Editorial

World Woman Trial: A New Evidence Based Approach Towards Treatment of Post Partum Hemorrhage

Rizwana Chaudhri[1], Aasia Kayani[2], Kiran Javeed[3]

[1]Professor and Head of Department Obstetrics and Gynecology, Rawalpindi Medical College and Allied Hospital, Rawalpindi, [2]Research Coordinator LSHTM- RMC Research Collaboration, Rawalpindi, [3]Assistant Research Coordinator LSHTM- RMC Research Collaboration, Rawalpindi

Address of Correspondence: *Prof Rizwana Chaudhri, Professor and Head of Department Obstetrics and Gynecology, Rawalpindi Medical College and Allied Hospital, Rawalpindi, Pakistan*
Email address: rizwanachaudhri@hotmail.com

Maternal Mortality refers to the death of mother's due to complications of pregnancy and childbirth.

Maternal Mortality is the highest single reason of premature deaths worldwide. Owing to great international commitments to tackle maternal deaths and addressing it through MDGs, the global maternal deaths reduced by 44% from 385 deaths to 216 deaths per 100,000 between 1990 and 2105.[1] However though substantial, this reduction is not uniform with 99% of maternal deaths still occurring in developing countries. Two regions, the Sub-Saharan Africa and South Asia contribute to 88% of maternal deaths burden globally.[2] The lifetime risk of maternal death is 1 in 4900 in developed countries as against I in 150 in less developed nations. However, this lifetime risk of death, in the least developed regions is 1 in 52 women. Thus, highlighting an important fact that majority of maternal deaths in less developed countries are due to preventable factors.[3]

Obstetric hemorrhage(PPH) is the leading cause of maternal deaths contributing to 27 % of all deaths. Out of 14 million cases of PPH reported globally each year ,127 000 resulted in a maternal loss. Most deaths (about 99%) from PPH occurs in low and middle-income countries with only 1% in industrialized nations.[4] Although PPH is not limited to developing countries only, but it is also a harsh reality that PPH is more fatal in these countries.

The maternal mortality rate is thus not only an important indicator of maternal health also it provides an insight into the overall functioning of the health system of a country.[5] Thus the intrinsic problem of health systems in less developed countries also reasonably adding there share to already existing grave situation of maternal health. Although giving birth in a health facility increases the chance of surviving post-partum hemorrhage, but unfortunately, in underdeveloped or even in developing regions women still die from the prevailing condition within the health facilities. Thus, most hospitals so far fail in providing the comprehensive health care facilities to these critically sick mothers.

According to the World Health Organization and partners, Pakistan has a maternal mortality rate of 178 deaths per every 100,000 live births. In 2015 there were an estimated 9,700 maternal deaths in the country, and post-partum hemorrhage was the single biggest cause.[1] On an average there is 3.4 % reduction in Maternal mortality between 2000 and 2015, but although the reduction is appreciable still we need to work even harder to improve maternal health to the level of developed regions.

Obstetric hemorrhage although considered to be relevant to low or middle-income countries, however on the contrary recent studies have shown an increase trend of PPH in developed countries as well, thereby underlining the need of further research.[6] As maternal health is the result of the interplay of a multiplicity of factors deeply embedded in the unique situation of each region, therefore it cannot be achieved by a single blanket strategy for all. A number of strategies are being used to address this monstrous health issue faced by the world.

Although their overall effectiveness has been proven there still a wide scope of research for more efficient, widely available yet cost-effective interventions.

The WOMAN TRIAL – World Maternal Antifibrinolytic Trial, is a step in the right direction.

The Woman Trial is an international, randomised, double-blind, placebo-controlled trial, that studied the effect of tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum hemorrhage (WOMAN). [7-11]

The London School of Hygiene & Tropical Medicine coordinated this research. It was funded by The Welcome Trust and UK Department of Health through the Health Innovation Challenge Fund, and the Bill & Melinda Gates Foundation.

Tranexamic acid is not a new drug, it was invented in the 1960s by a Japanese husband and wife research team, Shosuke and Utako Okamoto.[12] The researchers who invented tranexamic acid more than 50 years ago hoped it would reduce deaths from postpartum hemorrhage, but they couldn't persuade obstetricians at that time to conduct a trial. Now as we finally have Woman Trial's results and we are optimistic that we can help save women's lives around the world.

The study builds on a previous trial (CRASH-2) of 20,211 bleeding trauma patients from hospitals in 40 countries showed that TXA reduces bleeding deaths by a third if given soon after injury.[13] Based on evidence from studies on the use of TXA in surgery and trauma, in 2012 TXA was included in WHO guidelines for the treatment of post-partum hemorrhage, but not as a primary treatment (recommended instead if other treatments have failed).[14]

The Woman trial is so far, the largest designed trial of Tranxemic acid in obstetric haemorrhage.

This Trial was conducted in 193 hospitals from 21 countries of the world. Among them are also countries which have highest rates of maternal mortalities. 5,280 women from 47 hospitals in Pakistan took part in the global trial, which included 20,060 women in total, mainly from Africa and Asia, but also from UK and elsewhere. Pakistan is the second highest recruiting country after Nigeria in the world.

All the women who are above 16 years (18 years in some countries depending on legal adult age) who had been diagnosed clinically for PPH after a vaginal delivery or caesarian section, were enrolled into the trial. The eligible women were randomly assigned to tranxemic acid or placebo groups. Participants, caregivers, and those assessing outcomes were masked to allocation. The composite primary endpoint of trial was death from all-causes or hysterectomy within 42 days of giving birth. It was originally planned to enroll 15 000 women. However, during the trial it became apparent that the decision to conduct a hysterectomy was often made at the same time as randomisation. Although tranexamic acid could influence the risk of death in these cases, it could not affect the risk of hysterectomy. The sample size was then increased from 15 000 to 20 000 women in order to estimate the effect of tranexamic acid on the risk of death from post-partum hemorrhage.

Data analysed for 10,036 women given tranexamic acid and 9,985 women given the placebo. Death due to bleeding was significantly reduced with tranexamic acid: 155 deaths with tranexamic acid vs 191 with placebo (reduction of 19%). In women treated within three hours of giving birth the figures were 89 deaths of women given tranexamic acid vs 127 for those given placebo (reduction of 31%). Tranexamic acid and placebo were given in addition to routine care practiced in participating hospitals. No increase in thromboembolic events were found in TXA arm when compared with placebo. While the WOMAN Trial found that tranexamic acid significantly reduced death due to bleeding, it did not prevent hysterectomy. The reason being that in low- and middle-income countries where blood supplies are limited, a hysterectomy is sometimes carried out immediately after the onset of very severe postpartum hemorrhage to save the mother's life along with tranxemic acid administration. This means there is no time for tranexamic acid to have an effect.

Base on the results of Woman Trial we now have important evidence that the early use of tranexamic acid can save life of scores of mothers and at the same time ensure more children grow up with mothers. Tranexamic acid is safe, affordable, readily available and easy to administer. The drug is quite

robust and can be used in diverge climatic condition with resonablely good safety profile. Therefore, we can expect that doctors will use it as early as possible following the onset of severe bleeding after childbirth.

Young mothers are dying from heavy bleeding after childbirth on an unacceptable scale in Pakistan. We are losing far too many women from something which can be prevented and we need to learn from the WOMAN Trial and act on these very encouraging results. We face a number of challenges in Pakistan as the majority of babies are delivered in women's homes in rural areas with no trained medical staff or facilities available. This is particularly important when it comes to post-partum hemorrhage because time is such a crucial factor in treating it and saving lives or preventing hysterectomy. If tranexamic acid is given quickly enough we could see a reduction in the number of tragic deaths of young mothers. We should work together to tackle this PPH and at the same time urge our hospitals, doctors and community health centres to join this global drive to save mothers.

The success of Woman trial is indeed the success of all mothers and on boarder perspective of all women of the world. We are extremely grateful for all our collaborators who had worked really hard to make this research possible.

Recommendations:

1. Tranexamic acid should be included in the essential drugs list for PPH.
2. Tranexamic acid should be considered as primary rather than the secondary treatment of post partum hemorrhage.
3. Tranexamic acid should be administered in the following doses

Dose 1: 1 gram - to be administered by intravenous injection at an approximate rate of 1mL/minute as soon as possible after onset of PPH.

Dose 2: 1 gram - If after 30 minutes bleeding continues, or if it stops and restarts within the 24 hours after the first dose, a second dose may be given. To be administered by intravenous injection at an approximate rate of 1 mL/minute.

References

1. Trends in Maternal Mortality: 1990 to 2015 Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. www.who.int/about/licensing/ copyright form/en/index.html. 2016 http://apps.who.int/iris/bitstream/10665/194254/1/9789241565141_eng.pdf
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. The Lancet Global Health. 2014 ;2(6):e323-33.
3. *Bauserman M, Lokangaka A, Thorsten V, Tshefu A, Goudar SS, Esamai F, et al. Risk factors for maternal death and trends in maternal mortality in low-and middle-income countries: a prospective longitudinal cohort analysis. Reproductive health. 2015;12(2):S5.*
4. Potts M, Hemmerling A. The worldwide burden of postpartum haemorrhage: Policy development where inaction is lethal. International Journal of Gynecology & Obstetrics. 2006;94:S116-S121.
5. AbouZahr C, Wardlaw T. Maternal mortality at the end of a decade: signs of progress? Bulletin of the World Health Organization. 2001 ;79(6):561-73.
6. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle MH, Ford JB, Joseph KS, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC pregnancy and childbirth. 2009;9(1):55.
7. Woman Trial Collaborators, and others. Effect of early tranexamic acid administration on mortality, hysterectomy and other morbidities in women with postpartum hemorrhage(WOMAN): an international randomised, double blind, placebo-controlled trial. The Lancet 26 April 2017;389(10082): *http://www.thelancet.com/journals/lancet/article/piis0140-6736(17)30638-4/fulltext?elsca1=tlpr*
8. https://www.youtube.com/watch?v=X8DJ2XX0Al0
9. B-ROLL: Nigeria and Pakistan hospital footage, Nigeria interviews, plus high-quality version. https://www.eurekalert.org/pub_releases/2017-04/tl-tll042517.php
10. WOMAN Trial video without music and astons (only interview audio) available to download for broadcast on request. https://www.eurekalert.org/pub_releases/2017-04/tl-tll042517.php
11. https://www.dropbox.com/sh/jv3rxcav59gnckw/AABJgLlKKm-P4tvV4dKiqj70a?dl=0
12. VIDEO: History of TXA - interview with inventor Utako Okamoto: https://youtu.be/VbDDxzyp1rQ
13. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. The Lancet. 2011;377(9771):1096-1101.e2.
14. WHO recommendations for the prevention and treatment of postpartum hemorrhage www.who.int/ reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/. 2017 http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf