Antifibrinolytic therapy: new data and new concepts

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Activation of the fibrinolytic system is an integral part of vascular haemostatic mechanisms to maintain vascular patency. The basis of fibrinolysis is the conversion of the inactive substrate plasminogen to plasmin, an enzyme that cleaves fibrin but also has pleiotropic effects.[1,2] Multiple mechanisms are responsible for generating plasmin, including endothelial activation and release of tissue plasminogen activator, and contact activation and kallikrein-mediated plasmin activation.[1-3] Tissue-type and urokinase-type are the two major plasminogen activators expressed in many cell types and tissues.[3] As part of the haemostatic balance, plasmin generation and activity are also modulated by multiple inhibitors that include plasminogen activator inhibitor 1, thrombin-activatable fibrinolysis inhibitor, and α_2-antiplasmin.[1-3] Thus fibrinolysis involves several regulatory mechanisms under physiological conditions.

However, after the extensive tissue injury that occurs with trauma or surgery, the equilibrium is shifted and fibrinolysis that occurs is considered to be an important contributor to bleeding and coagulopathy.[4] In surgical patients, many studies reported the use of antifibrinolytic agents to decrease bleeding and need for allogeneic transfusions.[5,6] The agents most commonly used are the lysine analogues, ε-aminocaproic acid and tranexamic acid, and aprotinin. Lysine analogues interfere with the binding of plasminogen to fibrin, necessary for activating plasmin, whereas aprotinin is a direct plasmin inhibitor. Thus inhibition of fibrinolysis with antifibrinolytics reduces bleeding after tissue injury, as has been extensively studied in surgical patients.

In *The Lancet* today, the CRASH-2 investigators[7] report the use of tranexamic acid in trauma patients with or at risk for substantial bleeding.[7] CRASH-2 evaluated an impressive 20 211 trauma patients randomised and treated within 8 h of injury with either 2 g tranexamic acid (1 g load, then 1 g over 8 h) or placebo. In-hospital mortality within 4 weeks of injury was the primary outcome, while vascular occlusive events, transfusions, or surgical interventions were secondary outcomes. All-cause mortality was 14·5% in the tranexamic acid group (1463/10 060) compared with 16·0% with placebo (1613/10 067; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). Bleeding-related mortality was also reduced (4·9% *vs* 5·7%, respectively), without an increase in fatal or non-fatal vascular occlusive events. Despite the reduction in mortality, there were no statistically significant differences in transfusion requirements in patients receiving tranexamic acid or placebo.

A crucial aspect of the original idea for the study was to reduce bleeding, an important cause of mortality after trauma, by use of an antifibrinolytic agent. Because tissue injury in trauma and surgery are similar, the investigators hypothesised that tranexamic acid could reduce mortality. Although there were no statistical differences in transfusion between the groups, how inhibition of fibrinolysis might have reduced mortality is important. The study did not show an antifibrinolytic effect on the basis of laboratory values; however, the tranexamic acid dose of 2 g administered over 8 h is sufficient to inhibit fibrinolytic activity.[8] However, there

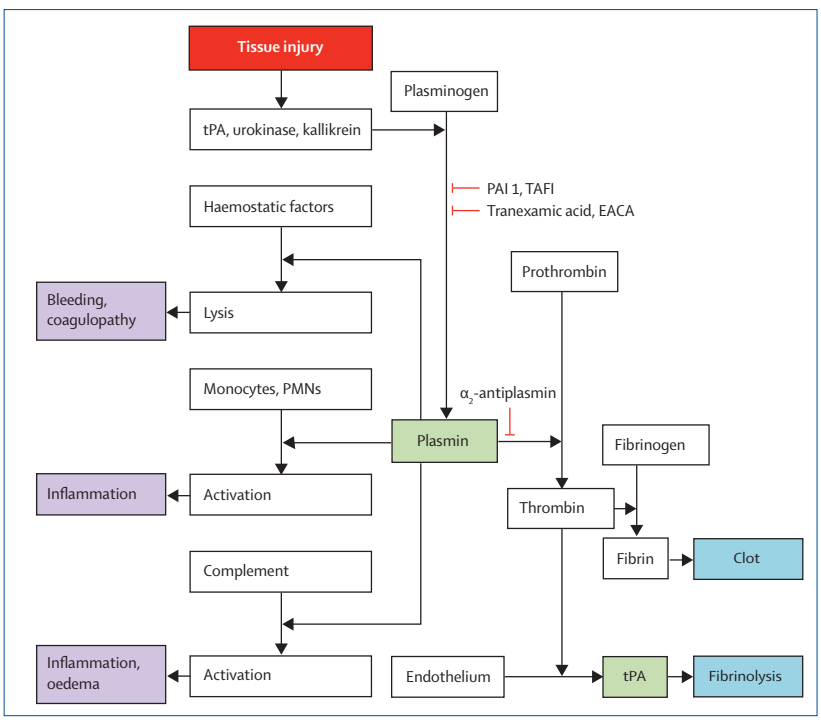

Figure: **Tissue injury and fibrinolysis**
After trauma, tissue injury shifts the complex balance of fibrinolysis to additional plasmin generation, and activation that increases coagulopathy, inflammatory responses, and bleeding. Multiple pathways are responsible for generation of plasmin, including endothelial activation and release of tissue plasminogen activator (tPA), contact activation, and kallikrein-mediated plasmin activation. Plasmin generation and activity are also inhibited by plasminogen activator inhibitor 1 (PAI 1), thrombin-activatable fibrinolysis inhibitor (TAFI), lysine analogues (tranexamic acid and ε-aminocaproic acid [EACA]), and α_2-antiplasmin. Plasmin generation after tissue injury can induce many other responses, including thrombin generation and cleavage of fibrinogen to fibrin. Plasmin also binds and activates monocytes, neutrophils, platelets, and endothelial cells, to increase proinflammatory responses and multiorgan system-failure. Attenuation of these pathophysiological responses with tranexamic acid might provide additional mechanisms to restore haemostatic balance and control of plasmin generation and fibrinolysis, as shown in CRASH–2. PMNs=polymorphonuclear leucocytes.

might be additional beneficial effects to inhibiting plasmin beyond clot lysis.

Plasmin can induce many other responses that contribute to coagulopathy and bleeding, including further activation of thrombin from prothrombin, cleavage of fibrinogen and fibrin to create fibrin(ogeno) lysis, and cleavage of receptors on platelets (including glycoprotein Ib and IIb/IIIa receptors).[1,2,9] In CRASH-2, there were 93 fewer patients receiving blood transfusions in the tranexamic acid group than in the placebo group. Plasmin also produces proinflammatory effects by binding and activating monocytes, neutrophils, platelets, and endothelial cells, and complement-releasing lipid mediators and cytokines, and by inducing proinflammatory genes.[3,10] Thus plasmin exhibits a broad spectrum of proinflammatory responses that could influence pathophysiological responses and multiorgan system-failure that might be attenuated with antifibrinolytic agents. A recent report supports this concept, by reporting that antifibrinolytic therapy can improve mortality in high-risk patients undergoing cardiac surgery.[11]

A note of caution is warranted about tranexamic acid. After cardiac surgery, more cases of postoperative convulsive seizures are being reported, a finding temporally coincident with tranexamic acid doses that are 2–10 fold higher than those used in CRASH-2.[12] A proposed mechanism for seizures is the structural similarity of tranexamic acid to γ-aminobutyric acid as a potential cause of neurotoxicity.

CRASH-2 is an important example of the complex relations between coagulation, fibrinolysis, inflammation, and outcomes after tissue injury.[4] Today's study shows that inhibition of fibrinolysis with tranexamic acid after major trauma is an important mechanism to reduce mortality. The similarities of tissue injury after trauma and surgery create a novel model for antifibrinolytic therapy with tranexamic acid. However, caution is needed before extrapolation of the results of CRASH-2 to other antifibrinolytic agents until they have been studied in a similarly robust manner.

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Operational research in HIV priority areas: the African way

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Since the unprecedented UNGASS Declaration of Commitment on HIV/AIDS in 2001,[1] more than 4 million people globally have now received HIV care, including provision of combination antiretroviral therapy (cART).[2] This effort has strained health-resource capacity in many countries, and has led to occasional criticism that the effort is lopsided and removes resources from other pressing public health needs.[3] In response, and as part of a strategy to maintain the momentum of providing access to HIV care, there has been an effort to task-shift roles between various levels of health-care worker, enabling, for instance, trained doctors to concentrate on the highest priorities and deal with a greater volume of patients. But there is little research that informs whether this approach is safe or effective.