

A conversation with Dr. Haleema Shakur and Aoife Jones, August 23, 2017

Participants

- Dr. Haleema Shakur – Co-Director of Clinical Trials Unit and Principal Investigator of the WOMAN Trial, London School of Hygiene and Tropical Medicine
- Aoife Jones – Head of Philanthropic Giving, London School of Hygiene and Tropical Medicine
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Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Haleema Shakur and Aoife Jones.

Summary

GiveWell spoke with Dr. Shakur and Ms. Jones of the London School of Hygiene and Tropical Medicine (LSHTM) as part of its shallow investigation into tranexamic acid (TXA) to prevent deaths from postpartum hemorrhage (PPH). Conversation topics included the efficacy of TXA, possible routes for administering TXA, and difficulties with making TXA available in developing countries.

LSHTM's work

Research

LSHTM has done several studies on the use of TXA to treat bleeding. These include the CRASH-2 trial, which used TXA to treat patients with major extracranial trauma, and the WOMAN trial, which looked at TXA as a treatment for new mothers with PPH.

The CRASH-2 trial found that TXA reduced risk of bleeding to death by about one third for trauma victims.

The WOMAN trial found that TXA reduced the risk of bleeding to death by about one third for new mothers, if administered within three hours of birth. The trial was jointly funded by the Bill and Melinda Gates Foundation (BMGF), the Wellcome Trust, and the UK Department of Health.

Advocacy

LSHTM is focusing its efforts on promoting take-up of TXA in five target countries: Pakistan, Nigeria, Ethiopia, Bangladesh, and India. Together these five countries have ~60% of all maternal deaths.

LSHTM has primarily engaged with health professional bodies, such as national professional bodies for obstetrics and gynecology in various countries. LSHTM aims to make sure that these bodies include TXA in their guidelines, but does not work with them to make TXA available in developing countries.

It has also engaged with charities, including Doctors Without Borders (MSF), and funders, such as BMGF. BMGF may fund work to roll out a package of interventions soon, which may include TXA.

Efficacy of TXA

Mitigation of bleeding

Administering TXA reduces a patient's risk of bleeding to death by about one third. This is true for trauma victims as well as for new mothers, and in the UK as well as in developing countries.

While TXA is effective at preventing deaths from PPH, its effect on all-cause mortality for new mothers is lower, and was not statistically significant in the WOMAN trial. This is because TXA has no effect on causes of mortality other than PPH, and women who are prevented from bleeding to death after giving birth may die of other causes, such as sepsis or complications from HIV.

Prevention of bleeding

LSHTM is planning another study, the WOMAN-2 study, to see whether TXA can be used to prevent PPH in high-risk women. TXA appears to prevent bleeding, not only stop it, so administering TXA earlier could prevent PPH.

There does not appear to be much risk of giving TXA to women who are not bleeding, since some women in Japan take TXA on a daily basis to lighten their skin and do not seem to experience adverse effects. However, it is generally advisable not to expose fetuses to unknown risks from medications. So, LSHTM's study will only target women at a high risk of PPH, who are most likely to benefit.

TXA for trauma

TXA is the only treatment that has been shown to be effective in stopping bleeding in trauma patients. Every year ~10 million people die from trauma, while ~100,000 new mothers die from PPH. Therefore, the majority of the potential beneficiaries of TXA are trauma victims. About 90% of trauma victims live in developing countries.

The UK is already using TXA to treat trauma. For roadside accidents, ambulance drivers will administer 1g of TXA intravenously if they suspect significant bleeding. It is important that they administer it on site rather than waiting to get to the hospital, because TXA must be given within three hours of when the bleeding starts.

In developed countries, trauma patients typically have access to intravenous TXA, blood transfusion, shock treatment, and quality intensive care. Patients in developing countries may not have access to any of these. All together, this means that the risk of death from trauma is about twice as high in Nigeria as in the UK.

Administering TXA

TXA can be administered by anyone who is legally allowed to give intravenous (IV) therapy. This varies by country, but generally includes doctors, nurses, and sometimes midwives.

Routes of administration

TXA is currently administered intravenously, which means that the treatment is only available in hospitals. Since it is common for women in developing countries to give birth at home with untrained birth attendants, women can still die of PPH even in areas where TXA is available in the local hospital.

LSHTM is writing a grant proposal to study the bioavailability of TXA when administered by different routes, with the goal of making the drug more available in communities. If TXA could be given as an intramuscular injection or as an oral tablet, women may be more likely to use it at home, which would increase their chances of survival.

Oral misoprostol is sometimes used in community settings to reduce risk of death from PPH – a pregnant woman is given a misoprostol tablet to keep, and then can take the tablet immediately if she starts bleeding. This buys her time, which is important because many women with PPH bleed to death before they can get to a hospital.

Making TXA available in developing countries

Difficulties

In high-income countries, medical recommendations are added to national guidelines as soon as evidence becomes available, but this process is often much slower in developing countries. TXA was added to the WHO Model List of Essential Medicines in 2011, but most countries have still not added it to their national essential medicine lists (NEMs), which means that many people in those countries do not have access to TXA. Dr. Shakur is not aware of any low income countries with TXA on their NEM.

Dr. Shakur is uncertain about how to go from having TXA in international health guidelines to ensuring that TXA is available in communities so that people actually benefit from it. In Nigeria, for example, the primary reason TXA is not being used is that it is not available in pharmacies. Dr. Shakur recently met with the Nigerian Minister of Health, who promised that TXA would be added to Nigeria's NEM.

Update: Since this conversation, the World Health Organization has updated its guidelines to include TXA in the package of care for treatment of PPH. However, TXA remains unavailable in many of the countries that need it most.

Delivery

Though simply providing TXA is a good first step, there are several considerations for how to make TXA delivery more effective.

- **Changing behavior** – A charity should not only provide TXA, but should also aim to get people used to using it. It is important to integrate TXA into established health care systems so that medical professionals will continue to use it after the charity withdraws.
- **Holistic care** – TXA needs to be included in a holistic care package for mothers, rather than only being made available to women who are already bleeding. LSHTM may be interested in trying to get TXA added to the existing MSF packages for trauma and PPH.

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