CRITICAL CARE

COMMENTARY

Tranexamic acid: less bleeding and less thrombosis?

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Abstract

The early administration of tranexamic acid (TXA) to bleeding trauma patients reduces all-cause mortality without increasing the risk of vascular occlusive events. Indeed, the risk of arterial thrombosis appears to be reduced with TXA. In this commentary we hypothesize that TXA has an antithrombotic effect and explore potential mechanisms. These include inhibition of the inflammatory effects of plasmin, effects on platelets and effects on factors V and VIII. If proven, these antithrombotic effects would have major implications for the systemic use of TXA in surgical patients, where TXA has been clearly shown to reduce bleeding.

Introduction

The antifibrinolytic agent tranexamic acid (TXA) has been shown to reduce bleeding in elective surgery. A recent systematic review of randomised controlled trials shows that TXA reduces the probability of receiving a blood transfusion by nearly 40% [1]. There was also a non-significant reduction in the risk of myocardial infarction (MI) with TXA (relative risk (RR) = 0.68, 95% confidence interval (CI) 0.43 to 1.09; $P = 0.11$).

The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) trial of TXA in bleeding trauma patients was motivated by the evidence that TXA reduces surgical bleeding and the knowledge that the haemostatic responses to trauma and surgery share common features. The results showed a significant reduction in death due to bleeding and all-cause mortality with TXA [2]. The reduction was largest for those treated soon after injury [2]. TXA treatment within 3 hours of injury reduced the risk of death due to bleeding by nearly 30%. Moreover, there were fewer vascular occlusive deaths with TXA (RR = 0.69, 95% CI 0.44 to 1.07; $P = 0.096$) and a significant reduction in fatal and non-fatal MI (RR = 0.64, 95% CI 0.42 to 0.97; $P = 0.035$). We hypothesize that TXA may have an antithrombotic effect and explore the possible mechanisms.

The reduction in MI could be due to the anti-inflammatory effects of TXA. Trauma and surgery are known to generate a systemic inflammatory response, characterized by systemic activation of fibrinolysis, coagulation, complement, platelets, and oxidative pathways [3,4]. This inflammation is associated with increased risk of thrombosis. While a causal role for chronic inflammation in atherosclerotic disease is well established, evidence that acute inflammation may promote vascular events is accumulating, with increases in risk after infection [5] and surgery [6].

TXA has anti-inflammatory effects. It is a synthetic derivative of the amino acid lysine that blocks the lysine binding sites of plasminogen and plasmin, inhibiting their effects, including their fibrinolytic and inflammatory effects. Plasminogen binds not only to fibrin, causing fibrinolysis, but also to receptors on cells involved in the inflammation process, such as monocytes, macrophages, neutrophils, endothelial cells and platelets. Plasminogen receptors include the annexin A2-S100A10 heterotetramer, α-enolase, histone H2B and the transmembrane plasminogen receptor Plg-R(KT). The binding of plasminogen to these receptors initiates inflammatory processes. For example, the binding to annexin A2 increases the expression and release of a major chemokine called monocyte-macrophage chemo-attractant protein (MCP-1) [7]. The binding to α-enolase is involved in monocyte recruitment in inflammatory lung disease [8]. Plg-R(KT) is a plasminogen receptor that is co-localized on the monocyte surface with the urokinase receptor (uPAR) and interacts directly with tissue plasminogen activator [9]. Plg-R(KT) is believed to play a role in plasminogen-dependent regulation of macrophage migration, invasion, and recruitment in the inflammatory response. In summary, after binding to its receptors, plasminogen has a range of potent pro-inflammatory effects, which may be inhibited by TXA.

Once activated, plasmin can stimulate lipid mediator release, increase the biosynthesis of leucotrienes,

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promote cytokine release and induce the expression of some inflammatory genes. Plasmin also causes degradation of extracellular matrix components, thus facilitating chemotaxis and inflammatory cell migration across adhesive substrates. Plasmin also activates inflammatory signalling networks, leading to phosphorylation and activation of the p38 mitogen-activated protein kinase (MAPK) and JAK/STAT signalling pathways [10]. By blocking the binding sites of plasminogen and plasmin, TXA could inhibit these inflammatory effects. A randomised controlled trial of TXA in patients undergoing cardiopulmonary bypass showed that perioperative TXA reduced the inflammatory response and vasoplegic shock [4].

TXA may also reduce thrombotic events via effects on platelets and coagulation proteins. There is some evidence that plasmin can cause platelet activation. This was clinically noted in the early trials of thrombolysis in myocardial infarction where fibrinolytic (plasmin) activators were used initially without anti-platelet agents. Re-occlusion occurred in approximately 20% of cases after stopping fibrinolytic agents [11]. However, the use of anti-platelet drugs prevented re-occlusion. Plasmin may mediate platelet aggregation through proteolytic cleavage of a thrombin receptor, protease-activated receptor 4 (PAR4) [12]. Other anti-platelet mechanisms have been suggested. Plasmin is believed to cause platelet aggregation by stimulating platelet degranulation and release of both dense granules, with ADP, and alpha granules, with fibrinogen and von Willebrand factor, which lead to the activation, recruitment, and aggregation of platelets. Plasmin also stimulates the arachidonic acid cascade, which leads to activation of prostacyclin biosynthesis and, hence, platelet activation. Finally, plasmin may cause platelet aggregation by complement activation [13].

Plasmin also has a role in coagulation. At high concentrations, plasmin has procoagulant effects. Plasmin proteolyses coagulation factors but has a unique biphasic effect on factors V and VIII: proteolytic breakdown is preceded by a brief burst of activation [14,15]. Incubation of factor V or VIII with plasmin results in a rapid increase in procoagulant activity, factor VIII levels increase two-fold within 3 minutes and then are undetectable within 45 minutes [16]. This brief activation may generate enough thrombin to produce a significant procoagulant effect. Another procoagulant effect of plasmin is that it causes proteolytic breakdown of a physiological anticoagulant, tissue factor protein inhibitor, a major inhibitor of tissue factor-mediated coagulation [17], and these changes are abolished by antifibrinolytic agents [18].

Conclusion

Plasminogen and plasmin have a wide range of potential pro-thrombotic effects. The reduction in MI observed with TXA in the CRASH-2 trial is compatible with a significant antithrombotic effect of TXA. This effect may be mediated via its impact on inflammation, platelet effects or coagulation factors. However, the data are limited and more *in vitro* and clinical studies are required.

If TXA reduces the need for blood transfusion and reduces the risk of thrombosis, this would have major implications for surgical patients. Every year, world-wide, between 500,000 and 900,000 patients experience perioperative cardiac death, non-fatal MI or non-fatal cardiac arrest [19]. If the effect of TXA on the risk of arterial thrombotic events seen in trauma also applies in surgery, TXA might prevent hundreds of thousands of cardiac events. Because thrombotic events are uncommon, small trials lack power and a meta-analysis of small trials would be vulnerable to publication bias. For this reason a large pragmatic trial of TXA administration in surgical patients is needed. The possibility that TXA could reduce surgical morbidity and mortality through a reduction in perioperative bleeding and postoperative thrombosis justifies the effort involved.

Abbreviations

CI, confidence interval; CRASH-2, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2; MI, myocardial infarction; RR, relative risk; TXA, tranexamic acid.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AG, IR and BH wrote the manuscript. The final version was approved by all authors.

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