Trauma and tranexamic acid

Research is needed to determine how patient selection and intercurrent treatment affect safety and efficacy

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Clinicians involved in the resuscitation of severely injured patients face a dilemma. On one hand, since publication of the landmark CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) study in 2010,[1] there has been an international push for inclusion of tranexamic acid (TxA) in trauma management protocols. On the other hand, the need for more evidence to solve ongoing knowledge gaps has been emphasised, especially evidence of who benefits and whether anyone is harmed when TxA is administered to patients treated to modern civilian and military trauma standards.[2,3] While both views represent well intentioned efforts to improve care, they create conflicting priorities that must be reconciled before patients can properly benefit.

Half a century ago, it was discovered that TxA competitively inhibits conversion of plasminogen to the active protease, plasmin, thereby inhibiting fibrinolysis and clot breakdown. In 126 studies of elective surgical patients, TxA was shown to reduce the probability of blood transfusion by about one-third, albeit without significant mortality benefit.[4] TxA was little used in trauma care until the publication of the CRASH-2 study, which enrolled 20 211 adult trauma patients with, or at risk of, significant bleeding in 274 hospitals in 40 countries and is the only completed randomised trial of TxA use in trauma patients. In CRASH-2, compared with placebo, TxA given within 8 hours of injury reduced 28-day all-cause mortality from 16.0% to 14.5%.[1] There was no apparent increase in vascular occlusive events, and the effect of TxA did not seem to vary by baseline risk of death. Re-examination of the 1063/3076 deaths (35%) that resulted from bleeding found that the benefit from TxA was greatest when it was given early (at $\leq$ 1 h, relative risk [RR], 0.68; at 1–3 h, RR, 0.79), but when given more than 3 hours after injury, an unexpected and unexplained increase in deaths due to bleeding was observed (RR, 1.44).[5]

The findings of CRASH-2 have been interpreted by some as definitive evidence that all trauma patients everywhere should be given TxA within 3 hours of injury. This message has been widely promoted to clinicians, the public, professional organisations, defence chiefs, and government and intergovernmental agencies. Many military and civilian trauma systems have included TxA in treatment protocols, no doubt swayed by emotive arguments that by doing so "more than 100 000 premature deaths could be averted",[6] and by promotional strategies such as the "Trauma Promise" (www.traumapromise.org).

Nevertheless, civilians and military experts, including the United States Department of Defense Hemorrhage and Resuscitation Research and Development Steering Committee, have highlighted numerous important knowledge gaps.[2,3,7] The first concerns the efficacy of TxA in patients treated to modern trauma care standards. Fewer than 2% of the patients in CRASH-2 were treated in countries that routinely provide rapid access to blood products, damage-control surgery and angiography, and advanced critical care. Even though only half received a blood transfusion, the baseline mortality rate in CRASH-2 was 16%,[1] which is much higher than that among patients treated in advanced trauma centres in Australia who could have met the CRASH-2 inclusion criteria. In trauma systems with far fewer preventable deaths, it seems unlikely that TxA could have equivalent mortality benefits. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) observational study[8] assessed whether the CRASH-2 findings were applicable to military trauma systems in Afghanistan. While TxA was found to have mortality benefit, the validity of these findings was compromised by practice changes during the study period and potential confounding due to differences in wounding mechanism, head injury severity and access to ongoing sophisticated medical care.

The second knowledge gap concerns the safety of TxA when combined with other treatments targeting bleeding and coagulopathies. Although some present with an early coagulopathy, many trauma patients go on to develop a hypercoagulable state, and pulmonary embolism (PE) and deep vein thrombosis (DVT) are common and potentially lethal problems in Australasian trauma centres. Thrombotic complications were reported very rarely in the CRASH-2 study (PE, 0.7% of all patients; DVT, 0.4%),[1] probably because they were not actively sought in many of the participating hospitals. In contrast, the MATTERs study showed that rates of PE and DVT among patients who received TxA were, respectively, 9 and 12 times the rates among those who did not.[8] Furthermore, more elderly patients are treated within Australasian trauma systems than were included in the CRASH-2 and MATTERs studies, and the interactions of TxA with age-related comorbidities and pharmacotherapy are not well understood.

The third major knowledge gap concerns the biological effects of TxA in trauma patients and, therefore, who should receive it. An important action of TxA is thought to be reduction of plasmin-mediated fibrinolysis that contributes to acute traumatic coagulopathy (ATC). However, emerging evidence attests that ATC is present in only about one in 10 patients with major trauma and ATC correlates poorly with major bleeding: less than half of patients who are given a massive blood transfusion have ATC, and less than half of patients with ATC receive a massive transfusion.[9] While TxA has most often been included in protocols for massive transfusion, this was not what was tested in CRASH-2, and this strategy appears to deny TxA to most patients with ATC while exposing many

patients without ATC to the drug. In part because no blood tests were done in CRASH-2, it is not known how the presence or absence of ATC affects a patient's response to TxA, and whether this is further influenced by other factors such as traumatic brain injury. It is also not known whether other treatments alter the 3-hour safety window. And furthermore, plasmin is known to affect other systemic processes, such as inflammation, that may influence patient outcomes, but their relative importance compared to fibrinolysis has not been determined.

Rarely has one study been the end of a story,[10] and the generalisability of one trial's results to clinical practice is often compromised by where and how patients were recruited. Patient selection and intercurrent treatment are likely to affect responses to TxA, and because substantial differences are likely between advanced and less developed trauma systems, hypotheses about TxA should be re-investigated.[11] North American trauma experts recently argued that a prospective randomised study performed in a controlled environment with laboratory monitoring of coagulation and standardised transfusion protocols is essential before TxA becomes standard care in trauma.[3] Similarly, the US Department of Defense committee identified the safety, efficacy and applicability of TxA in modern trauma care as current "priority 1 research needs".[2] These are the goals of our 4-year, 1200-patient, multicentre trial, the Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage study (the PATCH-Trauma study), funded by the National Health and Medical Research Council (NHMRC). The trial, for which recruiting will start in late 2013, will involve injured patients, prehospital providers and trauma centres throughout Australia and New Zealand. It will test, compared with placebo, the effect of early prehospital administration of TxA on mortality and recovery at 6 months. It will also examine the effect of TxA on coagulation, fibrinolysis, transfusion requirements and the incidence of vascular occlusive complications, as well as effects on inflammation, immune function and sepsis.

As practising clinicians, we understand the advantages of using protocols, especially in the time-critical management of trauma patients. We are concerned, however, that incorporation of TxA into guidelines, and rigid adherence to them, will make it difficult or impossible to properly define its role in modern trauma resuscitation, eschewing genuine opportunities to deliver better health care. We encourage clinicians, especially those responsible for institutional protocols, to consider the knowledge gaps, and to embrace this study, which will provide much needed answers.

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