

Research Article

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Tranexamic Acid Reduces Blood Transfusion, Postoperative Blood Loss and Length of Hospital Stay in Total Knee Arthroplasty

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Abstract

Total knee arthroplasty usually has an important blood loss which may lead patients to receive allogeneic blood transfusion up to 30-45% of cases. Allogeneic blood transfusion is not free of risks, like disease transmission, ABO incompatibility, transfusion-related lung injury, fluid overload and increased procedure costs. Blood saving strategies should be implemented in surgical patients with known blood loss procedures in order to reduce allogeneic blood transfusion risk. Prophylactic use of the anti-fibrinolytic drug tranexamic acid (TXA) is useful in preventing blood loss in orthopedic surgery. In this study, 90 unilateral total knee arthroplasty with prophylactic use of TXA were compared to 60 historical cases. Patients in both groups underwent total knee arthroplasty with the same surgical technique and the same surgeon team. TXA was administered in 2 doses of 10-15 mg/kg to those patients with no contraindications, 15 minutes before ischemia release and 3 hours later. In the TXA series, there was a reduced transfusion requirements from 0.85 PRBC/patient to 0.35 PRBC/patient ($p=0.0031$), and a risk reduction of 41, 17% (RR 0.56, IC95% 0.35-0.88). Visible bleeding in 24 h significantly decreased from 540 cc (IC95% 393-687) to 168 cc (IC95% 130-207) in the TXA series ($p<0.0001$), and a reduced length of hospital stay from 8.92 days to 7.09 days in the TXA series ($p=0.03$). As a conclusion, implementing a blood saving strategy based on TXA in orthopaedic patients is effective and reduces risk of allogeneic blood transfusion.

Keywords: Blood saving strategies; Total knee arthroplasty; Tranexamic acid; Perioperative anaemia

Introduction

Total knee arthroplasty usually includes the use of tourniquet in order to induce ischemia during the surgery, resulting in unapparent intraoperative bleeding but substantial postoperative blood loss. Postoperative drainage ranges 500 to 1000 cc, as illustrated in previous studies [1]. Different factors may influence in the surgical bleeding in total knee arthroplasty like coagulation disorders, medication (anti-agregants, NSAID, LMWH) and anesthetic technique. Allogeneic blood transfusion is associated with the blood loss during surgery and postoperative drainage, but also with the haemoglobin level before the surgery [2]. Allogeneic blood transfusion is the standard approach to increase haemoglobin (Hb) concentration. But this procedure is not free of risks despite all efforts to avoid them. In addition to well-known risks, such as volume overload, mistransfusion, the transmission of infections, transfusion febrile reactions, transfusion-related acute lung injury, allergic transfusion reactions, or alloimmunization [3], there is increased morbidity and mortality, and longer hospital stays [4]. These situations justify clinical strategies to minimize exposure to allogeneic blood transfusion. As hyper fibrinolysis is considered the major cause of postoperative bleeding after total knee replacement surgery [5], anti-fibrinolytic drugs have been proposed. Tranexamic acid (TXA) is a synthetic analog of serin than reversibly inhibits fibrinolysis by blocking lysine union sites in the plasmin and plasminogen activator molecules. It has been extensively used in cardiac surgery, urology, gynaecology, liver transplants and orthopaedic surgery. In the last Cochrane review about the use of anti-fibrinolytics for minimising perioperative allogeneic blood transfusion, twenty-seven trials of TXA versus control involved orthopaedic surgery, including a total of 1381 patients of whom of whom 722 were randomised to TXA and 659 were randomised to a control group who did not receive TXA. There was a significant 51% RR reduction in the rate of exposure to allogeneic

blood transfusion in those participants treated with TXA (RR 0.49, 95% CI 0.39-0.62) [6]. In this context, the aim of our study was to evaluate the efficacy of using TXA as a blood saving strategy in total knee replacement surgery analysing transfusion rate, postoperative bleeding and length hospital stay.

Material and Methods

We designed a prospective study analysing a cohort of 90 consecutive patients with total knee arthroplasty enrolled during 2011 to evaluate the efficacy of TXA use as a new blood saving strategy in our daily clinical practice. We compared our results with a historical control group of 60 patients who underwent total knee replacement without TXA attended along 2010. Baseline patient characteristics are shown in table 1. Interventional arm received 2 doses of tranexamic acid (Amchafibrin, Rottapharm, S.A. Barcelona, Spain). A first dose of 15 mg/kg weight in 100 cc saline was slowly infused in 15-20 minutes, before ischemia-induced release. A second dose was administered after 3 hours of the first one. Surgical technique, surgeons, pre and postoperative management, and transfusion criteria were the same

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between both groups. Variables under comparison included age, sex, medication with anti-agregants or anticoagulants, anesthetic technique, intraoperative and postoperative blood loss, transfusion requirements, and Recovery Room and hospital length stay. This observational study was approved by the local ethical committee.

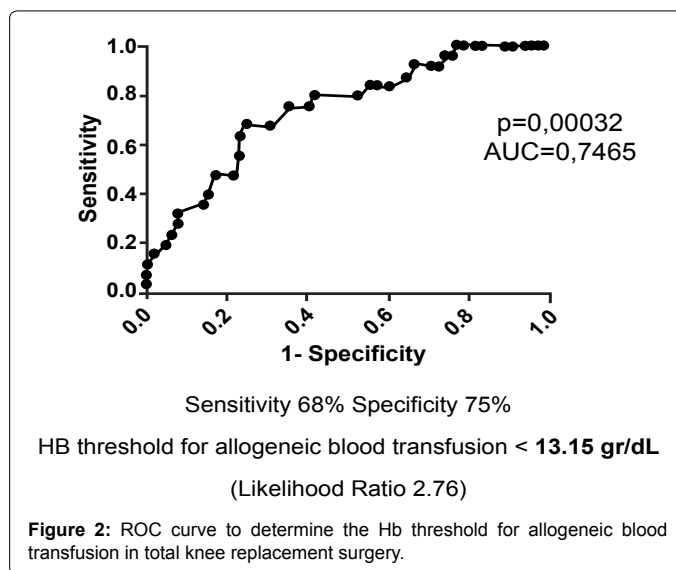
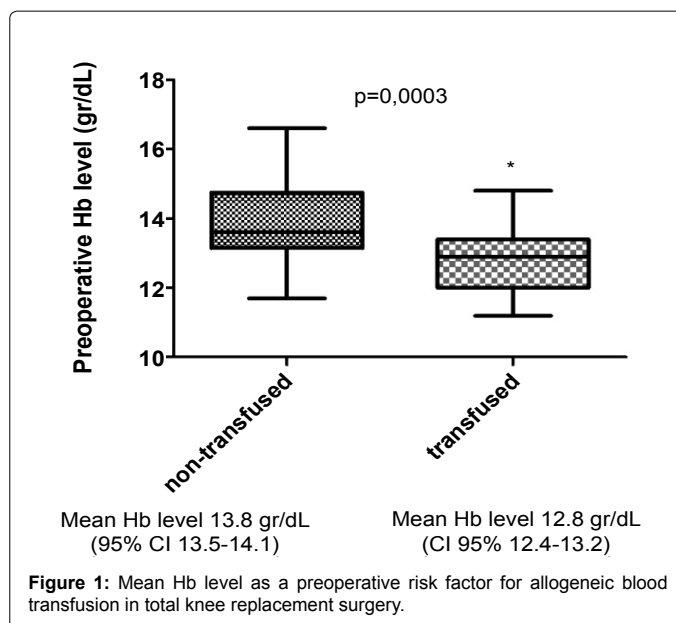
Exclusion criteria for using TXA in the interventional arm were previous thromboembolic disease, previous myocardial infarction, coagulopathy, neoplastic disease and renal disease. Patients who did not receive TXA in the interventional arm were included in the “intention-to-treat” analysis. Ischemia was performed with a pneumatic tourniquet at 100 mm Hg above systolic arterial pressure. Limited anterior incision followed by a parapatellar medial approach without patellar eversion and minimally invasive surgical instrumentation were used in all cases. The technique included cemented postero stabilized Nex Gen® (Zimmer, Warsaw, Indiana, USA) prosthesis with systematic patellar replacement. One single intra-articular drain (Drenofast CH-12/4.0 min Iber hospiteX, S.A. Barcelona, Spain) was used per surgery, at atmospheric pressure without vacuum, opened one hour after closure and systematically retrieved after 24 hours. Tourniquet release occurred after wound closure and knee bandage in all cases. Anti-thromboembolic prophylaxis in both groups were performed with enoxaparin (Clexane 40 mg, Sanofi-Aventis, S.A., Barcelona, Spain), 40 mg subcutaneously daily injection during 3 weeks. Antibiotic prophylaxis included cephalosporin 2gr 1 hour before surgery and 1gr/8h during 48 hours. Transfusion was decided in both groups by the Orthopaedic surgeon and/or Anaesthesiologist. As a general rule, haemoglobin laboratory determination under 8.0 gr/dL and/or related symptoms of acute anaemia required a transfusion, whereas in patients with cardiovascular or pulmonary comorbidities, the threshold was set at 9.0 gr/dL. In the statistical analysis, quantitative variables are expressed as mean and standard deviation, and qualitative variables by absolute and relative frequencies. The quantitative variables were compared with Student’s t-test and the comparison of qualitative variables was performed by Chi-square and Fisher’s exact test. Relative Operating Characteristic curve was used to calculate the threshold risk of Hb for blood transfusion. Graph Pad Prism 5.04 was used as statistical software (Graph Pad Software, Inc, La Jolla, CA, USA).

Results

Statistically significant differences were found in Hb level in patients receiving allogeneic blood transfusion. Hb mean level in the non-transfused group was 13.8 gr/dL (95% CI 13.5-14.1) versus 12.8 gr/dL (95% CI 12.4-13.2) in the transfused group (p=0.003) (Figure 1). In the ROC curve, with an Area Under the Curve (AUC) of 0.7465, with

	TXA group	Control group
n	90	60
Age (years)	71.20	71.78
range	50-83	54-85
Sex		
Male	19	23
Antiangregants		
yes	22	16
Anticoagulants		
yes	5	7
Anesthetic technique		
general anesthesia	21	13
epidural	48	40
spinal	21	7

Table 1: Baseline patient characteristics.



a sensitivity of 68% and a specificity of 75%, the Hb threshold to receive allogeneic blood transfusion was 13.15 gr/dL, with a Likelihood Ratio of 2.76 (p=0.00032) (Figure 2). In the univariate analysis, preoperative Hb level (p=0.0003), anti-agregants medication (p=0.034) and the use of TXA (p=0.0024) were risk factors to receive allogeneic blood transfusion. The Relative Risk (RR) for Hb level was 2.763 (95% CI 1.67-4.57) and for anti-agregants was 2.137 (1.125-4.066). Sixty-two patients who underwent total knee arthroplasty in 2011 were treated with TXA. Twenty-eight did not receive TXA because of contraindications. While 17.74% of patients received transfusion in the group treated with tranexamic acid, 14 out of 28 patients (50%) required transfusion in the control group (p=0.0024), with a RR 0.5608 (0.3539-0.8886) (Table 2).

The mean number of Packed Red Blood Cells (PRBC) transfused in the control group was 0.85 PRBC/patient (95% CI 0.45-1.26) in comparison with 0.35 PRBC/patient (95% CI 0.12-0.58) in the TXA group (p=0.0031) (Figure 3).

Postoperative bleeding was lower in the TXA group, with an

	p value	RR (95% CI)
Age	ns	
Sex	ns	
Preoperative Hb (Hb<13.15 gr/dl)	0.0002	2.763 (1.67-4.57)
Antiagregants (yes vs no)	0.034	2.137 (1.125-4.066)
Anticoagulants (yes vs no)	ns	
TXA (yes vs no)	0.0024	0.5608 (0.3539-0.8886)

Table 2: Univariate analysis of risk factor for allogeneic blood transfusion in total knee replacement surgery.

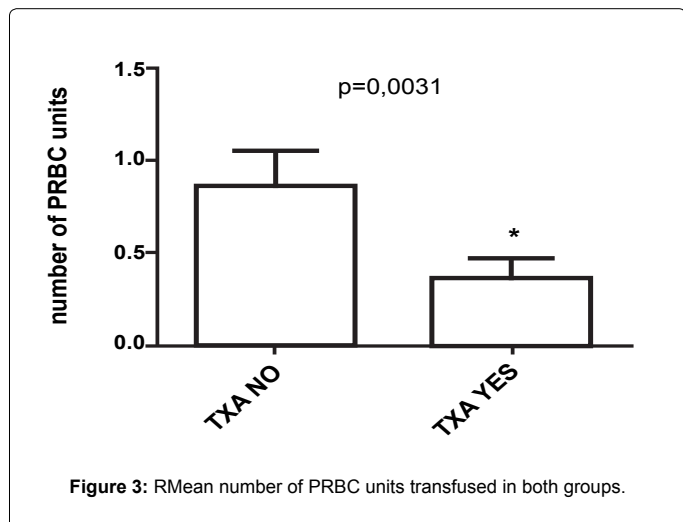


Figure 3: RMean number of PRBC units transfused in both groups.

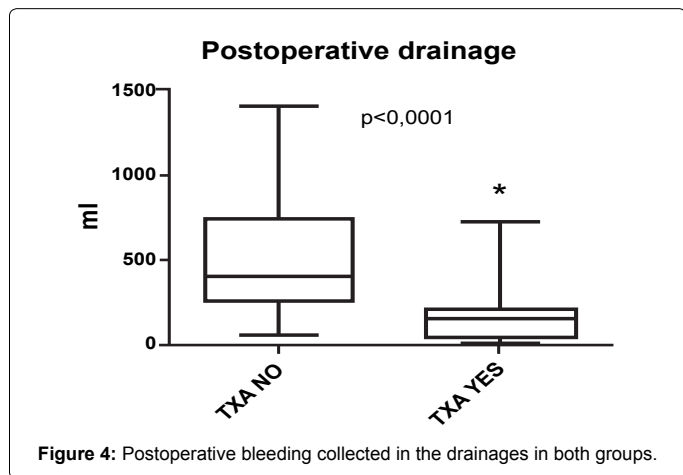


Figure 4: Postoperative bleeding collected in the drainages in both groups.

average blood loss of 540 ml (95% CI 393-687) versus 168 ml (95% CI 130-207) in the control group ($p < 0.0001$) (Figure 4).

Recovery Room stay was shorter for patients in the TXA group. In comparison with the 10.32 hours of the control group, stay of patients in the TXA group was only of 5.83 hours ($p = 0.0003$). No other complications but bleeding were seen in the Recovery Room stay (Figure 5).

Total hospital stay was also shorter for the group of patients who received TXA, with a mean hospital stay of 7.09 days versus 8.92 days ($p = 0.03$) (Figure 6).

Regarding the safety of the treatment, there were two pulmonary embolisms, one case in each arm. No other side effects were seen in the treatment arm.

Discussion

Different strategies have been established to decrease the risk of allogeneic blood transfusion in the postoperative patient. In our study, we significantly decreased the risk of allogeneic blood transfusion through a protocol that included two doses of tranexamic acid. As the risk of transfusion depends on the preoperative haemoglobin values, preoperative treatments such as erythropoietin and intravenous iron have been proposed to avoid postoperative transfusion [7,8]. We have identified in our series that patients undergoing total knee replacement with preoperative Hb level below 13.15 gr/dL are at risk to receive allogeneic blood transfusion. This group of patients could benefit of preoperative treatments with oral iron. Moreover, another group of patients at risk is the one undergoing anti-agregant medication, in which TXA is contraindicated in the majority of them. That would be another group in which preoperative strategies should be implemented in order to improve preoperative Hb levels.

Multiple surgical variables may affect postoperative blood loss. Tourniquet release after wound closure and bandage proved blood loss decrease in many studies [9,10]. Although tourniquet decreases total knee arthroplasty intraoperative bleeding, postoperative blood loss occurs due to an increased fibrinolysis in response to exsanguinations [11,12]. TXA inhibits fibrinolysis through a reversible molecular block of lysine union sites in the plasmin, plasminogen, and tissue activator of plasminogen. Effective plasmatic levels are reached 10-15 minutes

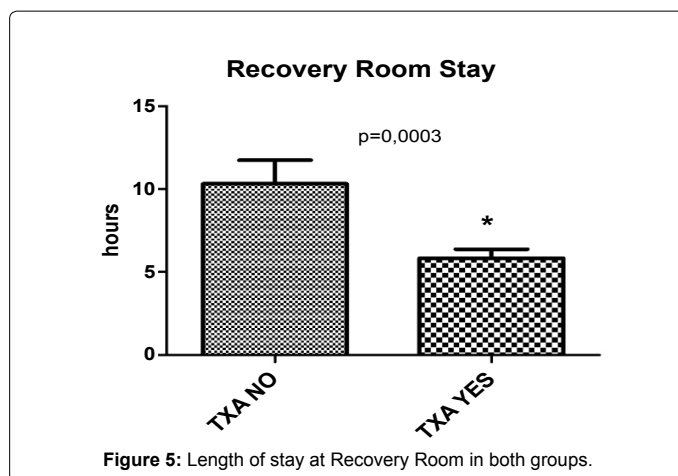


Figure 5: Length of stay at Recovery Room in both groups.

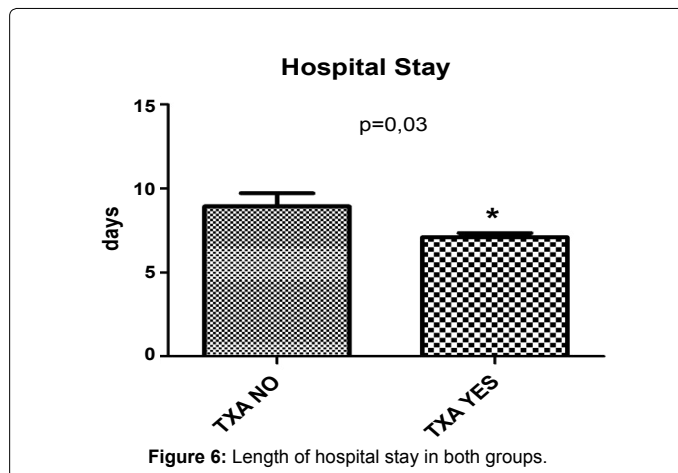


Figure 6: Length of hospital stay in both groups.

after infusion, and therapeutic level must be maintained at tourniquet release, being the initial dose administration crucial to efficacy [5,6]. Effectiveness is also a matter of controversy, as more recent randomized clinical trials proved a significant early postoperative decrease in blood loss, but one single TXA dose failed to confirm a significant association with total blood loss or transfusion requirements [13]. In a recent systematic review of randomized trials [6], the use of anti-fibrinolytic agents to reduce bleeding and transfusion risk to a 50% in orthopaedic patients, without increasing thromboembolic risk, is well proven. More controversy persists on the dosage and timing of administration, and heterogeneity limits the strength of conclusions on these aspects [14]. This debate justifies further studies to maximize effectiveness. The results of a multimodal protocol with tranexamic acid administration in two doses of 15 mg/kg, the first dose infused 15-20 minutes before tourniquet release, and repeated after 3 hours, virtually revoked the need of transfusion and reduce significantly the 24 hour drainage [15]. In our study, the use of TXA also reduces the Recovery Room and hospital stays, with a significant reduction of hospitalization costs.

Conclusions

In conclusion, based on this study, two-dose IV of tranexamic acid can be used in total knee replacement procedures with proven effectiveness and efficiency to decrease postoperative blood loss, decrease risk of allogeneic blood transfusion and decrease length of hospital stay in our patients undergoing total knee arthroplasty.

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