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EDITORIAL

Tranexamic acid – choosing the best dose

Ácido tranexâmico – a escolha da melhor dose

Tranexamic acid was initially described in the *Keio Journal of Medicine* in September 1962 by a Japanese research couple,[1] and has been used for decades to prevent and treat a variety of hemorrhagic incidents. Initially marketed and widely used in bleedings after tooth extractions, tranexamic acid has proved itself safe and cost-effective, even in critical scenarios associated with surgeries, trauma and obstetrics.[2,3] The important reduction in mortality with early use in trauma patients and women with post-partum bleeding, observed in the two major clinical trials CRASH-2 and WOMAN,[4,5] contributed decisively to the definition of medical management and recommendations in these populations. In the past 15 years, countless clinical trials in several surgical scenarios have been published. Many other records of ongoing or planned studies can be identified on specific sites, such as clinicaltrials.com.

The potent *in vitro* inhibiting effect of tranexamic acid in activating plasmin in the human plasma was shown in the original publication by Shosuke and Utako Okamato,[1] who observed action in this system at least ten times higher than epsilon-aminocaproic acid, the drug used at that time. Both drugs act as synthetic analogues of lysine and inhibit fibrinolysis, shifting fibrin from binding sites that depend on this amino acid present in the plasmin and plasminogen molecule.[6]

In addition to the expected effect on maintenance of clot stability, such drugs can present other benefits associated with the inhibition of the fibrinolytic pathway, given its components also act as pro-inflammatory agents. Both plasmin and plasminogen have proteolytic activity with activation of metalloproteases of extracellular matrix and act as monocyte activators with increased production of cytokins.[6]

Major orthopedic surgeries that include spine instrumentation and hip and knee arthroplasty, in turn, are procedures with potentially major blood loss, and several strategies are usually implemented to mitigate this risk, including use of tranexamic acid.[7] Similarly to other scenarios, the benefit in reducing perioperative bleeding has been well established; however, an ample heterogeneity of administration regimens, with different tranexamic acid doses, can be observed among the different clinical trials that approach the topic.[7]

Despite the documented effectiveness of antifibrinolytics, the hypothetical increase in risk of ischemic and thromboembolic events, particularly among patients submitted to orthopedic surgery, remains a groundless perception among some professionals. Tranexamic acid is generally well tolerated, and most adverse reactions are considered mild or moderate.[8] Severe events are rare in the clinical trials published, and literature reviews show safety of tranexamic acid in several surgical procedures, including orthopedics.[9] Still, high doses of tranexamic acid can trigger neurological symptoms such as myoclonia, visual disorders, changes in mental status and seizures.

In the present issue of the *Brazilian Journal of Anesthesiology*, two groups of researchers sought answers for the best dose of tranexamic acid in orthopedic procedures. In the article by Saravanan et al.,[10] the authors showed that using an initial low dose *bolus* of the drug (10 $mg.kg^{-1}$) followed by continuous intravenous infusion of 1 $mg.kg^{-1}.h^{-1}$ was more effective in reducing bleeding in spine surgery, femur fracture fixation and total hip replacement than placebo, single doses and even high dose regimens. Souza Neto et al.[11] showed there was no difference in total knee replacement postoperative blood loss when using 1 or 2 grams of intra-articular tranexamic acid at the end of the surgery.

Equal to trauma and obstetrics, standardization of tranexamic acid regimens in surgical procedures that best respond to the goal of reducing bleeding is anticipated. Unnecessarily high doses not only increase risk of complications and adverse effects associated with the drug but increase hospital costs. Certainly, more studies will be required to define the best dose. Efforts toward that end, as the one employed by the authors of the studies included in this issue of the journal, will contribute to perioperative care improvement.

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Conflicts of interest

The author declares no conflicts of interest.

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