing surgical bleeding and the need for blood transfusion, tranexamic

acid would increase the availability of blood in countries where there is a blood shortage so that more blood is available for use in life threatening bleeding including post-partum haemorrhage. In countries where there is no blood shortage, tranexamic acid use would reduce healthcare costs and prevent transfusion transmitted infections and reactions. Trauma affects women and men and violence is a leading cause of death in pregnancy. Increased use of tranexamic acid in trauma would significantly reduce trauma deaths . Efforts to increase the availability and use of tranexamic acid for obstetric haemorrhage should acknowledge its wider health benefits and aim to increase its use across health services more generally.

Tranexamic acid for the treatment of post-partum haemorrhage.

In 2017, the Woman trial showed that early treatment (within 3 hours of birth) with the antifibrinolytic drug tranexamic acid reduces post-partum haemorrhage deaths and the need for surgical intervention to control bleeding, without any increased risk of vascular occlusive events.[1] Within months, tranexamic acid was included in WHO guidelines for the treatment of PPH.[2] Based on the dosing regimen used in the Woman trial, the WHO recommended the intravenous (IV) administration of 1 gram of tranexamic acid with a second dose of 1 g IV if bleeding continues after 30 minutes, or if bleeding re-starts within 24 hours. Tranexamic acid is inexpensive, heat stable and has a long shelf life. A major advantage of tranexamic acid is that it reduces PPH deaths regardless of the cause of the bleeding. A subgroup analysis of the Woman trial data found no evidence of heterogeneity in the effect of TXA on deaths due to bleeding according to the cause of the bleeding. When interpreting the results of subgroup analyses, the best working assumption is that the overall result probably applies to everyone unless there is good evidence to the contrary. In this case, the effect of TXA on death due to bleeding was slightly different in the atony and non-atony groups, but the heterogeneity p value (p=0.36) showed that this difference is easily compatible with the play of chance. The Woman trial showed that tranexamic acid significantly reduces bleeding deaths and the need for laparotomy to control bleeding even when the primary cause of bleeding was uterine atony. This stands in contrast with uterotonic drugs which should only affect PPH resulting from uterine atony, which is variably estimated at 60-70% of PPH cases.

There is strong evidence that tranexamic acid is most effective when given as soon as possible after bleeding onset and the WHO recommended that tranexamic acid should be given immediately after PPH diagnosis, along with uterotonic drugs. On the other hand, the American College of Obstetricians and Gynaecologists (ACOG) recommended that tranexamic acid should be administered when initial therapies fail.[3] Waiting to see if initial therapies fail is likely to lead to delayed administration and will reduce the benefits of tranexamic acid treatment. Whatever the cause of the bleeding, waiting to see if uterotonics fail, can only lead to delayed tranexamic acid treatment, placing mothers at increased risk of consumptive coagulopathy.

Despite the lifesaving benefits of tranexamic acid as a treatment of PPH, in many low- and middle-income countries, where most deaths from PPH occur, tranexamic acid is often unavailable. Efforts to scale-up global access to tranexamic acid for PPH treatment are underway. The Reproductive Health Supplies Coalition, Clinton Health Access Initiative,

Concept Foundation, FIGO, E-MOTIVE trial and other organizations are working to bring tranexamic acid treatment to all women with PPH. As with any new drug, the barriers to scale up are bottlenecks in country procurement and distribution, with limited supply forcing up prices. However, it is not widely appreciated that tranexamic acid can improve maternal health in many other ways apart from the treatment of PPH and a more 'health systems-oriented' approach to its availability and use could have additional health benefits. Because market forces determine the availability and cost of tranexamic acid in many countries, appreciation of its wider health benefits could have strategic advantages since the potential demand for TXA is much more than as a PPH treatment. This potential demand could become effective demand if there was an appreciation of its other benefits within the health system. So what other health benefits could tranexamic acid have apart from as a treatment for PPH?

Tranexamic acid for the prevention of post-partum haemorrhage.

The knowledge that tranexamic treatment of post-partum haemorrhage improves outcomes has raised interest in the use of tranexamic acid for the prevention of severe bleeding. All women bleed after childbirth. As if anticipating this inevitability, the mother's blood becomes progressively prothrombotic in pregnancy.[4] Levels of clot-making proteins like fibrinogen and factor VII increase, while the activity of clot breaking (fibrinolytic) proteins is reduced due to higher levels of inhibitors. The placenta itself releases potent inhibitors of fibrinolysis (PAI-1 and PAI-2). Their blood levels peak at the moment of birth, falling away rapidly after placental separation.[5] Given the strong evolutionary links between coagulation and immunity, protection from pathogens might have been one of the selection pressures moulding the haemostatic system. Whatever the biological purpose, there are profound changes in the mother's blood around the time of birth.

Despite the prothrombotic tendency, bleeding after childbirth can be severe and sometimes fatal. In parts of sub-Saharan Africa and South Asia, one mother dies from bleeding for every 1,000 births.[1] In high-income countries, the risk is orders of magnitude lower, with less than 1 bleeding death per 100,000 births.[6] In these low risk settings, there are more thrombotic deaths than bleeding deaths. Due to propensity of the blood to clot and the pressure from the expanding womb, pregnant women have an increased risk of arterial and venous thrombosis. Compared to women who are not pregnant, the risk of thromboembolism in pregnancy is five times higher, rising to 20 times higher in the post-partum period.[7] To complicate matters, women giving birth are not exposed to one risk (bleeding) or the other (thrombosis) but to both risks simultaneously. Severe bleeding is a risk factor for thrombosis. For this reason, before deciding to use a treatment to prevent bleeding, we must consider the risk of bleeding and thrombosis and the effect of the treatment on both.

The Woman trial evaluated the effects of TXA in mothers with severe bleeding after childbirth. [1] All of the included women were bleeding profusely and most were haemodynamically unstable. Their risk of death from bleeding was extremely high, about 20 deaths per 1,000 births. Their risk of death from thrombosis was also high at 1 death per 1,000 births but much less than the risk of death from bleeding. TXA cut bleeding deaths by a third when given within three hours of birth, preventing about 6 deaths for every 1,000 women treated. There was no apparent effect of TXA on thrombosis deaths but because

there were only 21 thrombotic deaths in this 20,060-patient trial there is uncertainty about the effects of TXA on this outcome. Nevertheless, this uncertainty does not materially affect the treatment decision. Even if TXA doubled the risk of thrombotic deaths, which seems highly unlikely, in women with severe bleeding the benefit would outweigh the harms. As recommended by the World Health Organization, all women with severe post-partum bleeding should receive TXA.[2]

But does TXA improve outcomes for women without severe bleeding? The Woman-2 trial is evaluating the effects of TXA after childbirth in women with moderate or severe anaemia.[8] In this trial, anaemic women are treated immediately after birth, as soon as the umbilical cord is clamped. Anaemia is a strong risk factor for bleeding after childbirth.[9] The increased heart rate and cardiac output caused by anaemia and the reduced viscosity of anaemic blood increase blood flow from bleeding vessels.[10–12] Red cells also appear to have a clot-stabilizing effect and anaemic clots are more susceptible to fibrinolysis.[13] Women with severe anaemia have elevated D-dimer levels and lower platelet and fibrinogen levels.[14] The risk of death from bleeding in these anaemic women is about 1 per 1,000 births and much higher than the risk of thrombotic death. Because anaemia increases the risk of bleeding and decreases the risk of thrombosis, the net effect of TXA should be favourable in anaemic women.

There have also been trials of TXA for PPH prevention in low risk women in high income countries.[15–17] Because the risk of death from bleeding is low (about 1 per 100,000 deliveries) and similar to the risk of death from thrombosis, uncertainty about the effect of TXA on thrombosis is far more consequential. If there was an increase in thrombotic events with TXA this could outweigh the benefits of reduced bleeding. It is critical therefore that trials in low risk women are large enough to assess the effect of TXA on thrombosis. Because fatal events are so rare, we will need to study the effects of TXA on non-fatal thrombosis. But even then, we would only expect about 2 thrombotic events per 1000 births. Trials with just a few thousand low risk women will be underpowered and almost non-informative. Even the largest trial, which included 11,000 low risk women giving birth by Caesarean section, is too small to provide reliable information about safety. We will need larger trials and meta-analyses of these large trials before we can confidently offer TXA treatment to low risk women.

Are we being overcautious? Could a single injection of TXA to inhibit fibrinolysis for just a few hours, when the risk of bleeding is greatest, cause a significant increase in the risk of thrombosis? TXA has a short half-life and is almost completely eliminated within 6-8 hours. Severe bleeding that requires transfusion or surgery is itself prothrombotic and so by preventing bleeding we might even reduce the risk of thrombosis. Without reliable evidence we can only speculate but with over 140 million births each year world-wide, it would be rash to speculate about something so important.

Tranexamic acid and heavy menstrual bleeding

Anaemia is common and dangerous in women of reproductive age. Worldwide, half a billion women of reproductive age (1 in 3) have anaemia, with a particularly high burden in sub-Saharan Africa and South Asia.[18–20] Anaemia reduces capacity to benefit from education, to

work, and to participate in social and leisure activities.[21] Because it affects educational attainment and work productivity, anaemia impacts national development. In pregnancy, it increases the risk of low birthweight, preterm birth, and perinatal, neonatal and maternal mortality.[22–24]

Menstruation is a major cause of anaemia in women of reproductive age and affects quality of life. Higher menstrual blood loss (40ml on average) is correlated with greater losses of iron (1.6mg on average) and Hb.[25–27] The presence of anaemia strongly suggests that dietary intake of iron, B12 and folate is insufficient to compensate for menstrual losses of iron. As well as contributing to anaemia, menstrual symptoms like heavy menstrual bleeding affect women's ability to undertake physical, social and academic activities which greatly impacts quality of life.[28]

New strategies are needed to improve women's health and achieve global anaemia targets. The WHO aims to half anaemia prevalence in women of reproductive age by 2025.[29] The prevalence of anaemia is falling, but slowly. From 1995-2011, global mean Hb increased by just 1g/L.[20] Interventions to reduce menstrual bleeding have been neglected in anaemia control strategies, which largely focus on increasing the dietary intake of iron, B12 and folate but have had limited success. [30]

By reducing menstrual iron loss, tranexamic acid has the potential to reduce anaemia regardless of whether it is caused by iron deficiency, underlying diseases, infections or genetic haemoglobinopathies. Endometrial fibrinolysis in normal menstruation provides the biological basis for using TXA to reduce menstrual losses of iron and Hb in anaemic women.[31] Although the evidence that tranexamic acid reduces heavy menstrual bleeding is promising, further high-quality trials are needed in low- and middle-income settings.[32] Such trials could change anaemia control policy globally, improve the wellbeing of millions of women, and help achieve the WHO target. Early intervention to reduce the risk of anaemia during pregnancy offers the potential to reduce adverse maternal and birth outcomes and to improve maternal wellbeing.

Tranexamic acid and surgical bleeding

Evidence that tranexamic acid reduces surgical bleeding and the need for blood transfusion has been available for decades but uncertainty about the risk of vascular occlusive events has limited its widespread use.[33,34] Recent systematic reviews and meta-analyses of clinical trials of tranexamic acid in elective surgery show no increased risk of vascular occlusive events with tranexamic acid but because many of the included trials were small there was still some doubt about the balance of risks and benefits.[35,36] However, the recent publication of the POISE-3 trial results is a substantive addition to our knowledge of the effects of tranexamic acid in surgery and warrants urgent attention.[37] The POISE-3 trial randomly allocated close to 10,000 patients undergoing non-cardiac surgery to get tranexamic acid or placebo and showed that tranexamic acid reduced major bleeding by one quarter, significantly reduced blood transfusion and without increasing the risk of vascular occlusive events. For statistical reasons it is hard to rule out a very small increase in the risk of vascular occlusive events but because significant bleeding is surprisingly common in

surgery and vascular occlusive events are relatively rare, the balance of benefits and risks will be favourable. As demonstrated previously, the POISE-3 trial showed that tranexamic acid reduces bleeding in all types of surgery, including gynaecological surgery. In high, middle- and low-income settings, the greater use of tranexamic acid in people having in-patient surgery would reduce surgical blood loss, post-operative anaemia and risks of transfusion transmitted infection. Economic evaluation shows that TXA is a highly cost-effective intervention for reducing the cost and risks associated with surgical procedures requiring blood transfusions in low- and middle-income settings, particularly in sub-Saharan Africa.[38] By increasing the availability of blood, tranexamic could be lifesaving in those countries where there is a severe blood shortage. In most low-income countries there is a severely limited supply of safe blood for transfusion. The severe blood shortage is likely to explain the high frequency of single unit blood transfusions in women with severe postpartum bleeding, despite the need for higher volume transfusions. Use of tranexamic acid would also reduce health care costs and prevent transfusion transmitted infections including HIV, Hepatitis B and Hepatitis C in countries where blood is readily available. Given the recent outbreaks of new viral infections (Monkeypox and adenovirus causing hepatitis), avoiding unnecessary blood transfusion, whilst improving surgical outcomes, should have a high public health profile.

Tranexamic acid and traumatic bleeding

In 2010, results from the global CRASH-2 trial (20,211 polytrauma patients) showed that intravenous tranexamic acid given within 3 hours of injury reduces deaths due to bleeding and all-cause mortality.[39] Based on these results tranexamic acid was added to the WHO list of essential medicines. In 2019, results from the global CRASH-3 trial (13,000 patients with isolated traumatic brain injury) showed that tranexamic acid given within 3 hours of injury also reduces head injury deaths, almost certainly by reducing the extent of traumatic intracranial bleeding.[40] Early tranexamic acid treatment reduces trauma deaths regardless of country income, although misguided concerns about the generalisability of the trial results have limited the mortality benefits in some settings.[41] The implications for women of the lifesaving benefits of tranexamic acid in trauma patients become obvious when one considers that violence is the leading cause of death during pregnancy and the postpartum period in the United States. A recent analysis of mortality data from the US National Center for Health Statistics showed that violence during pregnancy or within 42 days of the end of pregnancy exceeded all the leading causes of maternal mortality by more than twofold.[42] The pregnancy associated homicide risk was particularly high in Black women and girls. Unfortunately, there is recent evidence that injured women are much less likely than men to receive tranexamic acid treatment.[43] Advocates for women should ensure that when women are victims of injury or violence, they receive evidence-based trauma care including the use of tranexamic acid.

Table: Established indications for tranexamic acid

PPH: 1-gram tranexamic acid as soon as possible after PPH onset (but no later than 3 hours from birth) reduces PPH deaths by a third and reduces the need for laparotomy for bleeding.

Surgery: 1-gram tranexamic acid just prior to incision reduces surgical bleeding and the need for blood transfusion by between one quarter and one third.

Trauma: 1-gram tranexamic acid as soon as possible after injury (but no later than 3 hours) reduces deaths from bleeding by about one third.

Future research priorities

Timely treatment with intravenous (IV) tranexamic acid (TXA) cuts PPH deaths by one third. To increase access in LMICs, WHO has made finding different ways to give TXA a research priority. Women die soon after PPH and so effective TXA levels must be achieved quickly. Many community health workers cannot give IV drugs but most are trained to give IM injections (e.g. vaccination). Further research is needed on IM tranexamic acid use since this has the potential to take this lifesaving drug out of hospital into the community so that more women can be treated and sooner. We will also need larger trials and meta-analyses of large trials before we can offer TXA for the prevention of PPH in low risk women. Clinical trials of the role of tranexamic acid in the treatment of heavy menstrual bleeding and the prevention of anaemia are also needed.

Conclusions

The inclusion of tranexamic acid into WHO guidelines on the treatment of post-partum haemorrhage has led to a profusion of initiatives to increase the availability and use of tranexamic acid for this specific indication. However, tranexamic acid can improve maternal health in many other ways and a more 'health systems-oriented' approach to tranexamic acid availability and use would have major additional health benefits. Tranexamic acid is a key component of the PPH treatment bundle and the Reproductive Health Supplies Consortium, CHAI, Concept Foundation, FIGO and other organizations are working to scale up access to tranexamic acid in low- and middle-income countries. Recognising the wider health system uses and benefits of tranexamic acid use has the potential to expand the hospital demand for tranexamic acid which should lead to increased supply. A health systems approach to tranexamic acid availability and use would have enormous benefits. Anaemia due to heavy menstrual bleeding debilitates millions of young women, reducing their ability to develop to their full potential. Access to tranexamic acid could be life changing for these women. By reducing surgical bleeding tranexamic acid could increase the blood supply for women who need it. Injury and violence kill 5 million men and women each year and wider use of tranexamic acid could save over one hundred thousand deaths each year.[44] Tranexamic acid is an essential medicine for surgical, traumatic and post-partum bleeding and must be available in hospitals everywhere.

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