bjh review

Post-partum haemorrhage and tranexamic acid: a global issue

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Summary

Post-partum haemorrhage (PPH) remains the major cause of maternal death worldwide, with the overwhelming majority of bleeding deaths occurring in low income countries. These bleeding deaths occur due to a complex network of biological and socioeconomic factors, including changes to haemostasis and fibrinolysis during pregnancy. Tranexamic acid (TxA) has been shown to reduce death in bleeding trauma patients safely and is effective in reducing bleeding in surgical patients, however its role in PPH has been less well established. We discuss the impact of the recently published World Maternal Antifibrinolytic (WOMAN) trial, which demonstrated a significant reduction in bleeding deaths (Risk ratio 0·81) in women with PPH who received intravenous TxA compared to those receiving placebo. There were no increases in post-partum thrombotic rates in mothers or breast-fed babies. This trial has shown that intravenous TxA can be used safely and effectively to treat PPH, and should be implemented widely to reduce death due to PPH. However, for the full benefit of TxA to be fully realised in resource-constrained settings, the effectiveness of oral or topical administration and/or pre-emptive dosing need to be investigated.

Keywords: clinical research, fibrinolysis, post-partum haemorrhage, tranexamic acid.

The global issue of maternal bleeding deaths

Each year, more than 300 000 women die from complications of giving birth (You *et al*, 2015). The fifth Millennium Development Goal aimed to reduce maternal deaths by three-quarters between 1991 and 2015, but very few countries achieved this (Victora *et al*, 2016). In Sierra Leone, where the maternal death rate is highest, one maternal death occurred for every 74 births during 2015 (You *et al*, 2015). The leading cause is haemorrhage, accounting for 27·1% of maternal deaths worldwide (Say *et al*, 2014). Most bleeding deaths are from primary post-partum haemorrhage (PPH) (Say *et al*, 2014), defined as blood loss of more than 500 ml within 24 h of birth (World Health Organization [WHO] Maternal and Newborn Health/Safe Motherhood Unit, 1996). Each death has tragic consequences for the new-born, the family and the wider community. PPH causes other morbidity, such as emergency hysterectomy, laparotomy or complications from blood transfusions. It also leads to an estimated 1·6 million women per year developing severe post-partum anaemia (AbouZahr, 2003).

Historically, PPH has been a major cause of mortality in woman in both resource-rich and resource-poor areas of the world. For example in the UK during the late nineteenth century, 108 maternal deaths from haemorrhage occurred for every 100 000 births (Kerr & Weeks, 2015). Significant progress was made throughout the twentieth century, and the most recent Confidential Enquiry into Maternal Deaths reported that the rate had dropped to 0·56 per 100 000 births (Knight *et al*, 2016). However, most countries with poorer healthcare resources have not replicated this progress and this is where the majority of bleeding deaths occur (Ronsmans & Graham, 2006). In many areas of Sub-Saharan Africa, maternal death rates from bleeding remain at least as high as that of 19th century Britain (6 deaths per 1000 births) (Kerr & Weeks, 2015).

Several factors are likely to contribute to the striking geographical distribution of maternal deaths from PPH although their relative contributions are uncertain and may vary from hospital to hospital and country to country. There is often poor infrastructure: hospitals may lack trained obstetric staff, key obstetric medications, safe blood components and basic equipment (Paxton *et al*, 2006). The women are often sicker at presentation due to socioeconomic factors resulting in poor diet and inadequate antenatal care, with some women at high-risk of PPH presenting to hospital for the first time during labour (United Nations, 2011). Some women present in established PPH, having previously given birth outside of the hospital. Others are already suffering pregnancy-related issues, such as eclampsia or a ruptured uterus, which would be difficult to manage even in a well-resourced setting. If a woman does suffer a severe PPH, effective critical care may not be available (Fowler *et al*, 2008).

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A further contributor to women dying after developing PPH is widespread anaemia in pregnant women. Anaemia is a global public health problem, which is particularly marked in low- and middle-income countries. Anaemia in Africa has been described as a syndrome due to its multiple aetiologies (Calis *et al*, 2008): iron deficiency, infection causing functional iron deficiency (due to infections, such as to malaria and human immunodeficiency virus); genetic conditions, such as sickle cell disease, thalassemia and glucose-6-phosphate dehydrogenase deficiency; parasitic infections leading to blood loss (e.g. hookworms); and lastly drugs, such as anti-retrovirals. A cross-sectional study at a teaching hospital in Nigeria reported that 55% of pregnant mothers were anaemic, and this anaemia was hypochromic in 80% of cases (Olatunbosun *et al*, 2014), a much higher rate than the incidence of thalassemia trait described, suggesting iron deficiency anaemia is very prevalent. Furthermore, there is a further drop in haematocrit in pregnancy due to the expansion of plasma volume (Eugster & Reinhart, 2005). A Nigerian study reported a rate of iron deficiency of 76% amongst pregnant women (Hassan *et al*, 2014). Anaemic mothers lack a reserve of blood to mitigate morbidity and mortality from PPH. Additionally, anaemia is associated with an increase in severity of PPH. One suggested explanation for this association is the loss of axial flow that occurs in anaemic patients, resulting in a dispersion of platelets and clotting factors away from the wall of the endothelium (Hunt, 2014).

If severe PPH does develop, international guidelines for best transfusion practice are based mainly on expert consensus and extrapolation of practice in managing bleeding in other areas, such as trauma. Low resource settings often lack robust laboratories, (Schroeder & Amukele, 2014) so that monitoring of coagulation may be slow, unreliable or even unavailable. The extent to which this impacts on maternal outcome is unknown, for there is little evidence that monitoring coagulopathy improves outcome. Many countries have no facilities to prepare specific blood components of plasma, platelets and cryoprecipitate, impairing their ability to correct haemostatic abnormalities in coagulopathic patients (Tapko *et al*, 2014), but again there is a lack of evidence that such practice in high income countries improves clinical outcome. Furthermore, the supply of safe blood for transfusion is often unpredictable and may be dependent on replacement or paid donors, with a concomitant increased risk of transmission of infections (Lund *et al*, 2013). We urgently need good quality trials to assess the utility of blood and blood components in PPH to inform both high- and low-income countries.

In many parts of the world, synthetic colloids are used to treat shocked, bleeding mothers. Colloid solutions, such as gelatin and hydroxyethyl starch (HES), came into popular usage as volume expanders in bleeding patients in developed countries. Since that time, they have been recognised to impair platelet and coagulation factor function, leading to an unstable clot which is very sensitive to fibrinolysis (Hartog *et al*, 2011), thus promoting bleeding. Whilst these concerns have led to a reduction in the use of synthetic colloids in the European Union, they are still widely promoted and used in less economically developed parts of the world (unpublished observations).

The combined effect of the issues highlighted above can create a perfect storm: overwhelmed obstetric services, anaemic and coagulopathic mothers, poor transfusion practice, and a dearth of safe blood for transfusion. The complexity and scale of this problem means that it will require prolonged and thoughtful investment to address fully. However, given the importance of each maternal death, simple and cost-effective interventions to reduce PPH mortality and morbidity are an important short-to-medium term goal. This review will focus on the potential of antifibrinolytic agents to contribute to this global health need.

Haemostatic changes and fibrinolysis in pregnancy

Pregnancy causes profound changes to the coagulation and fibrinolytic pathways. Increased levels of von-Willebrand factor promote platelet adhesion and activation. Fibrinogen, VII, VIII, IX, X and XII increase during pregnancy and reach their peak levels at term. Concurrently, there is a reduction in the circulating level of free Protein S, leading to a marked reduction in the activity of Protein C (Ku *et al*, 2003). The combined effect is enhanced coagulation and a reduction in endogenous anticoagulant activity (Lockwood, 2006). The thromboelastography (TEG) trace in pregnancy is different to that in non-pregnant women, reflecting underlying prothrombotic changes (Karlsson, 2017).

Maternal fibrinogen levels increase during pregnancy, as do the circulating levels of plasminogen activator inhibitor-1 and 2 (PAI-1 and PAI-2) (Kjellberg *et al*, 1999). The process of trophoblastic invasion into maternal vasculature presents a particular haemostatic challenge, reflected in further modifications at a decidual (uterine) level. There is significant upregulation of PAI-1 and PAI-2 on uterine cells, impairing local fibrinolysis (Lockwood, 2001). Furthermore, local haemostasis is promoted by the expression of large amounts of tissue factor on endometrial stromal cells (Brenner, 2004). Circulating thrombin activatable fibrinolysis inhibitor (TAFI) is also increased by the third trimester of pregnancy (Ku *et al*, 2003). Systemic levels of tissue plasminogen activator t-PA increase throughout pregnancy, but due to the increase in inhibitors of fibrinolysis, net t-PA activity decreases (Ishii *et al*, 1994). Whilst the sum of these changes suggest a pregnancy-associated reduction in fibrinolysis, this is a nuanced effect as plasminogen levels are increased, α_2-antiplasmin is decreased and there is evidence of increasing fibrinolytic activity demonstrated by a rise in circulating D-dimers throughout pregnancy (Holmes & Wallace, 2005).

What happens to fibrinolysis during PPH has been poorly studied (Fig 1). Levels of fibrin degradation products (FDP)

are raised in all women in the hours following delivery, but, as expected, this rise is several times higher in women with PPH (Bonnar *et al*, 1969). If women do bleed there is a relationship between fibrinogen levels and risk of mortality. A low fibrinogen level in women with PPH predicts increased blood loss and the need for interventions to stop genital tract bleeding more than other basic parameters of coagulation (Gayat *et al*, 2011; Cortet *et al*, 2012). After controlling for other risk factors, one study reported a 2·6-fold increase in severe PPH for every 1 g/l decrease of fibrinogen (Charbit *et al*, 2007). The mechanisms are not clear, but the low fibrinogen level may reflect the extent of bleeding in addition to exacerbating further blood loss. There has been little research into the pathogenesis of the fall in fibrinogen in PPH. However, studies in traumatic bleeding suggest a combination of fibrinogen consumption in clot formation, fibrinogen loss from bleeding, dilution from the use of volume replacement and fibrinogenolysis (Cap & Hunt, 2015).

Clinical evidence for antifibrinolytics in other situations of acquired coagulopathy

Fibrinolysis can be reduced by several different agents. Aprotinin is a serine protease inhibitor that acts directly on plasmin to reduce its activity. It was widely used in elective cardiac surgery but was withdrawn after the Blood conservation using Antifibinolytics in a Randomized Trial (BART) study reported an increased 30-day mortality of the aprotinin group compared to lysine analogue groups (6% vs. 4%) in the context of high-risk cardiac surgery (Fergusson *et al*, 2008).The European Medicines Agency subsequently reintroduced aprotinin after concluding that the BART study analysis was flawed, and it remains in use for coronary artery bypass grafting (Koster *et al*, 2015). However, it is a bovine product and therefore may cause allergy. This restricts its use in the emergency setting as a test dose is required, and it is expensive when compared to lysine analogies (Godier *et al*, 2017).

Lysine analogues act indirectly by blocking lysine residues on plasminogen, preventing binding to fibrin and thus activation to plasmin (Fig 2). Aminocaproic acid was the first lysine analogue to be used as an antifibrinolytic, but required large doses to be clinically effective, leading to gastro-intestinal side effects. It is used occasionally in elective surgery and traumatic hyphema but has generally been superseded. In 1962, the Japanese husband and wife team Shosuke and Utako Okamoto discovered a more potent lysine analogue, trans-4-aminomethyl-cyclohexane-carbonic acid, more commonly known as tranexamic acid (TxA) (Okamoto & Okamoto, 1962). Its use was initially directed at patients with inherited bleeding disorders and in treating menorrhagia, but the wider potential of TxA to reduce bleeding was developed first in cardiac surgery, after aprotinin was shown to reduce perioperative bleeding. Subsequently TxA has been shown in multiple clinical trials to be successful in reducing bleeding in many areas of surgery (Tengborn *et al*, 2015) and in trauma. Pharmacokinetic properties of these three most commonly used antifibrinolytic agents are compared in Table I.

The surge of interest in TxA in acute severe bleeding followed the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) study, which enrolled 20 211 trauma patients with or at risk of significant haemorrhage, who were within eight hours of their precipitating injury (CRASH-2 trial collaborators, 2010). Participants were randomised to receive either intravenous TxA or placebo. Patients receiving TxA within three hours of injury had significantly better outcomes, with approximately a one-third reduction in bleeding deaths, whereas there was no evidence of benefit in those treated beyond three hours. When considering all patients receiving TxA (at any time post-injury), the relative risk of bleeding death was 0·85 and there was a significant overall survival benefit [Risk ratio (RR) of death: 0·89] (CRASH-2 trial collaborators, 2010).

Prior to the trial there had been concerns that the use of TxA could lead to a higher risk of thrombotic events, but a pre-specified analysis of the data showed a surprising and

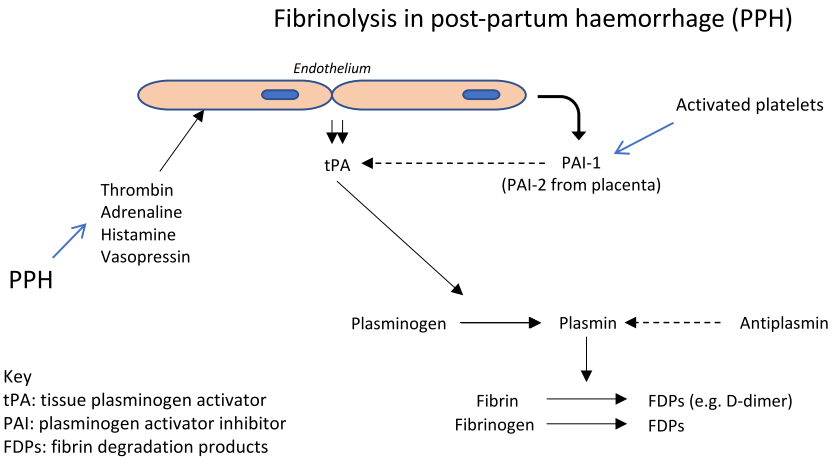

Fig 1. Proposed pathways of the changes of fibrinolysis in post-partum haemorrhage.

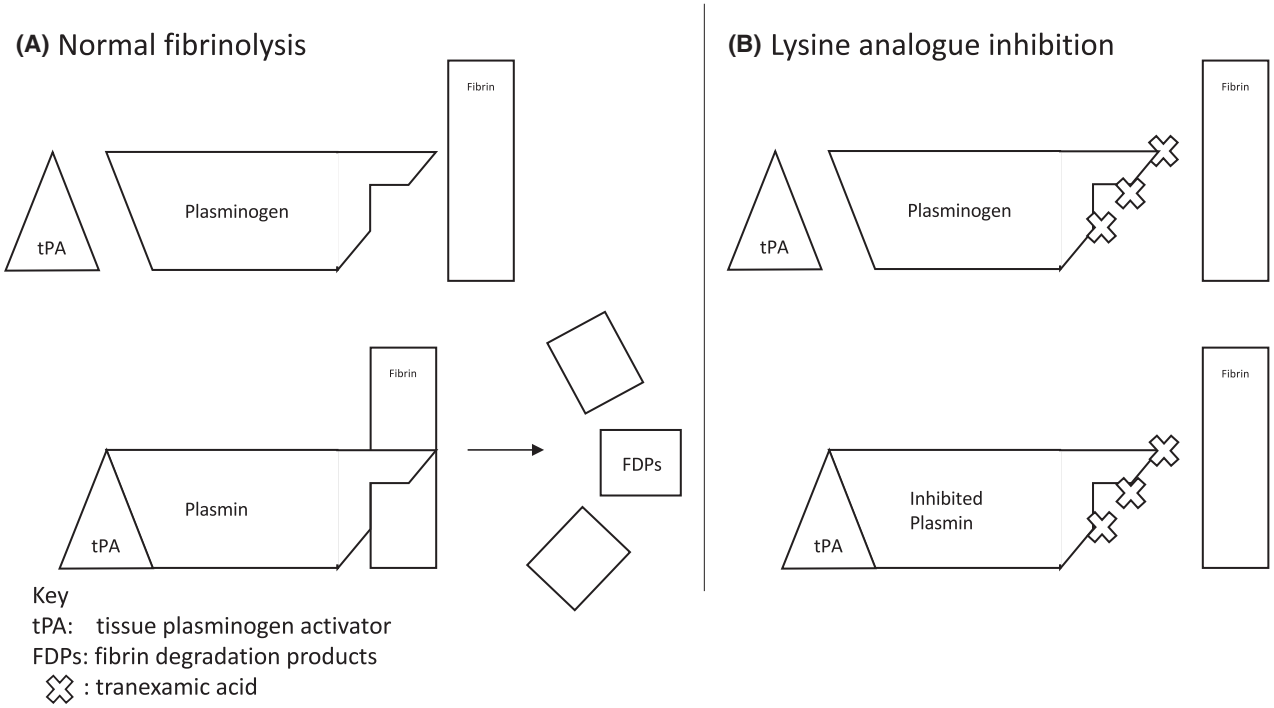

Fig 2. The effect of tranexamic acid inhibition of plasminogen.

significant reduction in arterial thrombosis in patients receiving TxA and no evidence of any increase in venous thromboembolism (CRASH-2 trial Collaborators 2010). Following publication of this study, the World Health Organisation (WHO) have included TxA on their list of essential medicines (WHO Expert Committee, 2011).

Although there is not a comparatively large single study in the context of elective surgery, a meta-analysis of over one hundred randomised controlled trials including 10 488 patients demonstrated that TxA reduces requirement for transfusion in elective surgery, although evidence for an effect on mortality is less certain (Ker *et al*, 2012). Subsequently, multiple analyses have shown that there is no evidence that TxA confers any increase in the risk of hospital-acquired venous thromboembolism. The UK's National Institute for Health and Care Excellence (NICE) have made usage of TxA in surgical patients at risk of moderate blood loss (500 ml or greater) a key quality standard (NICE, 2015). There are large ongoing trials assessing the impact of TxA in traumatic brain injury (the CRASH-3 study) and in upper gastro-intestinal bleeding (the HALT-IT study) (Dewan *et al*, 2012; Roberts *et al*, 2014).

Clinical evidence for antifibrinolytics in PPH

Given the efficacy of antifibrinolytic agents in other settings of acquired coagulopathy, several groups studied their use in preventing or treating PPH. The use of aminocaproic acid to avert emergency hysterectomy in severe PPH was reported as early as 1972 (Bowen-Simpkins, 1972). During the planning of the WOMAN study, a systematic review searched the literature up to 2008 for all randomised controlled trials in PPH comparing any antifibrinolytic agents to placebo or no treatment (Ferrer *et al*, 2009). Three trials were identified, for which the population was women with spontaneous vaginal delivery in one (Yang *et al*, 2001), and caesarean delivery in the others (Gai *et al*, 2004; Mayur *et al*, 2007). Each included a comparison of 1 g of intravenous TxA with a control group who did not receive any active agent. Pooling the results from these three studies estimated a reduction in blood loss of 92 ml (95% CI: 76–109 ml) in patients treated with TxA (Ferrer *et al*, 2009).

Notably, each of the studies gave TxA before or during birth (i.e. pre-emptively) and measured the impact of TxA on preventing PPH; there were no studies of the effect of TxA in treating established PPH. The methodological quality of all three studies was poor. Each suffered from inadequate allocation concealment, the lack of placebo, small sample size and short follow-up. These studies could not provide information on the impact of TxA on mortality, which had been the primary outcome of the review and the most important uncertainty to address (Ferrer *et al*, 2009).

The WOMAN Trial

This uncertainty led to the conception of the World Maternal Antifibrinolytic Trial Shakur *et al*, 2017). The aim of the trial was to ascertain whether TxA can reduce mortality, hysterectomy and other morbidities in women with established PPH. Given the high-risk of venous thromboembolism in the

Table I. Pharmacokinetic comparison of the three most widely used antifibrinolytic agents (https://www.medicines.org.uk/emc/, drugs.com)

	Aprotinin	Aminocaproic acid	Tranexamic acid
Mechanism	Serine protease inhibitor of plasmin, kallikrein and trypsin	Lysine analogue, blocks binding of plasminogen to fibrin	Lysine analogue, blocks binding of plasminogen to fibrin
Route(s) of administration	Intravenous, topical	Intravenous, oral, eyedrop	IIntravenous, oral, topical
Half-life (h)	0·5	2	3
Elimination	Predominantly proteolysis	Renal	Renal
Placental transfer	No data in humans	No data in humans	Similar concentration to plasma in cord blood
Breast milk concentration	No data in humans	No data in humans	1% of plasma concentration

post-partum period and that TxA passes into breast milk, the WOMAN trial also sought to establish whether TxA increased thromboembolic events in mothers or breastfed babies. As with the CRASH-2 trial, the WOMAN trial was designed to be applicable to all healthcare settings and the largest recruiting countries were Nigeria, Pakistan and Uganda. The biggest recruiter to the trial amongst high-income countries was the UK (Shakur *et al*, 2017).

Enrolment to the trial was designed to reflect real world practice: clinicians could only enrol patients if they were uncertain if TxA would be of benefit. If a clinician felt "reasonably certain" that TxA was indicated or contra-indicated, the patient was not eligible for the trial. The diagnosis of PPH was left to the recruiting doctors, but it was suggested that it would include blood loss of >500 ml following vaginal delivery, >1 litre following caesarean delivery, or blood loss leading to haemodynamic compromise. Patients randomised to the intervention received 1 g TxA intravenously as soon as possible, followed by a further 1 g of TxA if bleeding continued after 30 min or restarted within 24 h of the initial dose. The primary outcome was a composite of the proportion of women who died or who underwent a hysterectomy. The rationale for this was that the decision to perform a hysterectomy was made if bleeding continued after diagnosis of PPH and that this decision would be less likely if TxA reduced bleeding (Shakur *et al*, 2010).

The management of PPH varies from centre to centre and country to country, but by asking a simple question in very large numbers of patients, the effect of TxA could be detected despite this variability. Initial power calculations before the trial was commenced predicted that enrolment of 15 000 patients would be sufficient to show a significant difference in the primary endpoint. However, as the trial progressed, site monitoring observed that the decision to perform a hysterectomy often occurred prior to, or alongside, the administration of TxA or placebo. The impact of this timing would dilute the effect of TxA on the primary composite endpoint as the hysterectomy rate would remain constant. A recalculation of sample size based on mortality alone, given an observed death rate of 3%, led to an increase of the sample size from 15 000 to 20 000 patients (Shakur *et al*, 2016).

Of 20 021 women in the trial, 483 deaths occurred (2·4%). Patients receiving TxA had a significantly reduced risk of death from bleeding (RR 0·81) compared to those receiving placebo (Table II). There was no apparent reduction in the risk of hysterectomy or receipt of blood transfusion, probably reflecting the fact that during a severe PPH everything is done at the same time to save a mother's life. The timings of the decision to perform a hysterectomy (discussed above) and the decision to transfuse were usually prior to or concurrent with the administration of TxA. Lastly, there is the consideration that those who survived because they received TxA are alive to receive blood and other interventions.

The safety of TxA was a key outcome measure for the WOMAN trial. Many clinicians remain concerned that antifibrinolytic therapy could lead to an increase in thrombotic events, although there is no published evidence to support this concern. The WOMAN trial showed no difference in venous or arterial thromboembolic events in mothers between the two arms (Shakur *et al*, 2017). There were no

Table II. Results from the World Maternal Antifibrinolytic (WOMAN) study (Shakur *et al*, 2017).

	Tranexamic acid group	Placebo group	Relative risk (95% confidence interval)
Bleeding deaths	155/10,036 (1·5%)	191/9985 (1·9%)	0·81 (0·65–1·00)
Any cause deaths	227/10,036 (2·3%)	256/9985 (2·6%)	0·88 (0·74–1·05)
Bleeding deaths in those receiving treatment within 3 hours	89/7520 (1·2%)	127/7408 (1·7%)	0·69 (0·52–0·91)
Thromboembolic events	30/10,036 (0·3%)	34/9985 (0·3%)	0·88 (0·54–1·43)

Data extracted from: Shakur *et al* (2017). https://doi.org/10·1016/s0140-6736(17)30638-4. Published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

clinically apparent thromboembolic events in breastfed babies. In combination with the data from CRASH-2 showing a reduction in arterial thrombosis and no difference in venous thrombosis, a thrombotic concern for TxA is not warranted, at least at this dose and duration of treatment.

The results of CRASH-2 had shown that time from injury to TxA administration was a crucial effect modifier: those who received TxA within three hours of their injury received significant benefit whereas those who received it after three hours had poorer outcomes (Roberts *et al*, 2012). Similarly, in the WOMAN trial, patients receiving TxA within three hours of giving birth had the most marked reduction in bleeding deaths [89 deaths (1·2%) in the TxA group vs. 127 deaths (1·7%) in the placebo group, RR 0·69] (Shakur *et al*, 2017).

Remaining uncertainties

There are several questions that remain to be answered: clarifying the optimal dosage, whether oral TxA can be substituted for intravenous TxA, and whether TxA is safe and effective in a prophylactic setting. Answering these questions may help the findings of the WOMAN study to be implemented across the parts of the world where PPH mortality and morbidity are highest.

The WOMAN Trial used a dosage of 1 g ± 1 g of TxA based on previous trials in PPH and in other bleeding contexts (Shakur *et al*, 2010). However, a French study used a loading dose of 4 g TxA followed by an infusion of 1 g/h over six hours, demonstrating a reduction in blood loss and duration of bleeding (Ducloy-Bouthors *et al*, 2011). No adverse events at this higher dose were observed, although the study only included 144 women and was therefore underpowered to detect harms. The choice of such a high dose is controversial, as higher doses of TxA are associated with seizures (Kalavrouziotis *et al*, 2012), for some neurotransmitters have lysine binding sites. Prolonged exposure to higher doses of TxA in PPH patients has been associated with renal cortical necrosis (Frimat *et al*, 2016). The original studies of dose-response in cardiac surgery used D-dimer levels as a measure of fibrinolytic activity and did not detect any enhanced antifibrinolytic effect with doses of TxA above 10 mg/kg (Horrow *et al*, 1995). To maintain a similar dose across a feasible range of maternal weights, a standard loading dose of 1 g followed by a second 1 g was chosen for CRASH-2 and the WOMAN study. It is important to maintain a standardised dosing regimen as accurately measuring patient weight is unrealistic in many parts of the world (Shakur *et al*, 2010).

Although intravenous TxA is a relatively cheap medication, it may still be difficult to implement globally as it requires equipment and personnel to gain intravenous access. A pressing question is whether TxA or other antifibrinolytics can be effective as an oral preparation in the treatment of PPH. Not only would an oral preparation be cheaper, but it would circumvent delays in drug administration and be available even in a community setting, where the consequences of PPH are most severe.

Pharmacokinetic studies indicate that the oral bioavailability of TxA is around one-third, with peak plasma doses reached at around three hours after drug administration (Wellington & Wagstaff, 2003). Given the need for early (<3 h) administration of TxA highlighted in both the CRASH-2 and WOMAN trials, this delay in peak plasma concentration could be a significant limitation if the drug was administered once PPH was established. However, these pharmacokinetics may be acceptable if TxA is given during labour as a pre-emptive strategy to prevent PPH developing.

Given the importance of early administration, could TxA be as effective and safe if given at the time of delivery rather than waiting to see if PPH develops? Since the systematic review pre-dating the WOMAN trial, several other studies have examined the role of pre-emptive TxA in caesarean births (Sekhavat *et al*, 2009; Movafegh *et al*, 2011; Xu *et al*, 2013). These have consistently reported a reduction in blood loss, and have not shown any significant adverse effects. However, an updated systematic review in 2016 found mostly small and poor-quality studies, which were unable to clearly demonstrate a role for TxA in preventing PPH (Ker *et al*, 2016). Research priorities are to establish whether it is safe to the fetus for the mother to receive TxA prior to the cord being clamped; to assess whether pre-emptive TxA is cost-effective for resource-constrained systems and possibly to develop simple models to risk stratify which mothers will benefit most from TxA.

Another potential method of delivery is topical TxA. This has three theoretical advantages: faster bioavailability than oral TxA, no requirement for intravenous access, and a maximal concentration of antifibrinolytic effect to the site of bleeding. A precedent for its usage has been set in orthopaedic surgery, and a recent meta-analysis of trials in total knee arthroplasty found that topical TxA significantly reduced blood loss and transfusion rate (Chen *et al*, 2016). Careful thought is required of how topical TxA could be administered in either vaginal or Caesarean births, but there are case reports of innovations such as intrauterine balloon catheters impregnated in TxA-soaked gauze (Kinugasa *et al*, 2015).

Lastly, TEG is widely used to monitor haemostatic changes in bleeding patients, and preliminary work is exploring its use in PPH, although no algorithm has been validated in improving outcome. NICE have urged that further studies should be conducted in the management of PPH NICE, 2014). A major advantage of TEG is that, unlike standard coagulation assessment, it can detect fibrinolytic activation. However, it is a crude measure of fibrinolytic activation and a study in traumatic haemorrhage (Raza *et al*, 2013) has shown that it only detected the most severe cases of fibrinolytic activation. Thus, if one waited for TEG hyperfibrinolysis to occur before giving TxA, many patients who would benefit from TxA would be denied its use. We would

therefore urge those managing PPH not to use TEG to 'guide' the use of TxA, and is an affordable strategy in resource-limited settings.

Conclusions: moving from evidence to action

It is not enough simply to show that TxA is clinically effective in reducing bleeding deaths of PPH: this finding needs to be translated into implementation. Some of the most crucial questions are logistical ones. How will these findings be communicated to rural clinics in Sierra Leone, where more than one in 100 women will not survive birth? How can TxA be made consistently available in resource-poor settings which struggle to maintain a reliable supply of basic medicines? How can overstretched health systems deliver intravenous access and TxA administration within three hours of birth?

These questions require as much thought as addressing the scientific uncertainties of TxA, and they bring into sharp focus the importance of ascertaining the safety and effectiveness of oral and/or pre-emptive TxA. In the meantime, there should be no uncertainty about the pressing need to do all that we can to reduce maternal bleeding deaths globally. Whilst the tragic burden of maternal mortality cannot be fully addressed without major political and economic changes, there are elements that haematologists can and should address.

Author contributions

Beverley Hunt conceived the paper and wrote the first draft with Stephen Hibbs. Haleema Shakur and Ian Roberts provided extensive comments and editing. All agreed the final manuscript.

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