CRASH-3: a win for patients with traumatic brain injury

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Traumatic brain injury (TBI) is among the most dreaded and tragic of diagnoses. At least one clinical trial has shown that despite the most advanced care available, mortality from TBI, either in isolation or with concomitant polytrauma, can exceed 50%.[1] Every physician who has cared for patients with TBI has felt the frustration that stems from being unable to alter the fatal course of traumatic brain haemorrhage in a previously healthy person.

Over the past several decades, patients with TBI, their families, and their health-care providers have hoped for improved approaches to treating this condition. Indeed, governments have devoted considerable resources to developing improved management strategies for TBI. What have we learned? Despite compelling physiological logic and promising preclinical data, attempts to treat patients with TBI with such diverse approaches as corticosteroids,[2] progesterone,[3] and brain cooling[4] have been ineffective or worse. Interventions designed to target specific injury mechanisms such as increased permeability of the blood–brain barrier through bradykinin receptor inhibition (anatibant[5]) are promising but require further study.[6] The hard truths of TBI care learned from war and everyday TBI are quite simple and obvious: control bleeding, and avoid hypotension[7] and hypoxia,[8] or the patient will die.

Bleeding can potentially be targeted to alter the clinical course of TBI. Coagulopathy is a widely acknowledged contributor to TBI mortality and is associated with TBI severity.[9] Although many aspects of coagulation function have been studied in this context, fibrinolysis is clearly a major driver of TBI-associated coagulopathy[10] and haemorrhagic progression[11] of injury. Clinical assessment of the antifibrinolytic drug tranexamic acid to reduce TBI-associated mortality is logical, particularly in view of the mortality reductions observed with tranexamic acid use in polytrauma patients without TBI[12] and in women with post-partum haemorrhage.[13]

In *The Lancet*, the CRASH-3 trial collaborators[14] report the results of a randomised, placebo-controlled trial of 12 737 adults with TBI (mean age 41·7 years [SD 19·0]; 80% men, 20% women). In patients treated within 3 h of injury, the risk of head injury-related death was 18·5% in the tranexamic acid group versus 19·8% in the placebo group (855 *vs* 892 events; risk ratio [RR] 0·94 [95% CI 0·86–1·02]). There was a significant reduction in risk of head injury-related mortality when tranexamic acid was administered within 3 h of injury to patients with mild-to-moderate TBI (RR 0·78 [95% CI 0·64–0·95]), but not in patients with severe head injury (0·99 [0·91–1·07]).

This study represents an enormous effort in studying a difficult clinical problem. Considering the results of CRASH-3 with those of CRASH-2[12] (20 211 patients with trauma) and WOMAN[13] (20 060 patients with peripartum haemorrhage), more than 53 000 patients have been randomly assigned in the study of tranexamic acid and the drug's effects on patients with bleeding. The results of each study independently and together are clear: tranexamic acid reduces risk of death due to bleeding, regardless of the cause. Furthermore, tranexamic acid must be given early—within 3 h of bleeding onset—to be effective. These data suggest a fundamental truth regarding the pathophysiology of life-threatening haemorrhage—namely, that early activation of the fibrinolytic protease cascade is intimately linked to poor outcomes in patients with bleeding, perhaps because of various mechanisms,[15] including worsened bleeding due to clot breakdown, activation of inflammatory pathways, and increased endothelial permeability leading to tissue, especially brain, oedema. Tranexamic acid offers a means to mitigate this maladaptive response to injury.

CRASH-3 is the first trial of a pharmacological intervention applied in the acute setting to show improved outcomes in patients with TBI. The use of

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28-day head injury-related mortality as the primary endpoint probably biased the treatment effect towards the null because tranexamic acid is most likely to benefit patients with TBI with intracranial bleeding at risk of early mortality, whereas late deaths are unlikely to be affected by tranexamic acid. Indeed, the authors report that the greatest reduction in head injury-related deaths occurred in the first 24 h after injury in a manner consistent with that observed in CRASH-2. Future studies of tranexamic acid or other haemostatic interventions should reflect what is physiologically plausible and focus on endpoints of early bleeding-related death that clearly link intervention to outcome.

In the CRASH-3 trial, tranexamic acid appears to be safe in patients with TBI, but as acknowledged by the authors, a clot-stabilising intervention such as tranexamic acid might cause an increase in risk of venous thromboembolism that was not captured in the study. An additional important limitation of the CRASH-2, CRASH-3, and WOMAN trials is that tranexamic acid dosing regimens were very similar. Future study might be warranted to explore the effects of increased tranexamic acid doses in bleeding patients, or possibly alternative routes of administration such as intramuscular administration that might facilitate earlier intervention. Future studies of TBI could consider combining the antifibrinolytic effects of tranexamic acid on bleeding with blockade of bradykinin receptors, which could reduce brain oedema and potentially yield greater reductions in mortality. Despite its limitations, CRASH-3 is a remarkable study that will change practice, and tranexamic acid will benefit future patients with TBI who might reasonably have a chance of recovery from their injuries.

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I declare no competing interests.

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Improving survival of infants with low birthweight cared for outside hospitals

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In 1978, Edgar Rey was the director of a large and overcrowded neonatal unit in Bogota, Colombia. Shortage of incubators and prolonged hospital stay were harming and resulting in the deaths of already stable premature infants. To overcome those circumstances, Rey started an early discharge programme in which infants were placed in skin-to-skin contact on top of their mothers' chests to ensure thermal stability (kangaroo