South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics

MEDICINE REVIEW:

1. Executive Summary

Date: 11 October 2017
Medicine (INN): Tranexamic acid, injection
Medicine (ATC): B02AA02
Indication (ICD10 code): Postpartum haemorrhage (O72.0-3)
Patient population: Pregnant women with post partum haemmhorhage (PPH)
Level of Care: Secondary level of care
Prescriber Level: Medical officer, doctor
NNT: 200 to prevent one maternal death from PPH (tranexamic acid vs. placebo)[1]
Current standard of Care: Tranexamic acid, injection recommended in cases not responding to oxytocin, ergometrine and dinoprost (secondary level of care).
Motivator/reviewer name(s): Dr E Bera
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2. Name of author(s)/motivator(s)

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3. Author affiliation and conflict of interest details

Dr E Bera: Department of Obstetrics & Gynaecology, University of the Witwatersrand; Adult Hospital Level Committee (2017-2020); No applicable conflicts of interest.

WOMAN TRIAL:TXA FOR PPH

The World Maternal aNtifibrinolytic (WOMAN) trial was an international randomized placebo-controlled trial, aimed at assessing the effects of early tranexamic acid (TXA) administration on death, hysterectomy, and other relevant endpoints among women with postpartum haemorrhage (PPH). Women who delivered vaginally (NVD) or by caesarean section (CS) were recruited from 21 countries over a 6 year period (2010-2016). Following the diagnosis of PPH they were randomised to either TXA 1g intravenously or placebo, in addition to standard care for PPH. The composite primary endpoint was all-cause mortality or hysterectomy.

Both investigators and participants were masked to treatment allocation. If the bleeding continued beyond 30 minutes, a 2nd dose of the study drug was given. Outcome data were collected until death, discharge, or 42 days post-delivery. The trial was sufficiently powered to detect a 25% reduction in death at a 5% significance level. Analysis was by intention-to-treat.

A total of 20 060 women were enrolled. Data were available for 10 036 (TXA) and 9 985 (placebo) women. There were 483 maternal deaths (2.4%); 77% of these deaths occurred within 24 hours of randomisation, and 9% occurred within an hour of randomisation.

TXA administered within 3 hours of PPH significantly reduced maternal deaths from PPH by 31% (1.2% vs. 1.7%): RR 0.69 (95% CI 0.52 to 0.91) regardless of the mode of delivery. Beyond 3 hours no significant difference in death was found between TXA and placebo (2.6% vs. 2.5%).

The effect of TXA was significant for PPH due to uterine atony (RR 0.74: 95% CI 0.55 to 0.99), but not significant for other causes of PPH (RR 0.90: 95% CI 0.66 to1.21) e.g. genital tract trauma.

A total of 709 women had hysterectomies, of which 86% were performed on the day of randomisation, and 27% within an hour of randomisation. Unsurprisingly, TXA had no effect on the rate of hysterectomy to control bleeding (2.8% vs. 3.0%; RR 0.95: 95% CI 0.81 to 1.12).

For women who required other surgical interventions to control bleeding, there was a significant reduction in laparotomy in the TXA arm (0.8% v s1.3%; RR 0.64: 95% CI 0.49 to 0.85).
Among the surgical interventions to control bleeding at laparotomy (uterine tamponade, brace sutures, systemic devascularisation, embolization), brace sutures were performed more frequently in the TXA arm (3.0% vs. 2.5%; RR 1.19: 95% CI 1.01 to 1.41).

Blood product transfusions were given to 54% of women in each group, and the mean number of blood products did not differ significantly between the 2 groups.

Secondary endpoints such as stroke, myocardial infarction and venous thromboembolism were uncommon (0.3%) and did not differ between the 2 groups.

Comments

This study took place in the UK as well as in a number of resource-poor countries, including Uganda, Pakistan, Cameroon, Nepal, Tanzania, Kenya, Ethiopia, Ghana, Burkina Faso, Sudan, Albania, Zambia, Jamaica, Egypt, Cote d'Ivoire, Bangladesh and Nigeria.[1]

The case fatality rate for PPH in this study population was 2.4% (240 per 10 000 PPH cases). This rate is considerably higher than the reported case fatality rates in the literature of 10 per 10 000 from developing countries.[2] In the most recent South African Saving Mothers' Report (2011-2013) the case fatality rates for PPH were 1.1 and 3.3 per 10 000 births following NVD and CS, respectively.[3]

Case fatality rates for PPH vary considerably by geographic region and may be a reflection of the availability of resources (uterotonics, theatres), local expertise (skilled surgeons), or the severity of PPH at presentation. It is conceivable that the number needed to treat (NNT) to prevent one death from PPH in this study, may not be generalisable to South Africa.

The investigators used results from the CRASH-2 study[4] to justify their rationale for this study, yet physiological coagulation at delivery and pathological fibrinolysis at trauma are different processes, albeit with some overlapping mechanisms.

The reduction in deaths was significant in the subgroup of women with PPH due to uterine atony, and not from other causes of PPH (e.g. trauma); which is at variance with the results from the CRASH-2 study, where trauma patients were enrolled.[4]

Of the 709 women who had hysterectomies, 191 women (27%) had a hysterectomy performed within one hour of randomisation. The effect of TXA on the need for hysterectomy would likely have been impossible to ascertain. It is plausible that these women were either randomised too late in the cascade of treating PPH, or that TXA administration may not have had any impact on the need for hysterectomy among these women.

There were 66 cases of thromboembolic events reported (0.3%). This study may have been underpowered to detect in a significant difference in thromboembolism between TXA and placebo.

Notwithstanding the limitations of this study, TXA should be included in the algorithm for the treatment of PPH in our setting.

Primary level of care

Currently, TXA IV is included in the Adult Hospital Level EML. If the medicine is be made available to midwives at primary health care there would be additional training and budgetary implications. However,

midwives do have access to oxytocin and ergometrine for postpartum care at primary level of care.

The Savings Mothers Report on confidential enquiries into maternal deaths in South Africa for the period 2011-2013 reported 684 maternal deaths were caused by obstetric haemorrhage (contributed 15.79% to total maternal deaths).[5] Two percent of these cases were reported to have occurred at primary level of care, whilst 36.7% deaths were reported from district level of care. The Primary Health Care Guidelines recommend that where blood loss is greater than 500 mL within 24 hours of birth, oxytocin/ergometrine to be administered with up-referral of all cases of post-partum haemorrhage to secondary level of care.

Both the CRASH-2 and the WOMAN studies showed a mortality benefit if TXA IV was administered within 3 hours of trauma or PPH. The WOMAN trial showed no additional benefit if TXA, IV was administered to women with PPH due to uterine atony beyond 3 hours. From a pragmatic perspective, early access to TXA IV at primary level of care may be beneficial due to the quick onset and severity of PPH and early administration of TXA, once it is clear that there has been no response to initial oxytocin/ergometrine treatment. Access to TXA at midwife obstetric units (MOUs) may reduce referrals for PPH up to a higher level of care. Furthermore, there may be considerable delay in transferring women with PPH from an MOU to a higher level of care, either due to the long distance to the nearest hospital, or from the delay awaiting arrival of emergency medical services (EMS) at the MOU. Availability of TXA at MOUs would necessitate some additional training of midwives in its administration.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [X] Not confident: [ ] Uncertain: [ ]	See above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [X]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [X] List the members of the group: n/a List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: n/a References: n/a Rationale for exclusion from the group: n/a References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [X] Uncertain: [ ]	Price of medicines: **Medicine** | **Cost (ZAR)*** Tranexamic acid, 100 mg/ml, 5 mL | @ 376.00 per unit Thus, treatment cost of 1 g, IV = 752.00 *Contract circular RT297-2019 **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	[ ]	[ ]	[ ]	[ ]

Recommendation: Based on this evidence review, the Adult Hospital Level Commitee recommends that the current treatment algorithm for PPH with TXA after oxytocinin and ergometrine be retained in the STG.
Rationale: RCT designed not to compare TXA to current standard of care, rather as add on therapy. i.e. failed first line. RCT recommendations are aligned with current PPH algorithm recommendations and it is noted that tranexamic acid should be given within three hours after bleeding onset
Level of Evidence: I RCT

NEMLC Recommendation: The NEMLC did not accept the Adult Hospital Level Committee recommendation to include TXA IV on the primary health care EML. (However, inclusion on the Adult Hospital Level EML was accepted).

Rationale:

- **"The composite primary endpoint of death from all causes or hysterectomy was not reduced with tranexamic acid (534 [5·3%] deaths or hysterectomies in the tranexamic acid group vs 546 [5·5%] in the placebo group, RR 0·97, 95% CI 0·87-1·09; p=0·65)"; statistically not significant. Death due to bleeding where tranexamic acid was administered within 3 hours of birth was a secondary endpoint. The effect size was small: ARR of 0.5% with NNT of 200 (1.2% in the tranexamic acid group vs 1.7% in the placebo group).**
- **Generalisability of the results of the WOMANS Trial to the local primary health care setting was not possible, as the trial was done in an emergency hospital setting.**
- **Referral to higher level of care for appropiate management from primary level may be delayed.**

Level of Evidence: I RCT

Review indicator: Evidence of efficacy and safety in the primary care setting.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		

VEN status:

Vital	Essential	Necessary
X		

Monitoring and evaluation considerations

Research priorities: Evidence of efficacy and safety of TXA for PPH be in the primary care setting

References

1. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017; 6736(17)30638-4.
2. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2014 Feb 13;(2):CD003249.
3. Pattinson RC ed. Saving Mothers 2011-2013:The Sixth Report of the National Committee for Confidential Enquiries into Maternal Deaths in South Africa. Pretoria: Government Printer, 2014.
4. CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised placebo-controlled trial. Lancet 2010; 376: 23-32.
5. National Department of Health: National Committee for the Confidential Enquiries into Maternal Deaths Saving Mothers Report, 2011-2013.