Recognition and management of persistent postpartum haemorrhage: Time to take timing seriously

Henriquez, D.D.C.A.

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The best timing of tranexamic acid administration for bleeding after trauma or childbirth remains to be established

Dacia D.C.A. Henriquez, Johanna G. van der Bom

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Haemorrhage is worldwide the leading cause of maternal death[1] and an important cause of death after trauma.[2] Antifibrinolytic drugs inhibit the lysis of a fibrin clot and are, therefore, used to stop or prevent haemorrhage. Intravenous administration of tranexamic acid has been shown to reduce the risk of death due to haemorrhage after trauma[3] and the risk of death due to postpartum haemorrhage.[4] Previous analyses have suggested that tranexamic acid needs to be administered early after the start of haemorrhage, because effects of delayed administration might be absent or even harmful for patients suffering life-threatening bleeding.[3,4] A recent systematic review and meta-analysis was set up to quantify the effect of treatment delay on the effectiveness of antifibrinolytics.[5]

This individual patient-level data meta-analysis included randomized placebo-controlled trials (RCT) with more than 1000 patients with traumatic or postpartum haemorrhage. The primary measure of treatment benefit was absence of death from bleeding. “Treatment delay” was defined as the interval between bleeding onset and start of tranexamic acid treatment, or, if not available, as interval between birth and randomisation. The association between “treatment delay” and treatment effect was examined in logistic regression models with adjustment for the confounders age and systolic blood pressure, and with and without various interaction terms for treatment and “treatment delay”, for treatment and study, for “treatment delay” and study. The protocol was registered with PROSPERO. The review clearly stated the question being addressed, the search strategy, study selection, assessment of study quality, data extraction and synthesis and it adhered to the recognised protocols for systematic reviews and meta-analysis from The Cochrane Collaboration and PRISMA.

Two RCTs were analysed: the CRASH2 trial reporting on 20 211 bleeding trauma patients,[3] and the WOMAN trial reporting on 20 060 women with postpartum haemorrhage.[4] Any cause of death and death due to haemorrhage occurred in 15.2% and 5.3% in the CRASH2 and 2.4% and 1.7% in the WOMAN trial. The numbers needed to treat to prevent one death due to haemorrhage

were 125 and 250 for patients with trauma and postpartum haemorrhage respectively. The odds for absence of death due to bleeding among patients treated with tranexamic acid compared to placebo was 1.7 among patients who had received tranexamic acid during the first hour of bleeding, and it was lower among patients who had been treated later.

Unfortunately, this analysis does not address the question whether tranexamic acid should be administered soon after the start of the bleeding or whether its administration might as well be postponed. What these findings do describe, is the effect of treatment among patients who were treated early, and the effect of treatment among patients who were treated later. However, the effect of late treatment among patients who were treated early, and vice versa, the effect of early treatment among patients who were treated late were not studied.

Patients who were treated early with tranexamic acid may have differed for several reasons from those who were treated late. Reasons for postponing randomization (and administration of tranexamic acid) may have been: less severe bleeding, or conversely, more severe bleeding and thus no time to include into trial, the clinical impression that the bleeding is about to stop or that haemorrhage can be stopped with other interventions than tranexamic acid. All these time-dependent factors influence the time-dependent effects of treatment, and, therefore, also the findings.

The authors attempted to correct for this time-dependent confounding by adjustments for age and blood pressure at inclusion. But in a bleeding patient, severity of bleeding and its proxies such as systolic blood pressure change constantly. So, adjustment for severity of bleeding only at baseline does not suffice; the results are biased by time-dependent confounding. A future study could randomize patients to different treatment delays in a multi-arm trial, or carefully measure and adjust for time-dependent confounders.[6,7]

Implications for practice

It is tempting to conclude from these findings that all patients with severe

acute haemorrhage need to be treated as soon as possible after the start of the haemorrhage, and that treatment three hours after the start of bleeding should be avoided, but this conclusion is not supported by these findings. These findings show that the effect of tranexamic acid differs in subgroups of patients who were treated at different times after the start of bleeding. Future research should examine the underlying clinical characteristics that determine whether and when a patient with severe bleeding would benefit from treatment with tranexamic acid.

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References

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet Global health 2014;2:e323-33.

2. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. Jama 2015;313:471-82.

3. Shakur H, Roberts I, Bautista R, et al. 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 (London, England) 2010;376:23-32.

4. 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 (London, England) 2017;389:2105-16.

5. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron FX, Roberts I. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet (London, England) 2018;391:125-32.

6. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology (Cambridge, Mass) 2000;11:550-60.

7. Lu B. Propensity score matching with time-dependent covariates. Biometrics 2005;61:721-8.