Is Tranexamic Acid Safe in Total Knee Replacement Surgery in Patients with Coronary Artery Disease?

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ABSTRACT

Introduction: Tranexamic acid (TXA) reduces blood loss and need for a transfusion after total knee arthroplasty (TKA). However, patients with a history of coronary artery (CA) stent placement might be at increased risk for thromboembolic complications. **Materials and Methods:** We performed a retrospective analysis of patients with a history of coronary stenting who had undergone primary and revision TKA and received preoperative TXA. A comparison was made with a group of patients without coronary stenting. The presence of any clinical or electrocardiographic changes of acute coronary occlusion, thromboembolic events (TEE), blood transfusion, and pre- and postoperative hemoglobin levels were analyzed. **Results:** 57 patients underwent 59 TKA surgeries (56 primary and 3 revisions) with a history of coronary stenting at least 1 year before arthroplasty. One patient presented symptoms of acute coronary syndrome and electrocardiogram (ECG) changes. There were no differences in the number of thromboembolic events. Only 1 patient received red blood cell transfusion in the control group. Relative bleeding was lower in the coronary group regardless of chronic use of aspirin and clopidogrel before surgery (2.09 vs 3.06 in the control group; p=0.01). In high-risk patients, TXA was not associated with higher TEEs. **Conclusions:** Although TXA seemed safe and effective in this database review of patients with previous placement of CAS; a larger prospective trial is warranted to confirm these results.
Keywords: tranexamic acid; total knee arthroplasty; coronary disease.
Level of Evidence: IV

¿Es seguro el ácido tranexámico en la cirugía de reemplazo total de rodilla de pacientes con enfermedad coronaria?

RESUMEN

Introducción: El ácido tranexámico reduce la pérdida sanguínea y los requerimientos de transfusiones luego de un reemplazo total de rodilla. Una de sus contraindicaciones relativas son los antecedentes de colocación de prótesis intravasculares coronarias, por un supuesto aumento de eventos tromboembólicos. **Materiales y Métodos:** Análisis retrospectivo de pacientes sometidos a un reemplazo total de rodilla primario y de revisión que recibieron ácido tranexámico y tenían antecedente de colocación de prótesis intravascular coronaria. Se los comparó con un grupo sin estas prótesis. Se analizó la presencia de cualquier cambio clínico o electrocardiográfico de oclusión coronaria aguda, eventos tromboembólicos, el requerimiento de transfusión sanguínea y el nivel de hemoglobina pre y posoperatorio. **Resultados:** 57 pacientes (59 cirugías, 56 reemplazos primarios y 3 revisiones) con colocación de prótesis intravascular coronaria, al menos, un año antes de la artroplastia. Un paciente tuvo síntomas de síndrome coronario agudo y cambios en el electrocardiograma. No hubo diferencias en la cantidad de eventos tromboembólicos. Solo un paciente del grupo de control recibió una transfusión de glóbulos rojos. El sangrado relativo fue menor en el grupo coronario independientemente del uso crónico de aspirina y clopidogrel antes de la cirugía (2,09 vs. 3,06 grupo de control; p = 0,01). En pacientes del alto riesgo, el ácido tranexámico no se asoció con más eventos tromboembólico. **Conclusiones:** El ácido tranexámico impresionó ser seguro y efectivo en nuestro grupo de pacientes con prótesis intravasculares coronarias; sin embargo, se necesita un estudio prospectivo con más casos para confirmar estos resultados.
Palabras clave: Ácido tranexámico; reemplazo total de rodilla; coronariopatía.
Nivel de Evidencia: IV

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INTRODUCTION

Postoperative bleeding is a common complication after total knee replacement (TKR), often requiring transfusion of packed red blood cells. Historically, the estimated bleeding after a TKR was 2 liters, which often required transfusions in a very high percentage of patients.[1,2] Currently, multiple protocols have been developed for the management of blood loss in joint replacement surgery. Many of these protocols include the administration of drugs that reduce bleeding by acting at the level of the coagulation cascade.[3-5]

Tranexamic acid (TXA) began to be used in cardiac surgery during the 1980s, along with other antifibrinolytic agents, and its use has gained popularity in orthopedic surgery in recent years with good results. It is a synthetic derivative of lysine with pure antifibrinolytic activity that stops the fibrinolysis system, preventing fibrin degradation (Figure 1).[5-7]

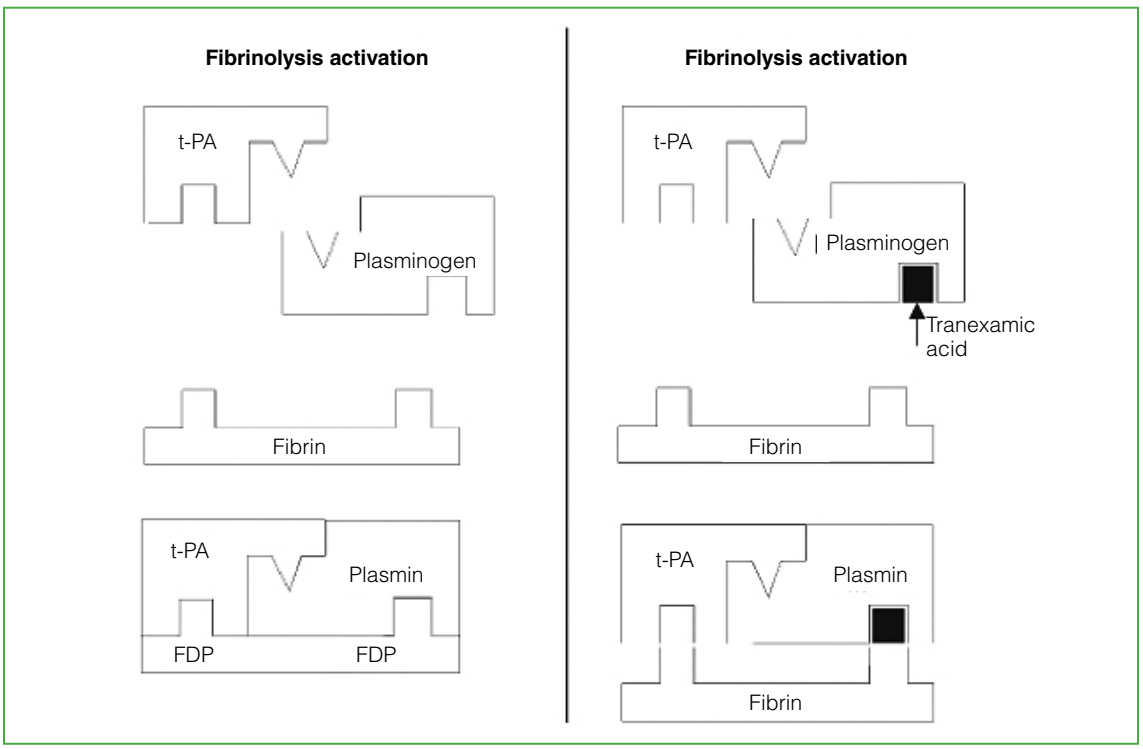

Figure 1. Diagram showing the mechanism of action of tranexamic acid in the coagulation cascade.
t-PA = tissue plasminogen activator, FDP = fibrin degradation products

The half-life of intravenous TXA is 2 hours. After a 15 mg/kg dose, its plasma concentration remains above the effective plasma concentration required to inhibit fibrinolysis (13 µg/ml) for 4 to 6 hours. On the other hand, TXA easily penetrates large joints; in joint fluid, it reaches a concentration comparable to that in plasma within 15 min of intravenous administration. It is metabolized by the kidney. The only absolute contraindication to the administration of TXA is allergy.[7]

Multiple prospective studies with patients undergoing TKR have shown a reduction in blood loss and packed red blood cell transfusion rates with TXA, and this has been substantiated by several meta-analyses, including a recent study examining efficacy and safety of TXA in TKR.[5,8] An increase in thromboembolic or cardiovascular complications has not been demonstrated in TXA trials, but these studies usually exclude patients with multiple comorbidities or known risk factors that could increase the risk of thromboembolic events.[8-10]

As a result of these limitations, it is not yet clear whether TXA increases the risk of postoperative thromboembolic events in patients with known coronary artery disease and a history of coronary artery stent placement.

The main objective of this study was to determine whether the use of TXA in patients undergoing primary or revision TKR with a history of coronary artery disease increased the incidence of acute ischemic cardiac events within 30 days of surgery. As a secondary objective, the risk of bleeding in patients with a history of coronary artery stenting compared with a control group was evaluated.

MATERIALS AND METHODS

A retrospective review was carried out in our institutional database of the medical records of patients who underwent primary or revision TKR between March 2012 and April 2015 and who were administered TXA. Questionnaires were recorded electronically, such as the functional and objective Knee Society Score (KSS), the Knee injury and Osteoarthritis Outcome Score (KOOS), in addition to the visual analog pain scale to assess surgical results, as well as patient satisfaction. In addition, we recorded the demographic data of the patients (age, sex, height, weight and body mass index), the date of operation, the surgeon, the side of the surgery (right, left or bilateral), the type of surgery (primary or revision) and risk factors, such as diabetes, smoking and relevant pathological history (cardiovascular, renal or oncological disease).

To evaluate the main objective, we recorded the incidence of acute coronary events within 30 days of knee surgery in patients with a history of coronary artery stenting with more than one year of evolution. A coronary event was defined as any clinical presentation, hospitalization or intervention due to an acute coronary occlusion event.

Estimated intraoperative blood loss was recorded, and preoperative hemoglobin level was compared with that of controls at 24 and 48 h postoperatively in patients undergoing primary replacement. These results were compared with those of a paired control group of patients without a history of coronary artery stenting. A transfusion of packed red blood cells was indicated for patients with hemoglobin levels <8 g/dl or <10 g/dl and clinical symptoms of anemia.

Before the operation, all the patients regularly took acetylsalicylic acid and did not discontinue it for surgery. Any other oral anticoagulant agent was discontinued 10 days before the intervention. The surgeries were performed through a medial parapatellar approach without a hemostatic cuff. The standard administration protocol for TXA is the infusion of 1000 mg in 50 cc of physiological solution, 30 min before the incision. All patients were clinically monitored for 48 h to detect any clinical evidence related to acute arterial occlusion.

Since all were taking aspirin and clopidogrel, and none had a history of thromboembolism, they were given 100 mg of aspirin every 12 h for 4 weeks as thromboprophylaxis, and then resumed their usual dose of both agents.

Statistical analysis included a standard t-test to compare both groups. Relative bleeding was calculated based on the drop in hemoglobin and hematocrit values before and after surgery at 48 h for each group separately, and they were compared with each other.

RESULTS

During the study period, 56 primary TKRs were performed in 54 patients and three revisions in patients with a history of coronary artery disease and coronary stent placement. The control group included 51 patients with 51 primary TKRs. Table 1 details the characteristics of the groups.

One patient attended the hospital emergency department with acute coronary symptoms 30 days after the operation. He was a male with a stent in the circumflex coronary artery placed two years before the TKR, with regular check-ups and with no other relevant history. Before the procedure, the hemoglobin level was 12.7 mg/dl, with a postoperative control of 10.7 mg/dl at 24 hours. He consulted due to chest pain seven days after the operation, studies were performed that revealed electrocardiographic changes compatible with ischemia. During the angiography, the patency of the previous stent and the acute occlusion of another vessel (right coronary artery) were verified; therefore, recanalization was carried out with a new stent (Figure 2). He evolved favorably and was discharged after 48 hours, without complications with the recovery of his knee.

Table 1. Demographic data.

	Coronary Group	Control Group	p
Female sex	17	20	0.625
Male sex	37	31	0.225
Age (mean)	71.8	70.9	0.874
BMI	30.12	29.7	0.945

BMI = body mass index. There is no evidence of differences between the two groups.

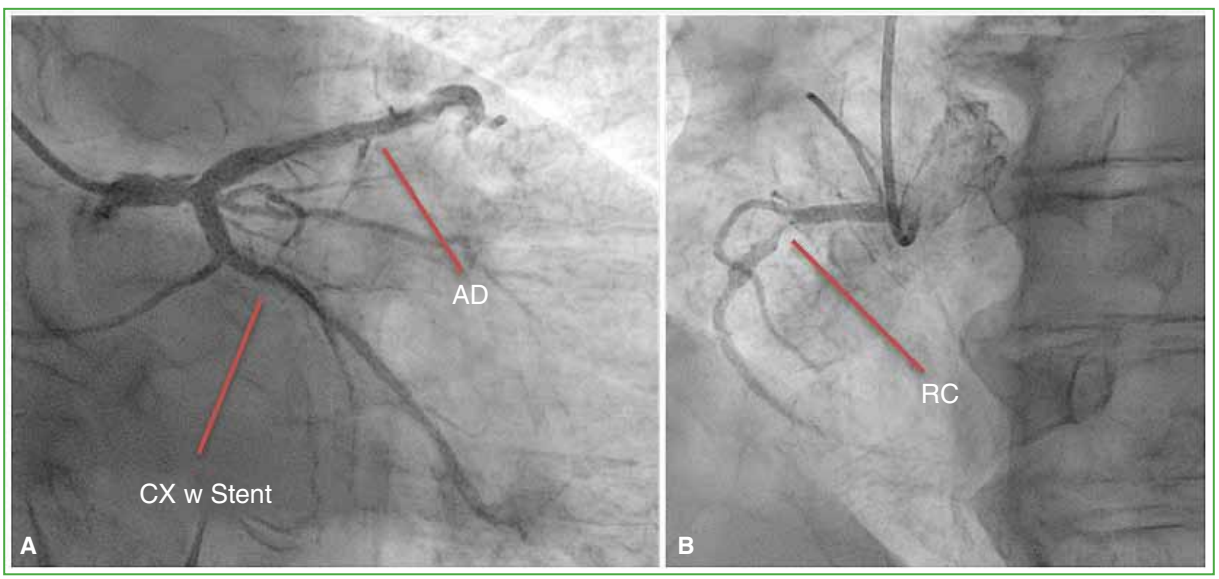

Figure 2. Coronary angiography images with stent in the circumflex artery (**A**) and obstruction of the right coronary artery (**B**).

Regarding the evaluation of the secondary objective of the study, the relative bleeding was measured with hemoglobin and hematocrit levels, and their fall 48 hours after surgery (Table 2).

Table 2. Hemoglobin and hematocrit levels before surgery and at 48 h.

	Coronary Group	Control Group	p
Preoperative hemoglobin, mg/dl	13.19	13.25	0.96
Preoperative hematocrit, %	40	39.9	0.89
Hemoglobin day 2, mg/dl	11.1	10.19	0.01
Hematocrit day 2, %	32.8	30.53	0.03

Relative bleeding was significantly lower in the coronary group.

DISCUSSION

TXA has been a great contribution because it reduces the need for blood transfusions in patients undergoing joint replacement. Its use has been popularized since 2010 with multiple studies in the field of orthopedics, both in joint replacement surgery and in acute trauma.[10,11] Its routine administration is endorsed by several societies, such as the *American Association of Hip and Knee Surgeons* (AAHKS) and the *American Academy of Orthopedics Surgeons* (AAOS), as well as *The Hip Society* and *The Knee Society*.[8,11,12] At the national level, some studies, such as that by Bidolegui et al., have also provided data on the safety of TXA in TKR without a hemostatic cuff.[9]

In trials such as CRASH-2 (Clinical Randomisation of Antifibrinolytic in Significant Head Injury), a significant difference was found in the mortality rate due to bleeding events in patients who had received TXA compared to placebo in the context of polytrauma.[13] In the field of joint replacements, Mayo Clinic studies demonstrated the safety and benefits of TXA in patients with a history of deep vein thrombosis and pulmonary thromboembolism, as well as in ASA III and IV patients.[10,12,14,15] However, the administration of antifibrinolytic agents to patients with coronary artery disease remains a relative contraindication.

No ischemic events were observed on previous stents in our study group. TXA was effective in preventing relative bleeding, minimizing the risk of coronary events due to anemia.

Certain hemodynamic stress factors (effect of anesthesia on the cardiovascular system, bleeding, arrhythmias, and hypoxia) can increase the risk of acute coronary events in this type of surgery. The risk of suffering an acute coronary event in the context of a knee joint replacement is low (between 0.18% and 0.25% according to reports in the literature).[16-20] This risk is at its highest in the first two weeks after the operation.

It is important to note that this higher-risk group of patients receives more aggressive prophylaxis for thromboembolic events than the general population, due to their usual antiplatelet therapies, and it is essential that patients restore full antiplatelet therapy as soon as possible after the operation.[17]

Another important factor is knowing the dosage and the different routes of administration of TXA. It can be administered not only intravenously, but also by oral and topical routes. The intravenous dose is 15 mg/kg of weight or directly 1 g, 30 min before the approach. When used orally, 2 g are given 2 hours preoperatively and 1 g at 3 and 9 hours postoperatively. Regarding its topical use, it is applied at a concentration of 3 g diluted in 50 cc of physiological solution, left to act for 5 min and then washed with physiological solution.[4,21-26] According to published scientific evidence, there are no differences in the therapeutic levels achieved in the blood, regardless of the route of administration. These results suggest that the systemic effects of TXA do not appear to be dangerous, as previously thought, in this group of patients and that it is potentially safe in patients with coronary artery stents.

This study has several limitations, such as its retrospective design and its limited number of patients.

CONCLUSIONS

Many surgeons and anesthesiologists are cautious about the use of TXA in patients considered to be at high risk, due to its pharmacological properties. However, our results show that its administration is safe and does not generate a higher risk of occlusion of coronary artery stents. We believe that patients with a history of coronary artery disease should undergo extensive and thorough preoperative evaluation, since their risk of developing atherosclerotic lesions in other vessels is high. In the future, prospective randomized studies may provide data on the benefits of its use and guarantee the safety of TXA in these patients.

Conflict of interest: The authors declare no conflicts of interest.

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