POINT OF VIEW

Tranexamic acid in patients with multiple injuries: good, elegant, and cheap?

Ácido tranexámico en el paciente politraumatizado: ¿bueno, bonito y barato?

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In 1962, the Okamoto family first described a new chemical structure, which exceeded the antifibrinolytic capacity of epsilon-amino-caproic acid at an experimental level[1]. The mechanism of action of this molecule, known today as tranexamic acid (ATX), is based on its analogy with lysine. Its binding to plasminogen prevents the tissue activator from transforming it into plasmin and, in this way, the fibrin is lysed. Therefore, the immediate effect generated by this drug enzymatically favours the creation of a stable clot and reduces the probability of bleeding. However, it is not until 40 years after its publication that the FDA (Food and Drug Administration) will approve its intravenous use in the context of dental extractions. Twelve years later, in 2009, its oral use was approved for the control of metrorrhages.

During this time, different studies have been carried out that are considered "off-label" to evaluate their antifibrinolytic usefulness during cardiac surgery. Henry et al.'s group, in a systematic review, included 3,836 patients, and objected that the use of ATX reduced transfusion needs in this type of surgery by up to a third, although this did not imply a benefit in terms of mortality[2]. Based on these evidences, and equating the aggression of a complex surgery with the polytraumatized patient, the bases were established to generate the hypothesis that would allow elucidating the potential benefit of ATX in the polytraumatized patient.

Recruitment for the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) clinical trial began in 2005, where the authors postulated that a loading dose of 1 g of ATX, followed by a perfusion, would improve prognosis in severe trauma[3]. The clinical criteria selected to generate the inclusion criteria were relatively simple: traumatic history, tachycardia and hypotension, among others. Thus, given the uncertainty of the clinician to use this drug in the first 8 hours, the possibility of randomization in the study was discussed. Finally, 20,211 patients were recruited and it was one of the largest clinical trials developed in this area. The authors found that the use of ATX reduced monthly mortality from any cause. The work revealed a high safety profile, without a higher incidence of thrombotic phenomena. One year later, the results of CRASH-2 were published, which selected polytraumatized patients with active bleeding[4]. This new analysis corroborated that the precocity in the administration of treatment, within the first 3 hours, was beneficial. However, after this time window, ATX changed its meaning and became a risk factor in terms of mortality. All this evidence led the World Health Organization to include ATX in its list of essential drugs in 2011. In fact, it was estimated that the systematic use of this drug could save 70,000-100,000 lives a year.

Although its effectiveness was reflected in the civilian field, its usefulness in the military field was evaluated from Camp Bastion in Afghanistan. In this retrospective work, a detailed explanation was made as to how CRASH-2 suffered from certain analytical parameters related to coagulation, as well as the fact that the profile of recruited patients did not adequately resemble (depending on the number of penetrating traumatisms and transfusion needs, among others) the combat scenario. Thus, the study Military Application of Tranexamic Acid in Trauma Emergency Resuscitation -MATTERs- was initiated, which identified 896 soldiers who had received at least one red blood cell concentrate, to later evaluate whether or not ATX had been used during its handling[5]. This work detected an improvement in coagulation parameters and prognosis in those patients who received ATX. However, there was an increase in the incidence of deep venous thrombosis and pulmonary embolisms, justified in the paper by the increased injury load of patients.

The Roberts et al. group, using a systematic review, found only two clinical trials that evaluated the use of ATX in severe traumatic pathology[6]: one was CRASH-2, and the other was a clinical trial developed in Thailand. Obviously, the effect of CRASH-2 and the large number of patients recruited made the benefit of ATX within the first 3 hours of the lesion unquestionable. The authors pointed to a reduction in the degree of hemorrhage in patients with severe head trauma (TBI) who received ATX. In view of these indications, the doors were

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Article Information: Received: 6-6-2018. Accepted: 31-8-2018. Online: 10-4-2019.
Editor in charge: Òscar Miró.

opened to the development of clinical trials on ATX aimed at 2 different profiles of neurocritical patients: severe isolated TBI (CRASH-3) and spontaneous cerebral haemorrhage (TICH-2)[7,8].

The cost-effectiveness analysis carried out on CRASH-2 data showed that regardless of the country's level of income, the use of ATX meant an efficient increase in health care costs, given that for each year of life gained, only expenditure increased by between 48-64$[9].

However, despite all these benefits, we must highlight that the physiopathological chain unleashed after trauma encompasses multiple factors and variables, fibrinolysis being one of the elements to be taken into consideration[10]. In fact, specific questions must be asked taking into account different factors. Firstly, the emerging management of all trauma patients is not homogeneous. Second, the evidence in these large series should be applied with caution to a specific trauma patient admitted to the emergency department. Third, its early administration forces its indication in the event of suspicion (which is not certain) of active bleeding. Fourth, a therapy is performed without really knowing if there is a situation of hyperfibrinolysis to be treated. Finally, if the alterations in the coagulation of the trauma patient were really known, it could be applied in a personalized and not generalized manner. All these facts are reflected in first-level trauma hospitals, where there was no evidence of a reduction in mortality when ATX[11,12] was used.

Considering that a drug directly reduces mortality in trauma overlooks a series of intermediate steps, such as the assertion that there must always be hyperfibrinolysis and that this, in turn, generates bleeding. However, these assertions cannot be assumed automatically and systematically[13]. In order to do so, viscoelastic tests would be necessary to demonstrate this situation. Studies that have done so have shown that the predominant role and the one that associates greater mortality is that of hypofibrinolysis in trauma[12,14]. As a consequence, adding ATX blindly could be a deleterious factor if it is administered indiscriminately in emergency departments, as the authors report. We also find groups that warn of these findings and consider that the thrombotic profile of ATX should be taken into consideration in this subpopulation of patients, both civilian and military[15].

In view of the available evidence, we can conclude that the use of ATX in critical haemorrhage of traumatic origin is a valid alternative. However, we suggest that its use in other indications should be prudent and aimed at the modulation of a situation of hyperfibrinolysis concomitant to the haemorrhagic process.

Conflicting interests: The authors declare no conflicts of interest in relation to this article.

Contribution of authors: All authors have confirmed their authorship in the author's responsibilities document, publication agreement and transfer of rights to EMERGENCIAS.

Financing: The authors declare the non-existence of funding in relation to this article.

Ethical Responsibilities: All authors confirm in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS that confidentiality and respect for patients' rights as well as international ethical considerations have been maintained.

Article not commissioned by the Editorial Board and peer-reviewed externally

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