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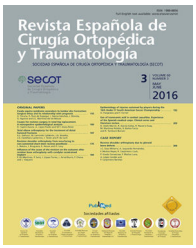

EDITORIAL

Tranexamic acid in orthopaedic surgery: A paradigm shift in transfusion☆

Ácido tranexámico en cirugía ortopédica: un cambio de paradigma transfusional

The strategy on the correct management of the patient's blood pool and transfusion in routine orthopaedic procedures, such as total hip arthroplasty (THA) and total knee arthroplasty (TKA) and spinal surgery, has changed in recent years. In the early 1980s, preoperative autologous blood donation and intra-and post-operative blood retrieval became standard clinical practice, primarily due to fear related to blood-born viral pathogens, and as a strategy to prevent allogeneic transfusion. The rate of allogeneic blood transfusions in elective orthopaedic surgery at that time was above 30%.[1]

From 2010, the concept of saving blood and allogeneic transfusion was extended with other measures including optimisation of preoperative haemoglobin, minimisation of intraoperative bleeding through the use of antifibrinolytic drugs such as tranexamic acid (TXA), and improvement of the patient's anaemia tolerance. This entire set of measures no longer focussed on the technique but on the patient, and was accepted in the scientific literature under Patient Blood Management" (PBM). Its main objective is to improve the clinical outcome by avoiding or minimising unnecessary transfusions. In many centres orthopaedic surgery has been a leader in implementing PBM.[1–3]

We know that during and immediately after major orthopaedic surgery a hyperfibrinolytic stage is observed that leads to increased bleeding.[3,4] Stimuli such as vascular hypoxia, cytokine circulation and endothelial release of the plasminogen activator, as a basic inflammatory response to surgical aggression, catalyse the conversion of plasminogen to plasmin. In addition, the use of ischaemia in knee arthroplasty adds activation of fibrinolysis by releasing fibrinolytic mediators after the tourniquet is released, thus encouraging postoperative bleeding. TXA acts by reversibly blocking the lysine receptor of plasminogen, thus preventing its activation to plasmin and in consequence blocking lysis of polymerised fibrin, thus reducing clot lysis and therefore bleeding.[3,4]

In orthopaedic surgery, the administration of TXA was initiated in TKA and later THA, spinal surgery, hip and knee replacement arthroplasty.[2,3] More recently it has been proposed to reduce bleeding in shoulder arthroplasty surgery and hip fracture surgery, although the degree of evidence is less than in the abovementioned surgeries.

The efficacy of TXA was assessed in a recent meta-analysis in 67 articles selected as best evidence for knee arthroplasty[5] (>9000 patients) and 34 for hip arthroplasty[6] (1668 patients assessed for bleeding and 2545 patients assessed for transfusion). For TKA and THA the reduction in bleeding was about 300 mL and there was a 25% reduction in the transfusion rate. Topical, intravenous and oral formulations of TXA were all superior to placebo in terms of decreased blood loss and transfusion risk, whereas no formulation was clearly superior when compared together. The use of repeated doses of intravenous and oral TXA and higher doses of intravenous and topical TXA did not significantly reduce blood loss or transfusion risk.

In spinal surgery, administration of TXA is effective in reducing bleeding, although not so effective in reducing transfusion requirements.[7] The evidence is not as clear as in TKA and THA because the different randomised studies included surgeries of different levels of fusion, aetiologies and sites, and therefore with different risk of bleeding. The results of a recent meta-analysis[8] highlight that stratification of the bleeding risk in spinal arthrodesis surgery would make it possible to identify the patients who could benefit most from antifibrinolytic treatment (e.g. 3 or more fusion levels) and the individualisation of the bleeding risk in each

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case necessary to support the decision for or against its administration.

More recently, TXA has been included for use in hip fracture. Although we do not have strong evidence for its recommendation, in a recent meta-analysis[9] including a total of 770 patients from 7 studies, intravenous TXA provided a 46% reduction in transfusion risk with no increased risk of thromboembolic events, but with low quality evidence. Hip fracture surgery causes blood loss, but bleeding begins at the time of fracture. Furthermore, the profile of elderly patients is not the same as that of orthopaedic patients, even in the case of a total hip prosthesis. All these considerations result in a lower efficacy profile and even more uncertain complications and side effects than with elective orthopaedic surgery. Therefore the indication for TXA in hip fracture should be individualised.

Safety of tranexamic acid in orthopaedic surgery

Despite the extensive documentation of the efficacy of TXA in major orthopaedic surgery, we have no large studies detailing clinical safety outcomes, especially those related to thromboembolic events and renal complications in the peri-operative period. Clinical trials often select patients with strict inclusion criteria that do not reflect usual clinical practice, thus generating a significant bias in assessing these side effects.

A review[10] of 510 US hospitals and the Premier Perspective database based on notifications for 2006–2012 included 872,416 patients who underwent THA and TKA. On comparing the patients in relation to age and comorbidity index, those treated with TXA (compared to those who were not treated) had a lower rate of thromboembolic complications (.6% vs. .8%), acute kidney failure (1.2 %vs. 1.6%) and combined complications (1.9% vs. 2.6%).

In another review study[11] in 73 randomised controlled trials with 6953 patients who underwent major orthopaedic surgery, the overall gross incidence of venous thromboembolism was 2.1% in patients who received intravenous TXA and 2% in the controls.

Another meta-analysis[12] that used the ASA classification as a proxy for the presence of comorbidities associated with a high risk of a thromboembolic event (78 randomised clinical trials with 7164 patients) concluded that administration of TXA did not increase the risk of thromboembolic disease in patients undergoing arthroplasty.

Tranexamic acid and administration route

The intravenous route is used most for administering TXA in orthopaedic surgery.[2,3] This route will provide us with drug levels in the blood capable of reducing the activity of the tissue plasmin activator by 80% in vitro (10 mg/mL). Maximum plasma levels of TXA are rapidly obtained after a short intravenous infusion and diffuse rapidly to the joint fluid and synovial membrane. Its half-life is 3–4 h. After administration of an intravenous injection of 10 mg/kg to 17 patients treated with a TKA, the concentrations in the joint fluids were similar to those observed in the corresponding serum samples.[4]

Topical administration of TXA emerged as an alternative to intravenous administration in patients in whom we suspect a thrombotic risk. Plasma levels achieved with intravenous administration of 10 mg/kg could be 18 mg/L, whereas topical administration of 1.5 and 3 g achieved plasma levels of 4.5 and 8.5 mg/L respectively.[12] Its effectiveness in reducing bleeding and transfusion is similar to intravenous administration as recent studies with a high level of evidence have shown,[13,14] although the topical administration route is more heterogeneous. Some studies describe pulverisation of the surgical area, administration through drains, sometimes added to the administration of local anaesthetic by infiltration for postoperative analgesia, which adds more variability to its form of administration.[12,15,16] Therefore, in the absence of thrombotic risk factors, intravenous administration seems reasonable to achieve effective and more reproducible plasma levels. Based on the available literature, the administration of multiple or high doses of TXA is not necessary, although its intravenous administration is potentially superior.[5,6]

Dosage of tranexamic acid

TXA dosage for TKA takes into account that most of these operations are performed with a tourniquet and therefore many of the clinical studies dose between 10 mg and 20 mg/kg before the release of ischaemia. Some authors have conducted studies by adding a perfusion of 1 mg–10 mg/kg/h for 3–12 h. Other authors have simplified the dosage with 1 g before releasing ischaemia and 1 g at 3 h. In an attempt to compare the studies, in the meta-analysis by Fillingham et al.,[5,6] they stratified the dosage and considered a high dose as above 1 g or $\geq$20 mg/kg for intravenous administration.

With regard to topical administration in TKA, most studies use total doses between 1 g and 3 g topically and any dose greater than 1.5 g[13,14] is considered a high dose. In the case of THA, the North American clinical guidelines published in 2016[10] recommend the same doses that we have noted for TKA.

In spinal surgery, the most frequently used doses are 10–30 mg/kg as the initial dose followed by 1–2 mg/kg/h during surgery.[8]

Action protocols

The evidence on the effectiveness and safety of TXA treatment in orthopaedic surgery should result in this treatment being included in all protocols of the different centres where these surgeries are performed.

It is advisable to reach a consensus with all of the team participating in the peri-operative period and reach an agreement on the form of administration, route, dose and dosage.[3] Added to this, it would be both desirable and essential to review the transfusion practice for these patients in hospital wards and to adapt them to the change produced by administration of TXA. It is advisable to review the transfusion protocol and make decisions regarding the prescription of packed red blood cells, informing all profes-

sionals involved in the transfusion process (anaesthesiology, on-call doctors, nurses and rehabilitators).[17]

To conclude, the cultural change in recent years with the inclusion of TXA in orthopaedic operating theatres has lead to a paradigm shift in the management of surgical bleeding.

Level of evidence

Level of evidence I.

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Conflict of interests

The authors have no conflict of interests to declare.

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