Tranexamic acid for the reduction of blood loss in total knee arthroplasty

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Abstract: *The Journal of Arthroplasty* recently published a paper entitled "The Efficacy of Combined Use of Intraarticular and Intravenous Tranexamic Acid on Reducing Blood Loss and Transfusion Rate in Total Knee Arthroplasty". Tranexamic acid (TXA) is an antifibrinolytic drug whose administration during the perioperative period either by intravenous route or topically applied to the surgical field has been shown to reliably reduce blood loss and need for transfusion in patients undergoing total knee arthroplasty (TKA). Although randomized trials and meta-analyses did not show an increase in thromboembolic events, concerns remain about its repeated systemic application. The authors of the study introduced a novel regimen of TXA administration combining a preoperative intravenous bolus followed by local infiltration at the end of surgery with the idea of maximizing drug concentration at the surgical site while minimizing systemic antifibrinolytic effects. The combined dosage regimen appears to be more effective than single dose local application in reducing blood loss and transfusion rate without any complications noted.

Keywords: Total knee arthroplasty (TKA); tranexamic acid (TXA); systemic; topical

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Total knee arthroplasty (TKA) is among the most commonly performed orthopedic procedures. With the ageing of the population, increase in life expectancy and our ability to more effectively manage comorbidities in the perioperative period, the number of people undergoing joint replacement surgery has been steadily increasing over the last decades and that trend is going to continue into the foreseeable future. Only in the US it is estimated that by the year 2030 almost 3.5 million total knee arthroplasties will be performed annually (1).

Orthopedic surgery accounts for a significant proportion of all perioperative packed red blood-cell transfusions, with arthroplasty accounting for nearly 40% of transfusions in orthopedic patients (2). It is known that perioperative anemia and RBC transfusions are associated with increased healthcare resource utilization, hospital length of stay, delayed recovery and higher rates of postoperative morbidity and mortality (3,4).

Various techniques have been introduced to reduce blood loss in the perioperative period and perioperative antifibrinolytic therapy is recommended as part of a comprehensive perioperative blood management strategy (5). The use of antifibrinolytic agents is based on the fact that surgical trauma besides promoting clot formation by activating the intrinsic and extrinsic coagulation cascades also leads to a concomitant activation of plasminogen inducing a state of hyperfibrinolysis accelerating clot degeneration and increasing surgical site bleeding.

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine that reversibly occupies lysine-binding sites on plasminogen preventing its binding to the surface of fibrin and activation, resulting in inhibition of fibrinolysis (6).

Since the pioneering work of Hiippala and Benoni and colleagues (7,8) many prospective randomized studies and meta-analyses have confirmed the effectiveness of TXA to reduce perioperative blood loss and the need for allogenic and autologous blood transfusion in patients undergoing TKA (9). The most widely reported dosage regimen is

systemic TXA administration by one initial intravenous bolus followed by another bolus or continuous infusion (10). However, to date there are no prospective randomized studies specifically designed and adequately powered to assess the safety of perioperative systemic TXA administration.

Recent reviews and meta-analyses have found no increased risk of thromboembolic events and renal failure with systemic TXA administration (11). The largest such analysis in orthopedic patients was recently published by Poeran and colleagues (12). In a retrospective cohort study encompassing over 870,000 cases of elective total knee or hip arthroplasty in 510 US hospitals perioperative intravenous TXA administration was not associated with increased risk of complications including a composite of thromboembolic complications, acute renal failure, cerebrovascular events, myocardial infarction and in-hospital mortality. Besides adding incremental evidence of safety of TXA use in orthopedic patients this study is also significant because patients receiving intravenous TXA were stratified into groups according to dose categories (none, ≤1,000, 2,000 and ≥3,000 mg). TXA use was significantly associated with a decreased need for allogeneic or autologous blood transfusions [odds ratio (OR) varying from 0.31-0.38 by dose category], and allogeneic blood transfusions (OR, 0.29-0.37), with no significantly increased risk for complications: thromboembolic complications (OR, 0.85-1.02), acute renal failure (OR, 0.70-1.11), combined complications (OR, 0.75-0.98), and admission to an intensive care unit (OR, 0.73-1.01). The authors concluded that 2,000 mg TXA seemed to have the best effectiveness and safety profile.

Despite these encouraging observations regarding safety of TXA use, repeated administration of an antifibrinolytic drug in elderly patients undergoing surgery which promotes a hypercoagulable state and who often are frail with comorbidities putting them at increased risk of DVT (e.g., diabetes, obesity, cardiovascular disease) still raises concerns. In order to address this issue, studies to establish the safety and effectiveness of topical TXA administration have been conducted. The idea is to maximize drug concentration at the site of surgery by intraoperative local infiltration resulting in negligent systemic absorption (13) and by doing so reducing or avoiding completely a generalized antifibrinolytic effect while retaining the beneficial effects on minimizing blood loss. Indeed, topical application has proven to have at least comparable effects to intravenous TXA on controlling blood loss (14,15). In a recently published meta-analysis of 14 randomized controlled trials (11 in knee replacement, two in hip replacement and one in both) which investigated the effect of topical TXA on blood loss and rates of transfusion Alshryda and colleagues found that indirect comparison of placebo-controlled trials of topical and intravenous TXA indicates that topical administration is even superior to the intravenous route without any significant difference in complication rates (16).

In a prospective randomized controlled study investigating various TXA routes of administration and dosage regimens Maniar and colleagues found a single topical dose of TXA to be more effective compared to a single systemic dose. However, the same study concluded that the most effective TXA dosage regimen consists of two intravenous doses, a preoperative one followed by an intraoperative one (17).

Lin *et al.* (18) recently published an interesting study introducing the concept of combining two modes of TXA administration. They randomized 120 patients undergoing primary TKA into three groups. One group received a single 1.0 g dose of TXA in 20 mL saline intra articularly after joint capsule closure (topical group); the second group received a combination of intravenous injection of 1.0 g TXA 15 minutes before skin incision followed by local intra-articular application of 1.0 g after joint capsule closure; and the third group received only 20 mL normal saline by local intraoperative infiltration (control group). Outcome parameters were postoperative hemoglobin levels, Hb drop calculated as the difference between preoperative and Hb values at postoperative days 1 and 3, total drain amount at 24 h after surgery, calculated total blood loss and transfusion rate. As expected, the mean total blood loss was significantly lower in both the topical and combined groups compared to placebo (705.1±213.9 *vs.* 578.7±246.9 *vs.* 948.8±278.5 mL, respectively; P<0.001) as was total drain amount (110.9±61.3 *vs.* 56.8±34.6 *vs.* 211.9±121.9 mL; P<0.001). There was also a significant difference in transfusion rates when comparing the two TXA groups to controls (3 *vs.* 0 *vs.* 15%; P=0.009) as well as in amount of blood transfused (12.5±79.1 *vs.* 0 *vs.* 62.3±167.4 mL; P=0.008). There was no significant difference when comparing mean total blood loss among the two TXA groups although there is a trend in favor of the combined regimen (P=0.063). The same holds true when comparing transfusion rates among those two groups. The study protocol also provided for screening patients for clinical signs of deep venous thrombosis (including Homan's sign and leg swelling) up to 3 months after surgery. The authors recorded no complications, including thromboembolic events during the follow up period. Of interest is the finding that in the combined

group the postoperative Hb levels were significantly higher and the postoperative Hb drop smaller when compared to the topical and control group. Total drain amount in the combined group was also lower when compared to the other two groups (P<0.001 for both). These findings are suggestive of a combined protocol consisting of an initial intravenous bolus followed by local infiltration at the end of surgery is more effective then local infiltration alone. Although further studies with larger numbers of patients are needed to compare this new combined regime to other modalities of TXA administration in TKA and corroborate its effectiveness and safety, the authors should be complimented on the innovative approach.

Conclusions

The need to optimize healthcare resource utilization and patient outcome in the light of evidence of serious adverse effects of perioperative anemia and allogenic blood transfusion and increasing demand for knee replacement surgery in an ageing, comorbidity laden population has led to the development of strategies aimed at reduction of perioperative blood loss and transfusion requirements.

Although the efficacy of TXA in reducing blood loss in TKA has been well established, there is still uncertainty about the optimal route of administration and despite meta-analyses supporting its safety concerns remain regarding risk of thromboembolic events with higher systemic concentrations and prolonged intravenous application. According to recent randomized studies local surgical site infiltration seems to be at least non-inferior to intravenous application of TXA in reducing blood loss during TKA.

For the concerned practitioner a regimen combining an initial preoperative intravenous bolus with local application by surgical site infiltration at joint closure seems to offer an effective and safe alternative to the more traditional approach using repeated IV administration of TXA. This combined regimen possibly maximizes the benefits of both systemic and local TXA application without exposing the patient to a prolonged increase in systemic antifibrinolytic activity.

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