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Full Length Article

Does tranexamic acid alter the risk of thromboembolism following primary total knee arthroplasty with sequential earlier anticoagulation? A large, single center, prospective cohort study of consecutive cases

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ABSTRACT

Introduction: In order to decrease the blood loss and transfusion requirement, tranexamic acid (TXA) has attracted the public's attention in total knee arthroplasty (TKA). However, the safety profile of TXA hindered its wide adoption. And the balance of anti-coagulation sequential anti-fibrinolysis has not yet been explored. This large, single center, prospective cohort study of consecutive cases aimed to investigate the epidemiology of vascular occlusive events associated with TXA and introduce our preliminary results of novel thromboprophylaxis.

Materials and methods: We prospectively collected patients' data of our institution through National Health Database. The primary outcome was the incidence of venous thromboembolism and mortality within 30 days following primary TKA. Subgroup analysis was performed on the basis of TXA administration methods.

Results: During 2012 to 2014, a total of 2532 unilateral TKA procedures were conducted in our institution, 2222 with TXA, 310 without TXA. The total occurrence of vascular occlusive events was statistically significantly higher (17.55% Vs 9.35%, $p < 0.001$) in the TXA group but this finding was confined to the calf veins, with the main difference being the incidence in the calf muscular veins (13.68% Vs 6.77%, $p = 0.001$). Statistical difference was not detected neither in the incidence of symptomatic DVT nor asymptomatic DVT. No episode of symptomatic PE and all-cause mortality within 30 days occurred postoperatively. Subgroup analysis revealed no significant difference with regard to the incidence of DVT ($p > 0.05$).

Conclusion: This study confirmed that the incidence of postoperative VTE was unchanged when TXA was administered in primary unilateral TKA. And our study further indicated that earlier anticoagulation should be adopted to keep the balance between anti-fibrinolysis and anti-coagulation after administering TXA.

1. Introduction

Total knee arthroplasty (TKA) is an effective practice to treat end-staged knee joint diseases [1], which will be more and more popular. Nevertheless, the substantial blood loss and postoperative anemia is still a concern for either patients or healthcare providers. According to previous studies, the total blood loss can be up to 2000 ml in TKA [2–4]. In order to treat postoperative anemia, patients may need allogenic blood transfusion, which is not free of risks, such as anaphylaxis, transfusion related acute lung injury (TRALI), transmitting virus, and so on [5–8]. Moreover, blood transfusion may increase the risk of surgical site infection or periprosthetic joint infection [9].

The massive blood loss during the operation may be owing to the hyperfibrinolysis, which is caused by trauma and enhanced by tourniquet [10–12]. Tranexamic acid (TXA), a synthesized antifibrinolytic agent, competitively inhibits plasminogen activation and plasmin binding to fibrin by blocking the lysine binding sites, thus inhibit clotting breakdown which results in the reduction of blood loss and transfusion requirement. An increasing body of evidences have confirmed the efficacy of TXA on blood loss and transfusion requirement during TKA [1, 13–16]. However, the concern about the incidence of vascular occlusive events (VOE) after administering TXA is still in debate because of the small sample in each study.

Patients receiving major orthopaedic surgery, especially total joint arthroplasty, are at high risk of venous thromboembolism (VTE). And the risk may increase theoretically when TXA plays a role in anti-fibrinolysis [17]. In order to prevent postoperative VTE, the application of physical prophylaxis and chemoprophylaxis is a consensus of practitioners. While, as far as we know, little study has figured out how to balance the contradiction between anti-fibrinolysis and anti-

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anticoagulation. So, in recent years, we focused on antifibrinolytic agents and anticoagulants to explore the compromising area between these two antithetical sides.

Therefore, by undertaking this large, single center, prospective cohort study of consecutive cases undergoing primary TKA with TXA, we want to address the following questions: 1. what's the effect of TXA on the vascular occlusive events? 2. What's the effect of TXA on adverse clinical events? 3. Can patients gain benefits from our preliminary results of anti-coagulation sequential anti-fibrinolysis?

2. Materials and Methods

2.1. Patients Selection

All the data were derived from National Health Database, which was funded by the China Healthy Ministry Program (No. 201302007), the database has enrolled the relevant data of hip, knee, shoulder, elbow and ankle joint arthroplasty which are mostly carried by the affiliated hospitals of higher medical colleges in China. The server of this database was set up in our institution, and our center was in charge of the management of the database, ensuring the standard and accuracy of data entry. This study only included the consecutive cases undergoing primary unilateral TKA from 2012 to 2014, January 2012 to May 2012 without TXA, June 2012 to December 2014 with TXA. The inclusion criteria were as follows: (1) Patients underwent primary TKA for OA or RA; (2) Normality of preoperative PLT, coagulation; (3) Preoperative Doppler Ultrasound of lower limb is normal. Exclusion criteria included patients with: (1) history of VTE (deep vein thrombosis, calf muscle vein thrombosis or superficial vein thrombosis, pulmonary embolism); (2) clotting disorders; (3) cardiovascular problems or cerebrovascular conditions (history of myocardial infraction, angina, atrial fibrillation, or previous stroke); (4) discontinuation of oral NSAID less than one week; (5) known allergy to TXA; (6) serious liver and kidney dysfunction. The study protocol was approved by the Institutional Review Board (IRB) of West China Medical Center of Sichuan University (2012-268). Written informed consent was obtained prospectively prior to surgery from all patients.

2.2. TXA Administration Protocol

There were two major methods of Tranexamic acid (Chongqing Lummy Pharmaceutical Co., Ltd. China; DAIICHI SANKYO PROPHARMA CO., LTD., Japan) administration in our institution, intravenous and combined administration. In IV group, 15 mg/kg TXA was administered before deflation of the tourniquet. In the combined group, 15 mg/kg IV-TXA was administered before deflation of the tourniquet, and a solution of 1 g TXA was injected through the drainage tube after closing the deep fascia. The drain tube was kept clamped for 2 h, then the tube was fully opened and was removed by the next morning. The decision on which way is adopted was dependent on the preference of surgeons.

2.3. Peri-operative Management

2.3.1. Anaesthesia and Surgery

all the operations were performed by the five senior surgeons in our center, of which, one was in charge of the joint replacement institution, and the other four had surgical training under his guidance. So the surgical technique and process were consistent and standard. All the surgeries were conducted under general anesthesia or spinal anesthesia. TKA was performed in the standard way, using a middle skin incision, a standard medial parapatellar approach and a measured resection technique. A tourniquet was applied to all the patients with a strategy of inflating before incision and deflating after compressing the lower limb with two elastic bandage under control at 100 mmHg above systolic pressure.

2.3.2. Thromboprophylaxis

A combination of physical prophylaxis and chemoprophylaxis was adopted. The dorsal and plantar flexion, quadriceps muscle strength exercise was initiated as soon as be awake from anesthesia. All the patients began to walk under partial weight-bearing after reviewing x ray of knee on postoperative day 1. An intermittent foot slope pump system was used as a routine practice to prevent deep-vein thrombosis (DVT) before walking. Besides, after application of TXA, half dose of low-molecular weight heparin (LMWH, 0.2 ml 2000 IU; Clexane, Sanofi-Aventis, France) was started 6 hours postoperatively and repeated at 24-h intervals with a full dose (0.4 ml 4000 IU) in the subsequent days; otherwise, the anti-coagulation was initiated 12 hour postoperatively in patients without the treatment of TXA. After discharge, 10 mg Rivaroxaban (Xarelto, Bayer, Germany) once a day was administered orally to the patients for 10 days. When DVT was detected, aggressive therapeutic regimen including LMWH, 0.4 ml bid and restrict bed rest would be adopted until the organization or recanalization are achieved. If calf muscle vein thrombosis or superficial vein thrombosis was detected, nothing special would be done.

2.3.3. Vascular Occlusive Events Screening

B-mode ultrasonography, an iU22 (Philips Medical system, Royal Philips Electronics, Netherlands), with compression and color Doppler flow imaging, were routinely performed for bilateral common femoral veins, superficial veins, popliteal veins and calf veins (peroneal, posterior tibial, anterior tibial veins, and calf muscle veins) by skilled physicians before surgery and 5-7 days after surgery. If DVT was clinically suspended, the Doppler Ultrasound was applied immediately. Augmentation by calf squeezing or Valsalva maneuver were included, as needed. Criteria for diagnosing DVT were: loss of vein compressibility, presence of intraluminal echogenicity and absence of venous flow determined using a sonographic scanner with a linear transducer (2-9 MHz). In patients with positive ultrasonography findings, if clinical symptoms such as lower limb swelling, pain, Homan's sign or Neuhof sign were presented, the patients were diagnosed as symptomatic DVT. Otherwise, asymptomatic DVT was defined. And pulmonary embolism (PE) was screened by symptom. If symptoms including shortness of breath, chest pain, light headedness or chest congestion were presented, enhanced spiral computed tomography (CT) was performed immediately. All the patients returned to the clinic at 2-, 4-, 12-weeks postoperatively. And all the symptomatic PE and all-cause mortality was recorded during follow-up period.

2.4. Outcome Measurements

Demographic data (age, gender, weight, height), diagnosis, surgery type, anesthesia type, TXA protocol, incidence of vascular occlusive events were retrieved from database. The primary outcome of the study was the incidence of DVT, symptomatic PE and all-cause mortality within 30-days.

2.5. Statistical Analysis

All the data analyses were performed using SPSS version 19.0(SPSS Inc. USA). Pearson chi-square test and Fisher exact test were used to analyze the qualitative variable. A p-value < 0.05 was considered to be statistically significant.

3. Results

3.1. Patients' Baseline Characteristics

During the study period, a total of 2532 primary TKA procedures (2222 in TXA group and 320 in control group) in 2352 unique patients were analyzed. Patient demographic information is summarized in Table 1. No significant difference were found between the groups