Editorial

Efficacy of combined use of intraarticular and intravenous tranexamic acid in total knee arthroplasty

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Introduction

Tranexamic acid (TXA) has come to light as an effective method to decrease blood loss and transfusion rates in total knee arthroplasty (TKA) without increasing the risk of thromboembolic events (TEE) (1). Many initial studies utilized intravenous (IV) TXA and more recently topical TXA has also been shown to be effective (2,3). In these studies, various dosing regimens have been used for both IV and topical TXA. Some have attempted to find the most beneficial regimen, demonstrating better results with two IV doses compared to a single IV dose (4,5). Others have compared various topical regimens to IV regimens, often comparing single topical doses to one or two IV doses (6-8). These have often shown similar results between IV and topical TXA; however, comparison is difficult due to variance in the regimens used (quantity of TXA, number of doses, route of topical administration). Our standard practice is to administer one gram IV prior to incision and one gram IV at initiation of closure. This provides an effective, easily reproducible routine for the entire surgical team.

Methods

In their study, Lin *et al*. have performed a prospective randomized controlled trial to investigate the effects of a combined regimen using both IV and topical TXA (9). They randomly assigned 120 patients to one of three groups: (I) one gram TXA in 20 milliliters (mL) normal saline injected intra-articularly via two deep drains after arthrotomy closure; (II) one gram TXA IV 15 minutes prior to tourniquet inflation combined with one gram TXA injected intra-articularly as in group 1; and (III) control group with 20 mL normal saline injected intra-articularly via two deep drains after arthrotomy closure. They utilized a tourniquet in all cases which was inflated prior to skin incision and deflated after wound closure. All drains were clamped for one hour after injection and removed after 24 hours.

Results

Their outcomes included postoperative hemoglobin (Hgb) levels, Hgb drop, total drain output, total blood loss, and transfusion rate. They provided a transfusion for any Hgb less than 8.0 grams/deciliter (g/dL) or symptomatic patients with Hgb less than 9.0 g/dL. They demonstrated a significant improvement in Hgb level, Hgb drop, and total drain amount with the combined group compared to both the topical and control groups. Both TXA groups also had a significant decrease in total blood loss and transfusion rates compared to the control group. Although the combined group had a lower mean total blood loss compared to the topical group, mean difference of 126 mL, this was not statistically significant (P=0.063). Six patients in the control group required transfusion, one in the topical group, and none in the combined group. No patient experienced a TEE within 3 months of surgery.

Discussion

This supports previous studies demonstrating an increased effect with multiple doses compared to a single dose of TXA (4,5), but with a novel regimen. We agree with the importance of administering TXA prior to tourniquet inflation and skin incision. This allows TXA to rise to a therapeutic level within the joint before the fibrinolytic cascade is initiated by the surgical trauma. This initial dose

may be especially important for surgeons who choose to perform TKA with no or reduced tourniquet usage as they experience increased intraoperative blood loss compared to surgeons who use a tourniquet throughout the entire surgery.

As noted above, the authors found some statistically significant improvements with the combined regimen in addition to a trend in lower total blood loss compared to the topical only group. Unfortunately, due to a lack of comparison with an established IV—only regimen in this study, one is unable to fully assess the efficacy of this combined regimen. We consider transfusion to be the clinically relevant manifestation of blood loss as it is a medical treatment which carries its own risks and costs to both the patient and the hospital (10). The small number of patients and low transfusion rates make it difficult to fully evaluate this clinically relevant measure in this study. The authors recognize these weaknesses and could more fully analyze the efficacy of their combined regimen in a subsequent study with larger patients groups comparing all possible TXA administration regimens (topical only, IV only, combined IV and topical).

As mentioned by the authors, one appeal to using topical TXA is due to concern of a theoretical increased risk of TEE (defined as deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or cerebrovascular accident (CVA). This concern primarily arises from previous case reports attributing various TEE to TXA use; these include cerebral thrombosis (11), arterial thrombosis (12), acute renal failure (13), and ischemic stroke (14). Rydin and Lundberg reported intracranial thrombosis in two women after taking 1 to 4.5 g of TXA daily during menstruation for 1 year (11). At the time of thrombosis both women were found to have a thrombocytosis, another plausible explanation for their thrombosis as was recognized by the authors of the report. A second report was of a woman who died of an arterial thrombosis after using antifibrinolytics daily for a total of 6 years; during 3 of these 6 years she took 6 g of TXA daily (12). The authors of the report did not believe TXA to be relevant in the patient's thrombosis, as she had discontinued its use 4 months prior to the event and she was also found to have Takayasu's arteritis, a known thrombogenic condition. Another report presented a patient who received 500 mg TXA daily for 3 days to treat uterine bleeding after undergoing an abortion (14). In addition to having been recently pregnant, the patient was also found to be heterozygous for the methylene—tetrahydrofolate reductase C677T gene. Homozygous patients with this mutation are known to have an increase in ischemic strokes (15), but whether there is an increased risk in heterozygous patients is not fully understood (14).

The above case reports include the use of TXA, but its direct relationship with the observed TEE remains unclear at best. TXA is an antifibrinolytic medication which prevents clot breakdown and not a prothrombotic medication. In two early studies Astedt found that TXA did not affect fibrinolytic activity within human vein walls (16) or the large heart arteries or coronary vessels of the rat (17). This is important as the fibrinolytic activity of the vessel wall is more influential in preventing thrombosis than the fibrinolytic activity in the blood stream itself (16). Furthermore, during TKA Benoni *et al*. found significantly increased fibrinolytic activity in blood taken from the wound bed when compared to that found in the peripheral venous blood (18). They also found that TXA decreased the fibrinolytic activity within the wound bed without affecting peripheral fibrinolysis.

Many randomized trials and meta-analyses from various surgical disciplines have contributed evidence demonstrating the safety of TXA (19). A meta-analysis of placebo controlled randomized studies demonstrated no increased risk of TEE in patients undergoing cardiac surgery who received significantly higher doses of TXA than those used in TKA (20). Other studies investigating TXA in high risk cardiac surgery included patients with a history of TEE and demonstrated no increased rate of TEE postoperatively (21,22). Conversely, almost all orthopedic studies, including Lin *et al*.'s, have excluded patients with a history of prior TEE. This exclusion criterion has persisted in orthopedics despite the uncertainty of the associations seen in the aforementioned case reports, multiple meta-analyses demonstrating no increased risk of TEE with TXA in TKA, and the significantly lower dose administered in TKA compared to that used in cardiac surgery. The recently published results showing our experience with IV TXA in patients with a history of previous TEE demonstrated no statistically significant increase in the rate of TEE with IV TXA (23). There was a significantly increased risk of postoperative TEE in patients with a history of previous TEE, but there was no statistically significant additional increase in risk when TXA was used in these patients.

Nevertheless, for those hesitant to use IV TXA in the setting of previous TEE, topical TXA provides an attractive route of administration with decreased, but not zero, systemic absorption. Wong *et al*. measured systemic TXA levels at a single time point after topical administration, finding

mean plasma levels of 4.5 and 8.5 mg/L approximately 80 minutes after application of 1.5 g and three grams respectively (2). In comparison, Pilbrant *et al*. found a mean plasma TXA level of 25.3 mg/L 90 minutes after administering 1 g TXA IV (24). The mean plasma level decreased to less than 10 mg/L approximately four hours after IV administration. Studies have shown topical TXA to effectively decrease blood loss during TKA (2,3), and others have shown comparable results to single dose IV TXA regimens (6,7). Thus, in patients with previous TEE, topical TXA presents an effective option to decrease blood loss, but the absorption of topical TXA may vary throughout the postoperative period and warrants further study.

At this time, we continue to use our standard IV TXA regimen in all total joint arthroplasty patients, including those with a history of previous TEE. This paper by Lin *et al*. provides additional evidence supporting increased efficacy with two doses of TXA compared to one. However, this study is unique, comparing their combined IV and topical regimen to a single topical dose. Again, we agree with Lin *et al*. on administering TXA prior to the initiation of traumatic fibrinolysis, thus inhibiting the initiation of this enzymatic reaction at the surgical site. Then, the second TXA dose, be it IV or topical, can be administered prior to the second time of increased fibrinolysis associated with the release of the tourniquet. We congratulate the authors on a well-executed study and look forward to continued investigation into the best use of TXA in order to provide maximal benefit to all patients.

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