EDITORIAL

Tranexamic Acid in Endoprosthesis

Prophylactic Intravenous Treatment is not for Everyone

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Editorial to accompany the article:

“Tranexamic acid prophylaxis in hip and knee joint replacement” by Matthias Goldstein, Carsten Feldmann, Hinnerk Wulf, and Thomas Wiesmann

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Based on large randomized trials (CRASH-2 and WOMAN), the antifibrinolytic agent tranexamic acid (TXA) appears as a „miracle weapon“ in the treatment and control of critical bleeding. It is used in areas such as traumatology, gynecology, and cardiac and liver surgery. According to the current guidelines of the European Society of Anaesthesiology (ESA), “Tranexamic acid can reduce perioperative blood loss and transfusion requirements; this can be highly cost-effective in several major surgical and trauma settings.” (evidence grade B) (1). Although the articles published in orthopedics tend to be inconsistent overall, the meta-analyses published in high-level journals suggest that TXA reduces blood loss and transfusion frequency in major orthopedic surgery without increasing the risk of complications (2). The review published by Goldstein and colleagues summarizes the current state of studies on the prophylactic use of TXA in hip and knee joint replacements in the form of a narrative overview in a balanced manner (3).

Mechanism of action not completely deciphered

Although TXA was developed in Japan as early as 1965, the mechanisms of action of the substance have not yet been conclusively deciphered, and there are still ambiguities in the clinical management of TXA (4). Interestingly, in the large CRASH-2 trauma study, TXA reduced all-cause mortality, but did not affect the need for transfusions (5). In addition, reduced mortality was only associated with the prompt administration of TXA (within the first three hours after injury); indeed, administration outside this time window was associated with 1.44-fold increased mortality (5). It is currently being discussed whether perhaps tissue injury—as occurs for endoprosthetic access—triggers a shutdown of fibrinolysis with microvascular occlusion and organ dysfunction, while hemorrhagic shock with hypoperfusion rather paves the way for classic hyperfibrinolysis with acute clot lysis and uncontrolled hemorrhage (6). If this is indeed the case, using TXA alone for tissue trauma without shock would increase the prothrombotic risk. Hyperfibrinolytic conditions are often seen after cardiac/circulatory arrest with prolonged shock phases, and TXA has so far displayed the greatest effects in the trauma area for patients with shock symptoms who are severely transfusion-dependent.

The risk of thromboembolism with TXA should not be completely ignored

Although the thromboembolic risk associated with TXA use is considered to be low overall, a recent meta-analysis that took into account existing observational studies shows a non-significant higher rate with a pooled relative risk of 1.61 (95% confidence interval, CI [0.86, 3.01]) for a venous thromboembolic event in the context of TXA administration after trauma (7). In a recently published retrospective study, TXA was associated with an increased rate of postoperative strokes (1.7% versus 0.5%; adjusted risk 4.11; 95% CI [1.33, 12.71]; $P = 0.014$) and coma (1.8% versus 1.0%; adjusted risk 2.77; 95% CI [1.06, 7.26]; $P = 0.038$) (8). The study was conducted over an observation period of five years and included 2016 cardiac surgery patients, of which 664 had received a perioperative TXA dose.

Not yet approved for orthopedics

The use of TXA in orthopedic surgery is not yet listed in the product information. As no direct approval for use is available, its use in this area is off-label. Further, its indication approval is not expected to occur in the foreseeable future. Therefore, both the recommendation of the Working Group of Arthroplasty (*Arbeitsgemeinschaft Endoprothetik*, AE) of the German Society for Endoprosthetics (*Deutsche Gesellschaft für Endoprothetik*) for the perioperative administration of TXA (updated May 2017) (9), and the work of Goldstein and colleagues (3), emphasize the importance of preoperative assessment of possible complications, with careful indication determination and adequate documentation. Administering a substance intravenously—and thus systemically—although its mechanisms of action and dosage are still not clearly defined should be thoroughly considered and weighed up. This is especially critical in the context of a prophylactic administration, in the assumption that it could possibly lead to increased blood loss or hyperfibrinolysis perioperatively.

Option of topical application

Demographic change brings increased co-morbidities and polypharmacy as well as increased individual risk, not least with regard to the pro- and anticoagulatory spectrum of blood clotting. Even though it cannot be excluded that low amounts enter the systemic circulation,

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topical application may be an interesting option (10). According to the AE recommendation, intravenous administration of 15 mg TXA/kg body weight and/or intra-articular (and therefore topical) administration of 1 g to 3 g TXA is currently possible (9). No adequate data for oral use are available. Taking into account its rapid onset of action after intravenous administration, of 5 to 15 minutes, it should also be considered whether it would make more sense to use TXA in a needs-oriented manner—that is, only in the case of clinically relevant bleeding and/or proven hyperfibrinolysis.

Point-of-care viscoelastic testing methods, such as rotational thromboelastometry, detect at least fulminant or intermediate (hyper)fibrinolysis within a reasonable time frame. In the case of hyperfibrinolysis, the potential antifibrinolytic effect of the substance can be simulated before the actual clinical administration. This is done using a TXA additive in the assay to test the extrinsic pathway of blood clotting.

This testing system does not detect occult fibrinolysis and requires an hour to detect late fibrinolysis.

Caution with prothrombotic risk profile

Goldstein and colleagues rightly recommend, in line with the recommended practice of the AE, to refrain from the prophylactic intravenous use of TXA in knee and hip arthroplasty following careful risk/benefit assessment if (3):

- a prothrombotic risk profile exists;
- there is a temporal relationship with previous bleeding events;
- a known epilepsy is present.

Data on the use of the substance in high-risk patients are largely missing. Nonetheless, TXA—when and in whichever form administered—can and should properly only be a subcomponent of a patient blood management concept in the perioperative phase.

Conflict of interest statement

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