Editorial

Editorial on "Multiple boluses of intravenous tranexamic acid to reduce hidden blood loss after primary total knee arthroplasty without tourniquet: a randomized clinical trial"

Cheol Hee Park, Sang Jun Song

Department of Orthopedic Surgery, College of medicine, Kyung Hee University, Seoul, Korea

Correspondence to: Sang Jun Song, MD, PhD. Department of Orthopedic Surgery, College of medicine, Kyung Hee University, 26 Kyunghee-daero, Dongdaemun-gu, Seoul 130-701, Korea. Email: songsjun@khmc.or.kr.

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Currently, many surgeons use tranexamic acid (TXA) to reduce peri-operative blood loss and the requirements for transfusion without increasing the incidence of vascular thromboembolisms (VTEs) in patients undergoing total knee arthroplasty (TKA). TXA may be given by an intravenous (IV) or topical route (1). However, the optimal dosage, treatment duration, timing of administration, and best administration route all remain unclear. Both effectiveness and safety may be influenced by the dose, number of doses, timing, and route of administration (2); these factors vary greatly in the literature (3). In one meta-analysis of the use of TXA during various surgical procedures, the dose ranged from 5.5–300 mg/kg (4). In previous studies on TKA patients, the dose of topical TXA given ranged from 0.5–3 g, and that of IV TXA from 10–30 mg/kg (2,5). Previous work suggests that IV-TXA at 10–20 mg/kg seems to be reasonable for most patients undergoing TKA (3). However, the timing of dose(s) remains unclear.

Xie *et al.* performed a prospective, randomized clinical trial exploring TXA doses in patients who underwent TKA without a tourniquet. A total of 151 such patients were randomly divided into three groups: group A received a single bolus of 20 mg/kg IV-TXA before skin incision; group B both the initial and another bolus of 10 mg/kg IV-TXA 3 h later; and group C all of the initial bolus and two more boluses of 10 mg/kg IV-TXA 3 and 6 h later. The mean values of total and hidden blood loss; the maximum falls in Hb, serum C-reactive protein, and interleukin 6 levels; the visual analog pain score; and the swelling ratio were lower in group C than groups A and B. The Hospital for Special Surgery score, range of motion, and length of hospital stay were also better in group C; no episode of VTE was recorded. The authors concluded that multiple boluses of IV-TXA effectively reduced hidden blood loss during TKA without a tourniquet. The addition of another bolus of IV-TXA inhibited the Hb decline further; reduced postoperative inflammation, pain, and knee swelling; improved knee function, and shortened the length of hospital stay.

Pharmacokinetic studies have suggested that an additional bolus of IV-TXA is appropriate after TKA. IV-TXA becomes widely distributed throughout the extra- and intra-cellular compartments (6). The drug diffuses rapidly into the synovial membrane and fluid to attain the same concentration in joint fluid as in serum. The drug half-life in joint fluid is 3 h, similar to that in serum (7). This may be attributable to the fact that a TXA solution has a pH similar to that of sodium chloride (0.9% w/v) and solutions of blood products (8). Therefore, the concentration of TXA in the joint (the site of desired action) is similar to that in the serum. The TXA serum concentration is an important indicator of the duration of action of joint TXA.

Fibrinolysis after TKA peaks 6 h postoperatively but is maintained for about 18–24 h (9). The therapeutic TXA level is about 10 μg/mL; TXA should be maintained at this level to combat fibrinolysis associated with surgery (10). A single IV-TXA dose of 10 mg/kg

afforded a plasma drug concentration of 10–15 μg/mL for 3–4 h (6), and a dose of 20 mg/kg maintained the drug at that level for approximately 8 h (11). Thus, a single-dose-only protocol may yield an inadequate drug plasma concentration by 18–24 h. Repeat boluses are necessary to ensure that the plasma concentration does not fall below the therapeutic level.

The work of Xie *et al.* supports the need for repeat TXA injections. To the best of our knowledge, their study is the only work to compare the effects and safety of different IV-TXA doses in patients undergoing TKA without a tourniquet. Their findings provide important information for surgeons who do not use tourniquets. Additionally, the use of pneumatic tourniquets during TKA increases the activity of the fibrinolytic system (which regulates clot and thrombus formation) and may paradoxically accentuate peri-operative blood loss despite a reduction in intra-operative bleeding (12-15). The hyperfibrinolysis caused by the use of a tourniquet can confound evaluation of the detailed effects of TXA. Therefore, the cited study has the advantage of accurately assessing TXA action and reliably identifying the need for additional doses.

However, several methodological and evidential questions remain. Xie *et al.* had no control group that did not receive IV-TXA; the sample size was small; VTE follow-up was short; and the representativeness of the study subjects questionable. A previous meta-analysis reported that TXA reduced total blood loss by a mean of 591 mL (95% CI, 536–647 mL) (1). It is difficult to compare the new regimen with previous studies because, again, a control group that did not receive IV-TXA was not included.

Xie *et al.* calculated the study sample size by reference to the expected hidden blood loss; it was not sufficiently large to detect significant differences in other variables, including reductions in Hb and inflammatory marker levels, and clinical scores. Furthermore, their sample size was too small to detect meaningful differences between relatively uncommon, but serious, VTE events. Routine ultrasonography was performed before discharge and 30 days later. We are not sure that ultrasonography alone is sufficiently accurate, or the chosen follow-up period adequately long, to detect uncommon VTE events in Asian patients. In other words, the findings are limited by the small study populations. The study may be statistically underpowered, thus associated with the chance of type II error (failure to reject a false-null hypothesis).

The limited representativeness of the study subjects is also of concern. Patients were excluded if they had anemia, clotting disorders, a known allergy to TXA, a flexion deformity >30°, a varus and/or valgus deformity of >30°, and/or were at high risk because of cardiovascular disease or a prior VTE. Additionally, a combination of physical prophylaxis and chemoprophylaxis (enoxaparin and rivaroxaban) was used to prevent VTE. Thus, the results should be interpreted with caution. The safety of the IV-TXA protocol remains unproven in patients with the exclusion criteria listed above and those not prescribed chemoprophylaxis. Furthermore, the study was limited to Asian patients. The prevalence of VTE, obesity, dietary patterns, and genetic factors affecting coagulation, differ by ethnic status. These factors should be considered when extrapolating the findings to other populations.

Even considering these limitations, surgeons performing TKA without a tourniquet may choose to adopt the doses, timing, and TXA administration route of the present study. The effect of IV-TXA on hidden blood loss is influenced by the TKA dose, and the timing thereof, in TKA patients treated without a tourniquet. Multiple-bolus IV-TXA seemed to not only reduce hidden blood loss, but also postoperative inflammation, swelling around the knee joint, and pain. However, in addition to the limitations mentioned above, many factors can affect the clinical outcomes of TKA. Therefore, the present findings should be carefully interpreted; further well-designed studies are needed to evaluate the effects and safety of different TXA doses and dosing methods.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

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