EDITORIAL

Crash 3. A new international effort in the management of traumatic hemorrhagic brain damage

Crash 3. Un nuevo esfuerzo internacional para el manejo de la lesión cerebral hemorrágica traumática

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Despite the advances in recent decades in the monitorization, diagnosis and treatment of severe traumatic brain injury (STBI), and which have reduced mortality in the developed countries, 50% of all patients admitted to hospital due to STBI continue to suffer significant life-long sequelae. The probability of death or of sequelae is largely dependent upon the amount of brain tissue destroyed, and this in turn is conditioned by the extent of the primary damage resulting from the magnitude of the biomechanical impact and by the different causes of secondary brain lesions which inexorably worsen the outcome. Hemorrhagic lesions, in the form of intraaxial hematomas or extraaxial hematomas, are found in 50% of all STBIs and have a strong impact upon the outcome. In general, extraaxial lesions, specifically subdural hematomas and epidural hematomas, are identified from the first computed tomography (CT) scan after the traumatism, tend to be unilateral, and are mostly amenable to surgical drainage. In contrast, intraaxial lesions, in the form of intraparenchymal hematomas or hemorrhagic contusions, can be multiple, tend to increase in size or manifest as new lesions appearing in neighboring or distant areas in the first hours or days, and are difficult to deal with from the surgical perspective. It has been documented that in up to 50% of all cases, the hemorrhagic lesions increase in the hours following admission to hospital. Servadei et al. reported that among the 16% of STBIs without mass-type lesions showing worsening on the successive CT scans, 74% exhibited a new hemorrhagic lesion that was not present in the CT study upon admission. However, the most significant aspect of the increase or appearance of hemorrhagic lesions is the neurological deterioration they cause, and their negative impact upon the functional and life prognosis of the patient.

The most widely accepted mechanism for explaining the expansion of hemorrhagic lesions is continued blood loss secondary to vessel disruption at the time of trauma. Recently, a new mechanism has been proposed which could explain hemorrhagic progression of the initial injury, or the appearance of new lesions, due to late alteration of the cerebral microvasculature secondary to a molecular process triggered by the primary impact. The concomitant presence of coagulopathy—either latent or clearly demonstrable—would be responsible for the continuous bleeding, thus justifying the search for strategies to normalize coagulation. To date it has not been possible to firmly demonstrate the relationship between coagulation alterations and the late increase or appearance of brain hemorrhage in STBI. Nevertheless, Allard et al. observed progression of bleeding in 80% of

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the patients with some coagulation disorder versus in 36% without coagulation disorders.

With the purpose of normalizing coagulation and interrupting the progression of bleeding in STBI, Zaaraor et al. used recombinant factor VII in 12 patients, with relative success in reducing the development of hemorrhagic damage. The limited number of patients involved precluded the drawing of conclusions, however. Posteriorly, in a clinical trial with this same drug in which its efficacy in application to traumatic brain hematoma was investigated, no decrease could be demonstrated in either mortality or in the hematoma progression rate on contrasting the treatment group versus the placebo series, at any of the doses tested. On the other hand, in a series of patients with severe bleeding (trauma and perisurgical patients), recombinant factor VII produced thrombotic complications in over 6% of the cases—fundamentally in arterial territories. An added consideration here is the high cost of the drug, which presently makes it inaccessible in many countries.

In contrast, tranexamic acid, an inexpensive and widely used antifibrinolytic agent, significantly lowered mortality among trauma patients with hemorrhagic shock, with no additional increase in thrombotic complications. In a traumatic brain injury subgroup comprising individuals at risk or with significant extracranial bleeding and belonging to this same clinical trial, a cohort nested case-control study was made with the primary aim of determining whether tranexamic acid reduces the progression of intracranial bleeding. The investigation comprised 133 traumatic brain injury cases in the treatment arm and 137 subjects in the placebo arm. Forty-eight hours after trauma in the treated group, after adjusting for age, level of consciousness and initial bleeding volume, the authors found the mean total volume increment of the intracranial hematoma to be 3.8 ml less than that in the placebo group, and mortality furthermore was seen to be lower in the treated series (11% versus 18%). Likewise, the treatment group presented a lesser rate of new focal ischemic lesions attributable to the hemostatic drug (5% versus 9%).

These promising results have led to the proposal of a new randomized, placebo-controlled, multicenter, international clinical trial involving patients with traumatic brain injuries, a Glasgow score of <12 points, and intracranial hemorrhagic lesions. The primary objective is to determine whether the early administration of tranexamic acid improves the diagnosis of these individuals. This trial, known as Crash 3 (information available at http://crash3.ishtm.ac.uk), is currently in the screening phase for new research sites. To date, 8 Spanish hospitals, including our own, have entered the project. We consider that this clinical trial offers an opportunity to contribute to medical knowledge in a field where the therapeutic repertoire is severely limited. Moreover, the study will allow the inclusion of those Spanish Units treating moderate and severe traumatic brain injury cases that wish to participate in a consolidated and reputed international research network, the CRASH Trial Collaborators—the results of which are accepted for publication by the leading medical journals.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**