Tranexamic acid

Statut de médicament essentiel ✓

Section: 22. Medicines for reproductive health and perinatal care > 22.5. Other medicines administered to the mother

Codes ATC: B02AA02

Indication	Postpartum haemorrhage Code ICD11: JA43.Z
INN	Tranexamic acid
Type de médicament	Chemical agent
Type de liste	Liste de base
Formulations	Parenteral > General injections > IV: 100 mg per mL in 10 mL ampoule
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Féminin
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Tranexamic acid
DrugBank	Tranexamic acid

Recommandation du comité d'experts

The Committee recommended listing of tranexamic acid (TXA) intravenous injection on the core list of the EML for the new indication of treatment of postpartum haemorrhage. While the evidence presented in the application supporting the effectiveness of TXA for this indication was limited and came primarily from a single trial, the Committee considered there was benefit associated with the use of TXA in addition to standard care, when administered within three hours of childbirth. The Committee also considered that the use of different medicines with different pharmacological mechanisms of action may be useful in the management of PPH. The Committee noted that there did not appear to be significant harms or adverse events associated with use of TXA in mothers or newborns, but that evidence was limited. The committee considered that further evidence of safety would be desirable.

Contexte

The application requested inclusion of tranexamic acid (TXA) on the core list of the EML for the new indication of treatment of postpartum haemorrhage. Tranexamic acid (TXA) had not previously been considered for inclusion on the EML for the treatment of postpartum haemorrhage. In 2009, an application requesting EML listing of TXA to reduce blood loss during cardiac surgery was rejected as the indication was considered to be of uncertain public health relevance (1). Tranexamic acid was recommended for inclusion on the EML in 2011 for treatment of adult patients with trauma and significant risk of ongoing haemorrhage (2).

Pertinence pour la santé publique

Postpartum haemorrhage (PPH) is defined as blood loss of 500 mL or more within 24 hours after birth. Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries, it is the main cause of maternal mortality (3). Improving health care for women during childbirth to prevent and treat PPH is a necessary step towards achievement of the health targets of the Sustainable Development Goals.

Bénéfices

The application presented the findings of a Cochrane systematic review on antifibrinolytic drugs for treating primary PPH (4) that included two trials: WOMAN and Ducloy-Bouthors (5, 6), and GRADE tables extracted from the WHO recommendation on tranexamic acid for the treatment of PPH (7). For the comparison of TXA (plus standard care) versus standard care alone, there was moderate certainty evidence that TXA was associated with slightly reduced all cause maternal mortality (RR 0.88, 95%CI 0.74 to 1.05, not statistically significant) and maternal mortality due to PPH (RR 0.81. 95%CI 0.65 to 1.00). For maternal morbidity outcomes, moderate certainty evidence suggested little or no difference between treatment groups for any outcomes reported (respiratory failure: RR 0.87, 95%CI 0.67 to 1.12; seizure: two studies; RR 0.76, 95%CI 0.49 to 1.20; hepatic failure RR 0.96, 95%CI 0.58 to 1.60; cardiac failure: RR 0.95, 95%CI 0.73 to 1.23; renal failure: two studies; RR 1.09, 95%CI 0.85 to 1.39). Moderate certainty evidence suggests little or no difference between treatment groups for transfusion of blood products, with more than half of the women in both arms of the WOMAN trial receiving a transfusion (two studies; RR 1.00, 95%CI 0.97 to 1.03). Ducloy-Bouthors 2011 reported additional blood loss > 500 mL or > 1000 mL. Low quality evidence suggests TXA probably reduces blood loss > 500 mL (RR 0.50, 95%CI 0.27 to 0.93, 151 women). Although the direction of effect was the same for loss > 1000 ml, the study was insufficiently powered to demonstrate a difference between groups (4/77 women versus 8/74). There was high certainty evidence of no difference between treatment groups in the use of additional uterotonics (99.3% vs 99.1%, two studies; RR 1.00, 95%CI 1.0 to 1.0). High or moderate certainty evidence suggests there is probably little difference between treatment groups for most surgical interventions to control bleeding (hysterectomy (all): two studies; RR 1.01, 95%CI 0.88 to 1.17; ligature: RR 0.88, 95%CI 0.74 to 1.05; embolization: RR 0.82, 95%CI 0.42 to 1.62). High certainty evidence suggests laparotomy to control bleeding is reduced for women in the TXA group (0.8% vs 1.3%) (RR 0.64, 95%CI 0.49 to 0.85) while brace sutures are increased (RR 1.19, 95%CI 1.01 to 1.41). High certainty evidence suggests there is probably little or no difference in intrauterine tamponade (one study; RR 0.96, 95%CI 0.87 to 1.06) or manual removal of placenta: (one study; RR 0.95, 95%CI 0.87 to 1.04). Sub-group analysis examining treatment effect by mode of birth (vaginal or caesarean) suggests no clear difference in effect on maternal death (all causes) and maternal death due to PPH for type of birth (moderate certainty evidence). A sub-group analysis of the WOMAN trial investigated the effects of timing of TXA administration. There was a reduced risk of maternal mortality due to bleeding in women given TXA within three hours of delivery (RR 0·69, 95%CI 0·52 to 0·91; p=0·008) compared with women given TXA more than three hours after delivery (RR 1·07, 95%CI 0·76 to 1·51; p=0·70). Compared to the control group, women who received TXA within one hour of delivery had a similar risk of death (any cause) (RR 0.98, 95%CI 0.72 to 1.33), as did women receiving TXA more than three hours after delivery (RR 1.00, 95%CI 0.75 to 1.33). However, women receiving TXA between one and three hours after delivery were at reduced risk of death from all causes (RR 0.69, 95%CI 0.49 to 0.96). There were similar findings for the composite outcome of death or hysterectomy: within one hour (RR 1.08, 95%CI 0.91 to 1.28), more than three hours (RR 1.01, 95%CI 0.82 to 1.25) and between one and three hours (RR 0.80, 95%CI 0.63 to 1.00). Compared to the control group, women receiving TXA within one hour of delivery had reduced risk of laparotomy for bleeding (RR 0.48, 95%CI 0.29 to 0.79), as did women receiving TXA at one to three hours after birth (RR 0.54, 95%CI 0.31 to 0.95). Women receiving TXA more than three hours after birth were not at reduced risk of laparotomy for bleeding (RR 0.89, 95%CI 0.59 to 1.35). In summary, there is evidence that TXA is associated with benefits in reducing maternal deaths due to bleeding and reducing the need for laparotomy to stop bleeding. Treatment within three hours of delivery appears to optimize benefits.

Torts

The application presented the findings of a Cochrane systematic review on antifibrinolytic drugs for treating primary PPH (4) which included two trials – WOMAN and Ducloy-Bouthors (5, 6), and GRADE tables extracted from the WHO recommendation on tranexamic acid for the treatment of PPH (7). Moderate certainty evidence suggests there is probably little or no difference between treatment groups for thromboembolic events (any maternal thromboembolic event: RR 0.88, 95%CI 0.54 to 1.43; deep venous thrombosis: two studies; RR 0.62, 95%CI 0.20 to 1.88; pulmonary embolism RR 0.85, 95%CI 0.44 to 1.61; myocardial infarction: RR 0.66, 95%CI 0.11 to 3.97; stroke: RR 1.33, 95%CI 0.46 to 3.82). Available neonatal outcome data were limited (data from WOMAN trial only). There were no neonatal thromboembolic events and no clear differences in deaths in breastfed neonates (eight deaths with TXA vs seven deaths with placebo) in the WOMAN trial. Available data on longer-term outcomes was limited (data from the WOMAN trial only). Outcomes in the WOMAN trial were measured up to hospital discharge or 42 days if still in hospital. There was no information on longer-term outcomes in women or babies. On balance, there does not appear to be evidence of maternal or newborn harms, or significant side-effects. While no difference in newborn thromboembolic events were seen, in the

WOMAN trial most women and babies were followed until discharge from the health facility, thus this evidence is more likely representative of the first few days after birth.

Preuves supplémentaires

N/A

Rapport coût/efficacité

Research evidence on cost-effectiveness of TXA can be extrapolated from cost-effectiveness analysis of TXA for bleeding trauma patients (9). The study found that administering TXA to bleeding trauma patients within three hours of injury saved an estimated 372, 315 and 755 life-years (LYs) per 1 000 trauma patients in Tanzania, India and the United Kingdom respectively. The cost of giving TXA to 1000 patients was US$ 17 483 in Tanzania, US$ 19 550 in India and US$ 30 830 in the UK. The incremental cost of giving TXA versus not giving TXA was US$ 18 025 in Tanzania, US$ 20 670 in India and US$ 48 002 in the United Kingdom. The estimated incremental cost per LY gained of administering TXA is US$ 48, US$ 66 and US$ 64 in Tanzania, India and the United Kingdom respectively. Early administration of TXA to bleeding trauma patients is likely to be highly cost effective in low-, middle- and high-income settings. The cost of TXA varied between settings, with an approximated range of US$ 1.00 to US$ 5.70 per gram. The use of TXA may also reduce subsequent costs related to surgical procedures for PPH treatment (such as laparotomy) as well as any complications associated with surgery. Out-of-pocket costs to individual women might be higher when TXA is added to standard care for PPH in settings where women incur financial costs for birth.

Directives de l'OMS

In 2012, WHO published 32 recommendations for the prevention and treatment of PPH, including a weak recommendation on the use of TXA for treatment of PPH if oxytocin and other uterotonics fail to stop bleeding of if it is thought that bleeding may be partly due to trauma (8). In 2017, in response to important new evidence, the existing WHO recommendation on the use of TXA for PPH treatment was updated to recommend early use of intravenous TXA within three hours of birth in addition to standard care for women with clinically diagnosed PPH following vaginal birth or caesarean section (strong recommendation, moderate quality of evidence) (7). In making this updated recommendation, the Guideline Development Group (GDG) also made the following remarks (7): “Based on the dosing regimen used in the WOMAN trial, the GDG supports the administration of tranexamic acid (TXA) at a fixed dose of 1 g (100 mg/mL) intravenously (IV) at 1 mL per minute (i.e. administered over 10 minutes), with a second dose of 1 g IV if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose. The WOMAN trial defined “clinically diagnosed postpartum haemorrhage” as clinically estimated blood loss of more than 500 mL after a vaginal birth or 1000 mL after caesarean section, or any blood loss sufficient to compromise haemodynamic stability. Based on evidence from the WOMAN trial, the reference point for the start of the 3-hour window for starting TXA administration is time of birth. If time of birth is unknown, the best estimate of time of birth should be used as the reference point. As most deaths due to PPH occur within the first 2 to 3 hours after birth, it is critical that TXA is given as soon as possible to achieve clinical benefits. Analysis of the effects of timing of administration in the WOMAN trial, as well as an individual patient data (IPD) meta-analysis of 40 138 bleeding patients (including WOMAN trial participants), indicates that TXA administration beyond 3 hours does not confer any clinical benefit. Furthermore, the point estimates of effect of TXA use beyond 3 hours on death for trauma or after PPH were both in the direction of harm, albeit not statistically significant for women with PPH. In view of this evidence, the GDG does not support the use of TXA more than 3 hours after birth. Administration of TXA should be considered as part of the standard PPH treatment package. Standard care in the context of this recommendation includes routine care for PPH treatment, including fluid replacement, medical (uterotonics), monitoring of vital sighs, nonsurgical (e.g. bimanual compression, intrauterine balloon tamponade, nonpneumatic antishock garment, aortic compression) and surgical interventions (e.t., brace sutures, arterial ligation, or hysterectomy) in accordance with WHO guidelines or adapted local PPH treatment protocols. TXA should be used in all cases of PPH, regardless of whether the bleeding is due to genital tract trauma or other causes. The use of TXA should be avoided in women with a clear contraindication to antifibrinolytic therapy (including TXA) (e.g. a known thromboembolic event during pregnancy). This recommendation applies only to IV use. The evaluation of benefits and potential harms of other routes of TXA administration is a research priority. Regardless of the level of health system resources, TXA should be recognized as a life-saving intervention and be made readily available for the management of PPH in settings where emergency obstetric care is provided.”

Disponibilité

Tranexamic acid 100 mg/mL injection is available from multiple generic manufacturers.

Autres considérations

N/A

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 958). Geneva: World Health Organization; 2009. Available from https://apps.who.int/iris/bitstream/handle/10665/44287/WHO_TRS_958_eng.pdf, accessed 30 October 2019.
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2011 (including the 17th WHO Model List of Essential Medicines and the 3rd WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 965). Geneva: World Health Organization; 2012. Available from https://apps.who.int/iris/bitstream/handle/10665/44771/WHO_TRS_965_eng.pdf, accessed 30 October 2019.
3. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J et al. Global causes of maternal death: a WHO systematic analysis. ance t Globl Health. 2014;2(6):e323–33.
4. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2018;2:CD012964.
5. 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;389(10084):2105–16.
6. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117.
7. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. Geneva: World Health Organization; 2017. Available from https://www.who.int/reproductivehealth/publications/tranexamic-acid-pph-treatment/en/, accessed 30 October 2019.
8. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2012. Available from https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/, accessed 30 October 2019.
9. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. PLoS One. 2011;6(5):e18987.