Tranexamic acid for trauma

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After its publication in July, 2010, the CRASH-2 study[1] generated widespread interest in the early administration of the antifibrinolytic agent tranexamic acid to patients with traumatic bleeding. Tranexamic acid is an inexpensive, easily used, and relatively safe drug, and it seemed to have saved lives. However, how it did so was unclear—the blood-transfusion requirements of the tranexamic acid and placebo groups were similar and, survival bias notwithstanding, the mortality benefit might have been attributable to an effect of tranexamic acid on something other than acute traumatic coagulopathy.[2]

This issue is partly addressed with the publication in *The Lancet* of a follow-up analysis that used the outcome of death due to bleeding rather than all-cause mortality.[3] The CRASH-2 collaborators[3] report a 32% reduction in death due to bleeding when tranexamic acid is given within 1 h of injury. Although markers of coagulopathy were not measured, the mortality benefit is probably mediated through antifibrinolytic effects on clot stabilisation.[4] While it will not prevent the massive haemorrhage from disrupted vessels or organs that needs surgical intervention, tranexamic acid appears to improve survival through its effect on mild to moderate bleeding.

Early administration is necessary, however, and benefit was only seen in CRASH-2 when tranexamic acid was administered within 3 h of injury. Unlike coagulopathy that is secondary to haemodilution, hypothermia, or acidosis, acute traumatic coagulopathy is a hyperacute process in which systemic fibrinolysis releases D-dimers that are detectable within 30 min of injury.[5] While the mechanisms are poorly understood, shock and tissue injury seem to be important initiators.[6] Not all severely injured patients develop acute coagulopathy, but those who do are much more likely to die and to die early.[7] The earlier that tranexamic acid is administered, the more likely it might be to prevent full activation of fibrinolysis. Once fully activated, fibrinolysis has been shown to continue unabated until endogenous antifibrinolytic elements are restored.[8]

Importantly, the CRASH-2 collaborators[3] report increased mortality due to bleeding in patients receiving tranexamic acid when it is given more than 3 h after injury. The cause of these deaths is unclear. Reports exist of prothrombotic effects of each of the anti-fibrinolytic drugs. Alternatively, it might reflect some factor of the patients who received it late. Whatever the mechanism, the CRASH-2 collaborators[3] have cautioned against the use of tranexamic acid when more than 3 h have expired after injury.

Who, then, should be treated with tranexamic acid? Most of the 274 study sites in CRASH-2 were in low-income and middle-income countries, where other treatments directed at coagulopathy, such as fresh frozen plasma, platelets, and cryoprecipitate, are less available. Although many patients with acute coagulopathy will die before reaching hospital, tranexamic acid is a practical, affordable, and effective treatment for bleeding trauma patients in such centres, provided they receive it within 3 h of injury.

Far less clear is the place for tranexamic acid in high income countries where massive transfusion protocols incorporate fresh-frozen plasma that contains all the endogenous antifibrinolytic elements in plasma.[9] Plasma can cause harm as well as benefit, and there is little prospective evidence regarding its efficacy. However, because it is in widespread use, and because late administration of tranexamic acid can be harmful, it is unlikely that many clinicians in major trauma centres will choose tranexamic acid as first-line treatment.

The best place for tranexamic acid in developed trauma systems might actually be in the prehospital environment. Helicopter and road transport direct to major trauma centres has reduced overall injury mortality, but has extended the time before patients

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reach hospital.[10] Prehospital administration of blood products, especially plasma, is uncommon in civilian settings, resulting in little directed management of coagulopathy. By contrast, tranexamic acid can be safely stored in vehicles and simply administered. In view of the new findings from CRASH-2, the best outcomes might be achieved with simple measures for haemorrhage control and early inhibition of coagulopathy with tranexamic acid, followed by rapid transport for surgery or angiography and tailored management of coagulopathy in hospital.

CRASH-2 was an extraordinary achievement, with randomisation of more than 20 000 patients in 40 countries. It has established tranexamic acid as an effective hospital-based treatment for traumatic haemorrhage, provided that the drug is given within 3 h of injury. In trauma systems that have advanced prehospital services and that use other hospital-based treatments for coagulopathy, CRASH-2 raises more questions—and more possibilities—that are worth investigating.

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