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Editorial

The CRASH-2 trial of an antifibrinolytic agent in traumatic haemorrhage: an international collaboration

The CRASH-2 trial is a World Health Organization (WHO) supported large international multi-centre randomized placebo controlled trial of the effects of the antifibrinolytic agent tranexamic acid on death and transfusion requirements in adult trauma patients with significant haemorrhage. The trial aims to recruit 20,000 patients worldwide. This article gives the rationale for the trial, an update on its progress and is an invitation to doctors in India to join CRASH-2 trial.

Between the ages of 5 to 45 yr, trauma is second only to HIV/AIDS as a cause of death. Worldwide over three million people die every year as a result of trauma, many after reaching hospital¹. It is well documented that funding for trauma research is less than almost any other cause of human suffering. A WHO study compared the level of research funding with current and projected (2020) disease burden. The results showed clearly the relative under-funding of research on injuries. A more recent study from the UK shows that injury remains the most under-funded of all health issues^{2,3}. Trauma is a major public health problem in India, particularly given the increasing number of road traffic crashes.

Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths⁴. Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding⁵.

The haemostatic system mounts a similar response to maintain the integrity of the circulatory system after severe vascular injury, whether the cause is traumatic or surgical⁶. Any consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma, in any patient, is stimulation of fibrinolysis (clot breakdown) which may become pathological (hyper-fibrinolysis) in some⁶. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of post-operative complications. Moreover, there is no apparent increased risk of venous thromboembolism⁷.

Systemic antifibrinolytic agents are widely used in major surgery to reduce surgical blood loss. A systematic review⁸ of randomized controlled trials of antifibrinolytic agents (mainly aprotinin or tranexamic acid) in elective surgical patients identified 89 trials including 8,580 randomized patients (74 trials in cardiac, eight in orthopaedic, four in liver, and three in vascular surgery). The results showed that these treatments reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding. These differences were all highly statistically significant. There was also a statistically non significant reduction in the risk of death (RR=0.85: 95% CI 0.63 to 1.14) in the antifibrinolytic treated group.

The haemostatic changes after injury are similar to those after surgery, and thus it seems logical to test the hypothesis that antifibrinolytic agents may reduce blood loss, the need for transfusion and mortality following trauma. However, to date there has been only one small randomized controlled trial (70 randomized patients, drug versus placebo: 0 versus 3 deaths) of the effect of antifibrinolytic agents in major trauma⁹. As a result, there is insufficient evidence to either support or refute a clinically important treatment effect.

It is important to investigate a simple and widely practicable treatment that might reduce blood loss following trauma, for worldwide it might prevent thousands of premature trauma deaths each year and could reduce exposure to the risks of blood transfusion. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Indeed trauma is common in parts of the world where the safety of blood transfusion is not assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around 2 per cent, although some estimates are much higher^{10,11}. Only 43 per cent of the 191 WHO member states test blood for HIV and hepatitis C and B viruses. Every year, unsafe transfusion and injection practices are estimated to account for 8-16 million hepatitis B infections, 2.3-4.7 million hepatitis C infections and 80,000-160,000 HIV infections¹².

A large randomized trial is therefore needed of the use of a simple, inexpensive, widely practicable antifibrinolytic treatment such as tranexamic acid (aprotinin is considerably more expensive and is a bovine product with consequent risk of allergic reaction and hypothetically transmission of disease). The trial population should comprise a wide range of trauma patients, who when they reach hospital are thought to be at risk of major haemorrhage that could significantly affect their chances of survival. To this end a large international, placebo controlled trial of

the effects of the early administration of the antifibrinolytic agent tranexamic acid on death, vascular events and transfusion requirements has been designed¹³. Known as CRASH 2 (Clinical Randomisation of Antifibrinolytic in Significant Haemorrhage), this trial will be one of the largest clinical trials in trauma ever conducted.

The trial aims to recruit 20,000 patients worldwide and recruitment began in May 2005. Recruitment is expected to be completed in December 2009. To date, over 3,500 patients have been recruited at over 80 participating hospitals. Recruitment in India is particularly strong with over 500 patients recruited to date. However, in order to reach the recruitment target of 20,000 patients many more hospitals in India are required. The Data Monitoring Committee convened on August 2006 and reviewed data on more than 1800 randomized patients. The Committee commended the collaborators on the excellent recruitment and it was the view of the committee that "the interim analyses provided no reason for modifying the CRASH-2 protocol on the basis of safety or efficacy."

The CRASH-2 trial collaborators have made an outstanding contribution by ensuring that the trial is already the largest clinical trial in traumatic haemorrhage. However, to achieve the CRASH-2 trial objectives, many more participating hospitals are needed. We invite doctors in India to join this international collaboration and in this way help to build the evidence base for trauma care.

Please visit the trial website for further information about how to join: <http://www.crash2.lshtm.ac.uk>.

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