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Anti-fibrinolytic agents in traumatic haemorrhage.

Carta al Editor

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A large scale randomised controlled trial is needed.

For people berween the ages of 5 and 45, trauma is second only to HIV/AIDS as a cause of death. Every year, over three million people worldwide, die as a result of trauma, many after reaching hospital (1). Among trauma patients who do survive and reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths (2). Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding (3).

The haemostatic system helps maintain the integrity of the circulatory system after severe vascular injury, whether traumatic or surgical in origien (4). Major surgery and trauma trigger similar haemostatic responses and 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 clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) (4). Anti-fibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparent increase to the risk of post-operative complications, most notably there is no increased risk of venous thromboembolism (5).

Systemic anti-fibrinolytic agents are widely used in major surgery to prevent fibrinolysis and thus reduce surgical blood loss. A recent systematic review (6) of randomised controlled trials of anti-fibrinolytic agents (mainly aprotinin or tranexamic acid) in elective surgical patients identified 89 trials including 8,580 randomised patients (74 trials in cardiac, eight in orthopaedic, four in liver, and three in vascular surgery). The results showed that these treatments reduced the number 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 anti-fibrinolytic treated group.

Because the haemostatic abnormalities that occur after injury are similar to those after surgery, it is possible that anti-fibrinolytic agents might also reduce blood loss, the need for transfusion and mortality following trauma. However, to date there has been only one small randomised controlled trial (70 randomised patients, drug versus placebo: 0 versus 3

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deaths) of the effect of anti-fibrinolytic agents in major trauma (7). As a result, there is insufficient evidence to either support or refute a clinically important treatment effect. Systemic anti-fibrinolytic agents have been used in the management of eye injuries where there is some evidence that they reduce the rate of secondary haemorrhage (8).

A simple and widely practicable treatment that reduces blood loss following trauma 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. 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%, although some estimates are much higher (9,10). Only 43% of the 191 WHO member states test blood for HIV, 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 infections (11). A large randomised trial is therefore needed of the use of a simple, inexpensive, widely practicable anti-fibrinolytic 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), in 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.

The CRASH 2 trial will be a large international, placebo controlled trial of the effects of the early administration of the anti-fibrinolytic agent tranexamic acid on death, vascular events and transfusion requirements (12). The trial aims to recruit some 20,000 patients with trauma and will be one of the largest trauma trials ever conducted. However, it will only be possible to conduct such a trial if hundreds of healthcare professionals worldwide work together to recruit patients to the trial in order to make it a success.

REFERENCES.

1.- Murray CJL, Lopez AD. Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. Harvard School of Public Health, Boston: Harvard University Press, 1996.

2.- Sauaia A, Moore FA, Moore E, Moser K, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. J Trauma1995;38:185-193.

3.- The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Hypotension.
J Neurotrauma. 2000;17(6-7):591-5.

4.- Lawson JH, Murphy MP. Challenges for providing effective hemostasis in surgery and trauma. Semin Hematol 2004;41:55-64.

5.- Porte RJ, Leebeek FW. Pharmacological strategies to decrease transfusion requirements in patients undergoing surgery. Drugs 2002; 62: 2193-211.

6.- Henry DA, Moxey AJ, Carless PA, O'Connell D, McClelland B, Henderson KM, Sly K, Laupacis A, Fergusson D. Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

7.- Coats T, Roberts I, Shakur H. Antifibrinolytic drugs for acute traumatic injury. (Cochrane Review). In preparation for: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

8.- Aylward GW, Dunlop IS, Little BC. Meta-analysis of systemic antifibrinolytics in traumatic hyphema. Eye 1994;8:440-442.

9.- Kiwanuka N, Gray RH, Serwadda D, *et al*. The incidence of HIV-1 associated with injections and transfusions in a prospective cohort, Raki, Uganda. AIDS 2004;18:342-343.

10.- Heymann SJ, Brewer TF. The problem of transfusion associated acquired immunodeficiency syndrome in Africa: a quantitative approach. Am J Infection Control 1992;20:256-62.

11.- Goodnough LT, Shander A, Brecher ME. Transfusion medicine: looking to the future. Lancet 2003; 361: 161-9.

12. www.crash2.lshtm.ac.uk