Fibrinolytic shutdown: fascinating theory but randomized controlled trial data are needed

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This article is a counterpoint to: Moore EE, Moore HB, Gonzalez E, et al. Rationale for the selective administration of tranexamic acid to inhibit fibrinolysis in the severely injured patient. Transfusion 2016;56(Suppl 2):S109-S114.

Administration of tranexamic acid (TXA) to bleeding trauma patients who are within 3 hours of injury has been shown to safely reduce mortality in bleeding trauma patients. However, some believe that thromboelastography (TEG or ROTEM) can be used to subdivide these patients into those that will benefit from TXA and those that will be harmed by it. If thromboelastography can be used in this way there could be important patient benefits. However, if the approach is misguided, patients could be denied a lifesaving treatment. I believe that rather than debate the theoretical basis of this hypothesis, it should be tested by conducting a randomized controlled trial. Bleeding trauma patients who are within 3 hours of injury should be randomly allocated to receive TXA treatment or thromboelastometry-guided TXA treatment with the risk of death and complications compared between the groups. An adequately powered clinical trial would better serve patient interest than ongoing debate.

The CRASH-2 trial was a randomized placebo controlled trial of the effect of the antifibrinolytic tranexamic acid (TXA) on death and vascular occlusive events in bleeding trauma patients. A total of 20,211 trauma patients, with or at risk of significant bleeding, who were within 8 hours of their injury, were randomly allocated to receive TXA or matching placebo.[1] TXA significantly reduced death due to bleeding (relative risk [RR], 0.85; 95% confidence interval [CI], 0.76-0.96) and all-cause mortality (RR, 0.91; 95% CI, 0.85-0.97), with no increase in vascular occlusive events. Before the start of recruitment, we hypothesized that TXA would be most effective when given soon after the injury, when bleeding is profuse. In a prespecified subgroup analysis of the effect of TXA on death stratified by the time from injury to the initiation of treatment ($\leq$1, 1-3, 3-8 hours), we found strong evidence (Fig. 1) that early treatment was most effective ($p < 0.0001$). When started within 1 hour of injury, TXA reduced the risk of death due to bleeding by nearly one-third (RR, 0.68; 95% CI, 0.57-0.82; $p < 0.0001$); treatment between 1 and 3 hours reduced the risk of death due to bleeding by about one-fifth (RR, 0.79; 95% CI, 0.64-0.97; $p = 0.03$).[2,3] Treatment started after 3 hours did not reduce mortality and appeared to increase death due to bleeding. On the basis of the CRASH-2 trial results, early (within 3 hr of injury) treatment with TXA is now

ABBREVIATIONS: LY30 = clot lysis 30 minutes; RR = risk ratio; TXA = tranexamic acid.

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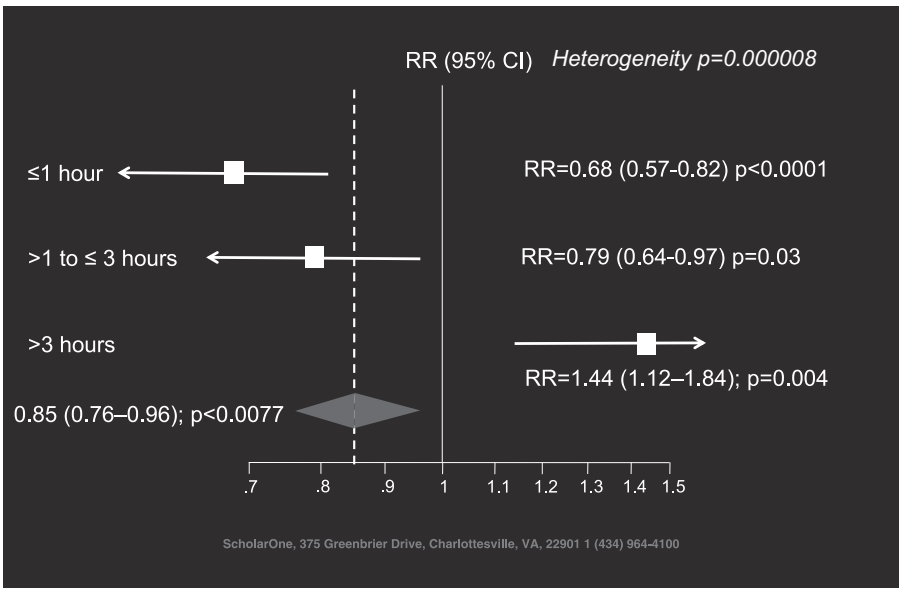

Fig. 1. Effect of TXA administration on hemorrhage death by time since injury.

widely recommended in trauma care. For example, on the basis of the results of the CRASH-2 trial, TXA was added to the WHO list of essential medicines and is included in trauma treatment protocols in many countries including the United Kingdom.

THE FIBRINOLYTIC SHUTDOWN HYPOTHESIS

Moore and colleagues[4,5] believe that they can subdivide patients treated within 3 hours of injury into two groups: a group that will benefit from TXA treatment and a group that will be harmed by it. The groups cannot be distinguished on clinical grounds but according to Moore can be distinguished by thromboelastography (TEG or ROTEM). They believe that fibrinolysis can be quantified on the basis of the percent of clot lysis 30 minutes after maximum strength is achieved (LY30). They claim that patients with an LY30 of 3% or more have "systemic hyperfibrinolysis," those with an LY30 of between 0.81 and 2.9% have "physiologic fibrinolysis," and those with an LY30 of less than 0.08% have "fibrinolysis shutdown." Moore claims that patients with an LY30 of 3% or more (systemic hyperfibrinolysis) will benefit from TXA treatment whereas those with an LY30 of 0.08% or less (fibrinolytic shutdown) will be harmed by it. Moore does not say how patients in the middle group (physiologic fibrinolysis) will respond to TXA treatment.

On the basis of their hypothesis, Moore and coworkers recommend the selective use of TXA based on thromboelastometry results. This recommendation has important implications for patients. The CRASH-2 trial showed that patients treated within 3 hours have a substantial reduction in death due to bleeding and all-cause mortality with no increase in thrombotic risk. If Moore is right and these patients can be further subdivided into a group that benefits and a group that is harmed, the benefits in the former group must be enormous. On the other hand, if Moore is wrong, many patients will be denied a lifesaving treatment. In this respect, it is worth noting that in Moore's data, 15% of patients with fibrinolytic shutdown bleed to death.[5]

POINTS OF AGREEMENT AND POINTS OF CONTENTION

Moore believes that inhibiting fibrinolysis through the untimely administration of TXA could be harmful. I agree. The results of the CRASH-2 trial provided strong evidence in support of our prespecified hypothesis ($p < 0.0001$) that time to treatment is an important determinant of the effect of TXA administration. But what biologic mechanism might account for this time to treatment interaction? Time is almost certainly a proxy for a change in the pathophysiologic state of the patient that is relevant to the mechanism by which TXA impacts on patient outcome. Like Moore we believe that the biologic mechanism responsible for the apparent harm from late TXA administration could be PAI-1–induced suppression of fibrinolysis with reduced fibrin clearance leading to the formation of microvascular thrombosis.[6,7] Late TXA administration might exacerbate this process. Although the underlying pathology is thrombotic, due to the consumption of coagulation factors, this thrombotic process often manifests clinically as bleeding. We suspect that this might explain why TXA appeared to increase the risk of bleeding when

given beyond 3 hours of injury. In summary, early TXA treatment works because bleeding is the major threat to life; late TXA treatment does not work because thrombosis rather than bleeding is the major threat.

The point of contention is this: I believe that time since injury, despite being a proxy for the relevant physiologic state, is currently the best way to differentiate those that will benefit from TXA treatment from those that will not. Moore believes that thromboelastography can be used for this purpose. The arguments in favor of basing the treatment decision on time since injury rather than thromboelastography are the following:

We have evidence from a large randomized controlled trial that when initiated within 3 hours of injury, TXA significantly reduces death due to bleeding and all-cause mortality, and there is no evidence that TXA increases the risk of vascular occlusive events. Indeed, when given within 3 hours of injury, there was a significant reduction in the odds of fatal and nonfatal vascular occlusive events (odds ratio, 0.69; 95% CI, 0.53-0.89; $p = 0.005$).[8] The beneficial effect of TXA on mortality does not vary by geographic region and should be widely generalizable even to "mature trauma systems" (Fig. 1).[9,10] Time may be a proxy for the relevant biologic state but has the advantage of being easy and quick to measure and there is strong evidence to show that on average there will be a substantial reduction in death due to bleeding and all-cause mortality in patients treated early. We may want to know the effects of treatments in individual patients but currently the best way to secure reliable information on treatment effects is from randomized trials in large groups of patients.

TXA reduces bleeding in patients undergoing elective and emergency surgery. Data from a meta-analysis of 104 clinical trials of TXA in surgical patients found that TXA reduces blood loss by about one-third (RR, 0.66; 95% CI, 0.65-0.67; $p < 0.001$) irrespective of the type of surgery.[11,12] Moreover, TXA appears to reduce blood loss by about one-third irrespective of whether the operation entails small, moderate, or large volumes of bleeding. There is also evidence that topical TXA administration reduces bleeding.[13] These results suggest that TXA reduces bleeding even in patients without hyperfibrinolysis.

As a method of identifying patients at risk of death due to bleeding thromboelastography is insensitive. Indeed, the 3% LY30 threshold has only a 64% sensitivity for identifying patients who will bleed to death.[4] Consequently, large numbers of patients who could benefit from TXA administration will not be treated using this threshold. There is no reason why the viscoelastic properties of venous blood should accurately reflect fibrinolytic activity in a bleeding internal organ, let alone predict the overall risk of bleeding to death.[14] Thromboelastography takes time and will delay the early administration of TXA in patients with acute severe bleeding.

FASCINATING HYPOTHESIS BUT RANDOMIZED CONTROLLED TRIAL DATA ARE NEEDED

I share Moore's view that the untimely administration of TXA could be harmful. I also believe that reduced fibrin clearance and the formation of microvascular thrombosis could be the biologic mechanism. However, I am skeptical that thromboelastography will identify patients who will benefit from TXA treatment and I am concerned that if we take this approach many patients will be denied a lifesaving treatment. If Moore and colleagues believe that the treatment approach they propose will result in improved patient outcomes they should test their hypothesis by conducting a randomized controlled trial. Bleeding trauma patients who are within 3 hours of injury should be randomly allocated to receive TXA treatment or thromboelastometry guided TXA treatment with the risk of death and complications compared between the groups. If Moore is right this will be an important treatment advance but this would not be the first fascinating theory to founder on the rocks of random allocation.

CONFLICT OF INTEREST

The author has disclosed no conflicts of interest.

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