



POINT OF VIEW

Tranexamic Acid Therapy Decreases Mortality of Traumatic Hemorrhagic Shock[☆]

A. Muñoz-Sánchez*, F. Murillo-Cabezas

Cuidados Críticos y Urgencias, Hospital Universitario Virgen del Rocío, Sevilla, Spain

Received 13 January 2011; accepted 18 January 2011

KEYWORDS

Tranexamic acid;
Traumatism;
Traumatic bleeding
shock

PALABRAS CLAVE

Ácido tranexámico;
Traumatismo;
Shock hemorrágico
traumático

Abstract The CRASH 2, a randomized, double-blind, controlled trial that enrolled 20,211 adult trauma patients, has shown that the administration of tranexamic acid significantly reduces all-cause mortality and that specifically associated with severe blood loss as well.

We consider it as a significant therapeutic advance, because, for the first time, a drug has been demonstrated to safely diminish mortality due to traumatic bleeding shock. On the basis of these results and the high rate of death due to traumatic bleeding, we suggest that tranexamic acid should be considered for compassionate use in bleeding trauma patients prior to its definitive approval for this medical condition.

© 2011 Elsevier España, S.L. and SEMICYUC. All rights reserved.

El ácido tranexámico disminuye la mortalidad del *shock* hemorrágico traumático

Resumen Un estudio aleatorizado, controlado con placebo y doble ciego, el CRASH 2, ha concluido, tras incluir a 20.211 traumatizados, que el ácido tranexámico reduce significativamente la mortalidad, tanto la global como la específicamente ligada a la pérdida sanguínea severa.

Consideramos que este es un avance terapéutico significativo, ya que por primera vez un fármaco se ha mostrado capaz de disminuir la letalidad del *shock* hemorrágico traumático. Dados los resultados, el elevado volumen de muertes por sangrado traumático que se producen en el mundo y la eficiencia del tranexámico, proponemos su uso compasivo hasta la inclusión de esta indicación en la ficha técnica.

© 2011 Elsevier España, S.L. y SEMICYUC. Todos los derechos reservados.

*The Lancet*¹ recently published a randomized, controlled clinical trial, which in our view may change the outcome of a

serious condition: traumatic hemorrhagic shock. This was a high quality trial, and thus contributed top class evidence. The study was not characterized by commercial interests, and the inclusion criteria were based on clinical judgments, i.e., it offered maximum external validity.

The investigators, under the name CRASH 2 Trial Collaborators, came from 274 hospitals in 40 countries, and were able to complete an ambitious project involving the recruitment of about 20,000 trauma patients (specifically 20,211) with significant blood losses.

[☆] Please cite this article as: Muñoz-Sánchez A, Murillo-Cabezas F. El ácido tranexámico disminuye la mortalidad del *shock* hemorrágico traumático. *Med Intensiva*. 2011;35:286–7.

* Corresponding author.

E-mail address: angeles.munoz.sspa@juntadeandalucia.es (A. Muñoz-Sánchez).

The study compared the use of a low-cost antifibrinolytic agent (tranexamic acid) versus placebo, in the context of a double-blind design. The drug was administered early, in the first 8 h after trauma, at a dosage of 2 g via the intravenous route, a 1 g bolus initially, and 1 g in perfusion over 8 h.

The trial methodology had been previously published in *The Lancet*.² The primary endpoint was mortality of any cause during the first four weeks. The losses during follow-up were minimal: 33 patients in the active treatment group and 47 in the placebo arm. The statistical analysis was carried out on an intention to treat (ITT) basis.

Global mortality, not the only mortality associated to bleeding, was significantly lowered in the tranexamic acid group ($p < 0.0035$). The incidence of occlusive vascular events, fatal or otherwise, was similar in both groups (placebo and tranexamic acid). Surprisingly, no significant difference was recorded in the number of red cell concentrate units transfused in either group.

Since the two study arms proved homogeneous in that they were balanced for multiple clinical risk parameters (age, gender, time from trauma, type of trauma, systolic blood pressure upon admission, respiratory frequency, capillary filling time, heart rate and level of consciousness according to the Glasgow coma scale), and the breaches in protocol were identical in each arm (0.4%), the early administration of tranexamic acid was identified as a first-order therapeutic option thanks to its impact upon the most relevant medical variable: patient mortality. In addition, given the low cost of tranexamic acid, the use of only 81.6 euros in treating 68 patients would allow the avoidance of one death in this group of patients.

The study has some limitations—the most important being the fact that the trial does not clarify the mechanism by which tranexamic acid reduces mortality among patients with traumatic hemorrhage. In fact, not only bleeding-dependent mortality decreases, but also global mortality among the trauma patients. Thus, the comment accompanying the article³ suggests that a plasmin-mediated antiinflammatory effect may be involved. A second study limitation would be the fact that the posology had not been previously tested in a phase II setting with this particular treatment indication. In any case, the dosage employed was

consistent with the specifications of the Summary of Product Characteristics, and with the data obtained from studies in heart surgery and other indications, where no increased effectiveness was observed with higher doses.

Some years ago, in this same journal, we asked ourselves what could be done to improve the results obtained in serious trauma cases.⁴ At the time we did not suspect that an old drug such as tranexamic acid—with an accessible price anywhere in the world—could offer a positive response in the arduous attempt to lessen mortality among such patients.

In conclusion, given the results obtained, the large number of traumatic bleeding deaths recorded worldwide, and the efficiency of tranexamic acid, we have supported the application to include this drug in the list of essential medicines of the World Health Organization (WHO). In our setting, and from June 2010, the Drug Commission has authorized the compassionate use of tranexamic acid in traumatic hemorrhagic shock patients treated in our hospital. Until the drug company includes this treatment indication in the Summary of Product Characteristics, we consider compassionate use to be the fastest way to make this drug available to patients with a view to improving the outcome of trauma cases involving significant blood losses.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

1. CRASH 2 Trial Collaborators Shaker H, Roberts I, Bautista R, et al. Effects of tranexámico acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23–32.
2. CRASH2 Protocol. 2005. Available from: <http://www.thelancet.com/protocol-reviews/05PRT-1>.
3. Levy JH. Antifibrinolytic therapy: new data and new concepts. *Lancet*. 2010;376:3–4.
4. Murillo-Cabezas F, Muñoz-Sánchez MA. Qué podríamos hacer para mejorar los resultados en el traumatizado grave? *Med Intensiva*. 2003;27:669–72.