Gayet-Ageron A, Preito-Merino D, Ker K, Shakur H, Ageron, FX, Roberts I. *Lancet*. 2018;391:125-32

Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe hemorrhage: a meta-analysis of individual patient-level data from 40,138 bleeding patients

Individual patient-level meta-analysis of randomized trials

Objective

- To quantify the effect of treatment delay on the effectiveness of antifibrinolytics in acute severe bleeding and whether this varies by site of bleeding

Acute severe bleeding is a leading cause of death, whether from traumatic extracranial hemorrhage, traumatic and spontaneous intracranial bleeding, severe surgical hemorrhage, gastrointestinal bleeding, or post-partum hemorrhage. Antifibrinolytic drugs (e.g., tranexamic acid, aminocaproic acid, aprotinin, and aminomethylbenzoic acid) reduce bleeding by inhibiting the breakdown of fibrin clots and can reduce surgical bleeding and the need for transfusion. The main effect of the antifibrinolytic drug tranexamic acid is a reduced risk of exsanguination on the day of injury.

The authors aimed to quantify the effect of treatment delay on the effectiveness of antifibrinolytics in acute severe bleeding and whether this varies by site of bleeding, which has not been previously examined. Individual patient-level data were analyzed from randomized placebo-controlled trials of more than 1,000 patients conducted between January 1, 1946 and April 7, 2017 that assessed the effects of antifibrinolytics in acute severe bleeding. Systematic searches of the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, PubMed, Popline, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov were conducted. For each trial, the reviewers rated the risk of bias and estimated treatment delay from the interval between bleeding onset and start of antifibrinolytic treatment.

The authors analyzed data for baseline, outcome, and predictor variables. The primary measure outcome was the absence of death from bleeding. Secondary outcomes were vascular occlusive fatal and non-fatal events. The effectiveness of antifibrinolytics on binary outcomes was examined using logistic regression and the effect of antifibrinolytics on survival was expressed as the odds ratio (OR) for absence of death from bleeding. All models were controlled for systolic blood pressure and age.

Three completed and nine ongoing trials were identified in the search. Of the completed trials, two allowed assessment of the effect of treatment delay. The CRASH-2 trial assessed the effect of tranexamic acid on death and vascular occlusive events in 20,211 bleeding trauma patients and the WOMAN trial assessed the effects of tranexamic acid on death, hysterectomy, and other morbidities in 20,060 women with post-partum hemorrhage. Individual patient-level data were obtained for 40,138 participants of these trials, of which 20,094 received tranexamic acid and 20,044 received placebo. Of the 3,558 deaths, 1,408 (40%) were due to bleeding, of which 884 (63%) occurred within 12 hours of bleeding onset.

Tranexamic acid significantly increased overall survival from bleeding (OR=1.20, 95% CI: 1.08-1.33; P=0.001). With the exception of the first hour, effectiveness decreased with time delays (P<0.0001 for the trend of increasing benefit with earlier treatment). When given immediately, tranexamic acid significantly improved survival (OR=1.72, 95% CI: 1.42-2.10; P<0.0001), but the benefit decreased with increasing delay in a non-linear association. The logistic regression model showed that the treatment benefit decreased by 10% for every 15 minutes of treatment delay, until 3 hours, after which there was no benefit. The risk of vascular occlusive events was higher in patients with traumatic bleeding than in those with post-partum hemorrhage. There was no increase in fatal vascular occlusive events with tranexamic acid (OR=0.73, 95% CI: 0.49-1.09; P=0.1204). Lastly, there were fewer cases of myocardial infarction (mostly reported in CRASH-2) with tranexamic acid (OR=0.64, 95% CI: 0.43-0.97; P=0·0371).

Most deaths from bleeding occur on the day of onset and many occur within the first few hours. Deaths from post-partum hemorrhage peak at 2 to 3 hours after childbirth. Tranexamic acid improves survival, but treatment delay reduces the benefit. The authors found no increase in vascular occlusive events with tranexamic acid. Study limitations included:

(1) The fact that time of death was only available for post-partum hemorrhage

(2) Treatment delay might be underestimated in trauma, since many injuries are unwitnessed, and it might have been over-estimated in post-partum hemorrhage

(3) Deaths due to bleeding and deaths from vascular occlusive events could have been misclassified

Sensitivity analyses, with a range of plausible errors, supported the conclusion that prompt treatment is essential. Several hypotheses have been proposed for why this effect is observed, such as the expectation that there will be some time lag between administration of tranexamic acid and its effect on mortality. Alternatively, early tranexamic acid treatment should protect fibrinogen stores thus ensuring sufficient fibrinogen concentrations to form a stable clot. The authors suggest that perhaps tranexamic acid should be considered as an intervention to prevent rather than treat coagulopathy.

Bleeding patients should receive antifibrinolytics as soon as possible for the following reasons:

(1) Most deaths from hemorrhage occur within hours of bleeding onset

(2) Benefits of tranexamic acid treatment appears to decrease with time

(3) Tranexamic acid can be safely as administered once bleeding is suspected

The authors conclude that patients with acute severe bleeding should receive antifibrinolytic treatment as soon as possible after bleeding onset. Trauma patients should be treated at the scene of injury and post-partum hemorrhage should be treated as soon as the diagnosis is made.

Conclusions

The authors concluded that:

- Treatment delay reduces the survival benefit of tranexamic acid administration
- The benefit of treatment decreases by about 10% for every 15 minutes of treatment delay until 3 hours, after which there is no benefit
- Patients with acute severe bleeding should receive anti-fibrinolytic treatment as soon as possible after bleeding onset
- Trauma patients should be treated at the scene of injury
- Post-partum hemorrhage should be treated as soon as the diagnosis is made

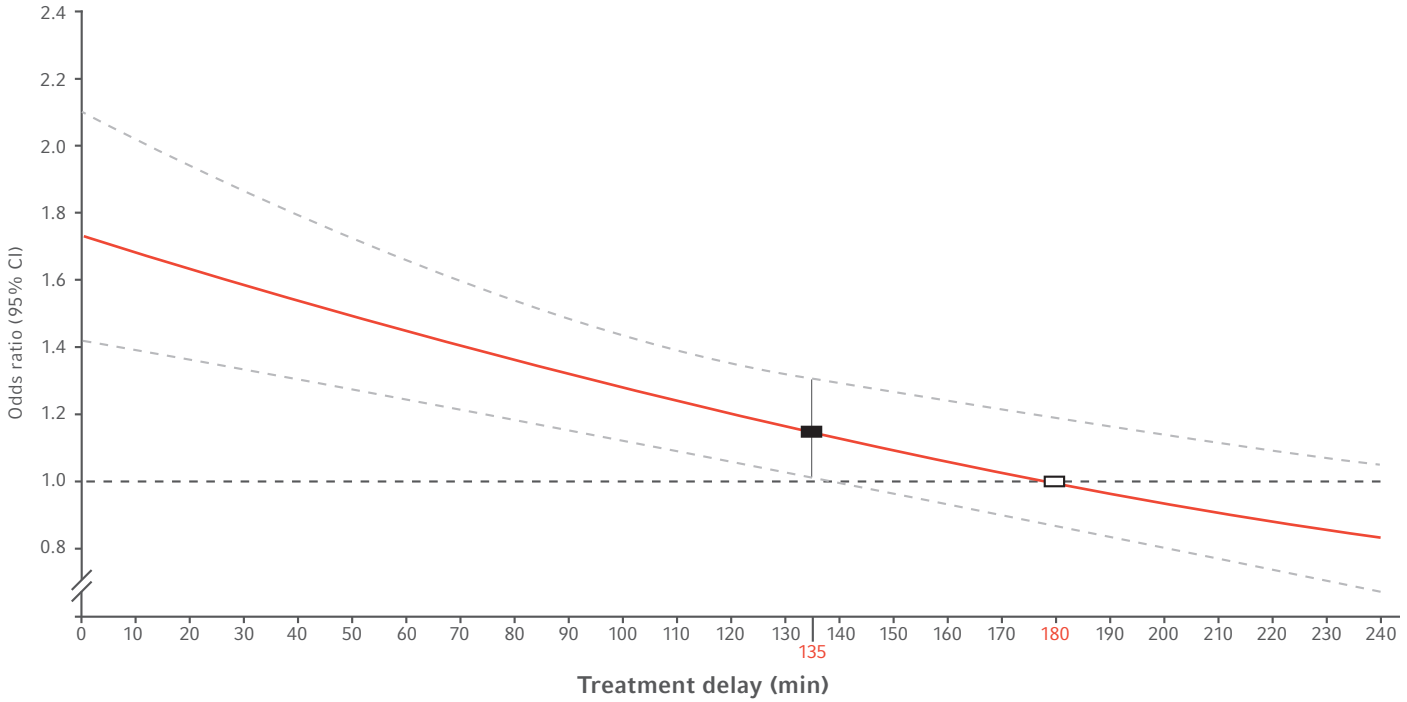

Figure 3: Effect of treatment delay on treatment benefit (model 3)
The red line shows the best fitted model for the association between the protective effect of tranexamic acid (odds ratio for not dying from bleeding) and duration of treatment delay in minutes (p_{slope}<0·0001). The grey lines are the lower and upper bounds of the 95% CI for this model. Estimates are derived from a logistic regression model of not dying from bleeding explained by the interaction of getting tranexamic acid and treatment delay (linear and squared terms) and adjusted for trial, age (5-year intervals), and systolic blood pressure (10-mm Hg intervals). The white square shows the timepoint at which the model estimates a null effect of tranexamic acid (a treatment delay of 180 min). The black square shows the timepoint at which the lower 95% CI model estimates a null effect of tranexamic acid (a treatment delay of 135 min).

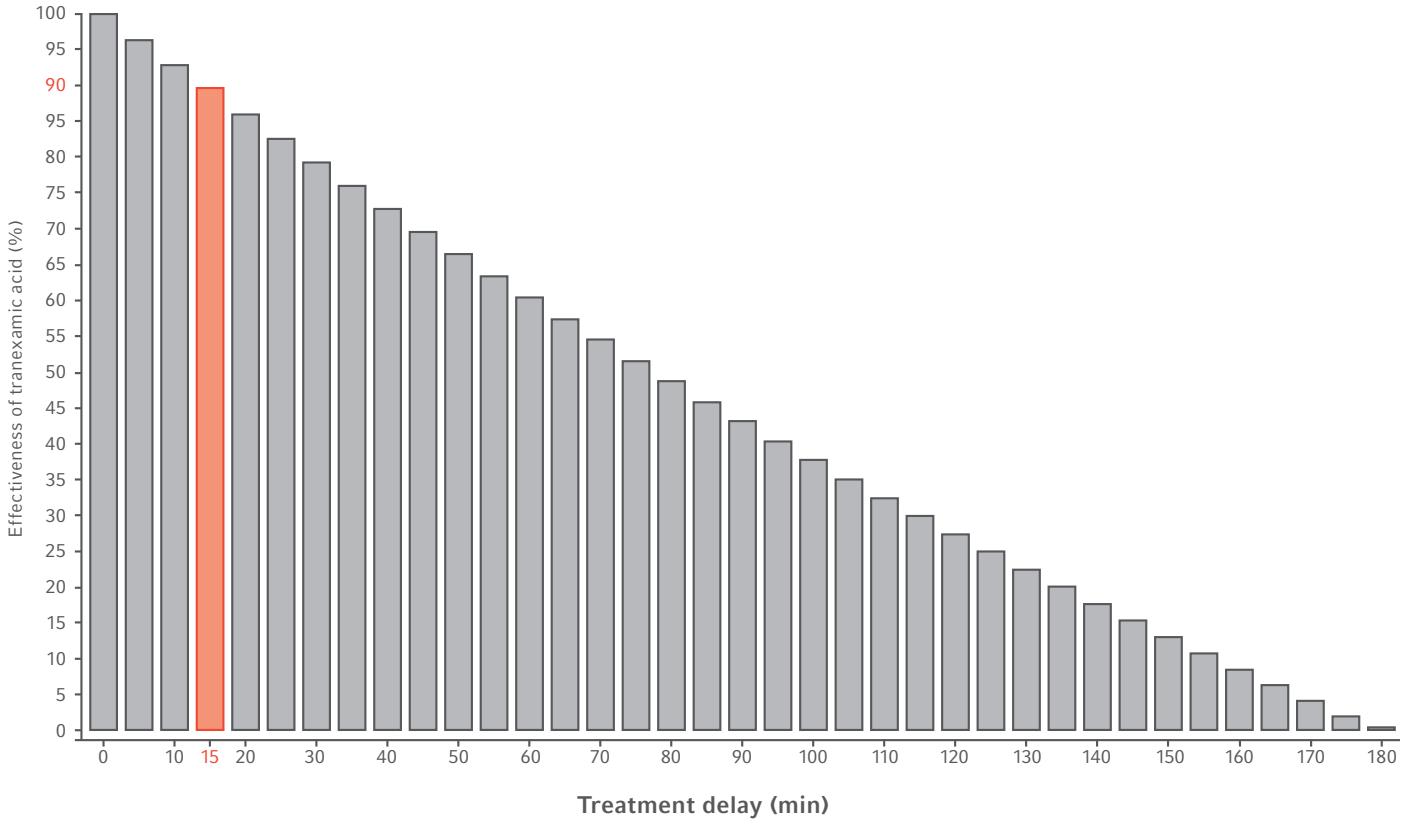

Figure 4: Reduction in effectiveness of tranexamic acid with increasing treatment delay
The bars represent the estimated treatment effectiveness (y-axis, estimated by [(OR at time t – 1)/(OR at t = 0 – 1) × 100] in %) at 5-min intervals of treatment delay. The bar highlighted in red shows the estimated treatment effectiveness (90%) with a treatment delay of 15 min.

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