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Impact of intraosseous regional administration of tranexamic acid in total knee arthroplasty on perioperative blood loss: a protocol for a randomised controlled trial

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ABSTRACT

Introduction Total knee arthroplasty (TKA) is a common surgical intervention to treat joint diseases. However, TKA is associated with significant blood loss. Tranexamic acid (TXA) has been used to reduce perioperative bleeding and postoperative blood transfusion. This study aims to explore the effectiveness and safety of intraosseous regional administration (IORA) of TXA in TKA and compare differences in perioperative blood loss between IORA of TXA, intravenous infusion of TXA, and combined IORA and intravenous infusion of TXA.

Methods and analysis This randomised controlled trial will enrol 105 patients with osteoarthritis who meet the inclusion criteria for unilateral TKA. Patients were randomly divided into three groups using the random number table method. Group A received 1.0 g of TXA via IORA, group B received 1.0 g of TXA via intravenous infusion 15 min prior to the tourniquet release, and group C received both IORA of 1.0 g of TXA and intravenous infusion of 1.0 g of TXA. The primary outcome measure is perioperative total blood loss. Secondary outcomes include bleeding events, venous thromboembolism events, inflammation reactions, other complications and knee function assessments.

Ethics and dissemination This study has been approved by the Ethics Committee of Peking Union Medical College Hospital and registered in the Chinese Clinical Trial Registry. Informed consent will be obtained from all the patients before enrolment. The trial will be conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The results of this study will be disseminated through peer-reviewed publications, conference presentations and social media platforms. The findings will provide valuable insights into the use of IORA of TXA in TKA and may lead to the development of new strategies for perioperative blood management in joint replacement surgery.

Trial registration number The Ethics Committee of Peking Union Medical College Hospital (approval number: K2371); Chinese Clinical Trial Registry (trial registration number: ChiCTR2200066293).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design is a randomised controlled trial, providing a comprehensive exploration of the effectiveness and safety of intraosseous regional administration (IORA) of tranexamic acid (TXA) in total knee arthroplasty (TKA).
⇒ The study uses a uniform cocktail injection formula for postoperative analgesia during the procedure and a uniform postoperative joint rehabilitation programme and blood management strategies, which may minimise potential confounding factors.
⇒ The study collects a wide range of medical data, including bleeding events, venous thromboembolism events, inflammation reactions, other complications and knee function assessments, which may provide a comprehensive evaluation of the efficacy and safety of IORA of TXA in TKA.
⇒ The study includes detailed eligibility criteria and exclusion criteria, which may ensure the reliability and validity of the study results.
⇒ The sample size is relatively small, which may limit the generalisability of the study. The estimation formula for total blood loss has certain limitations that may affect the accuracy of the results.

INTRODUCTION

Total knee arthroplasty (TKA) is a surgical intervention that is frequently used to treat knee arthropathy and improve knee joint function. It is a highly successful procedure that can bring pain relief, improved joint function and a higher quality of life. Despite the excellent rate of 10-year follow-up for TKA being over 90% due to the development of new prostheses and improvements in surgical instruments and techniques, TKA has been associated with significant blood loss as a result of the extensive trauma involved in the operation, resulting in a total blood loss (TBL) of 600 to 1550 mL, a postoperative drainage of 500 to 1000 mL and a transfusion rate as high as 10%–62% in bilateral TKAs.[1]

The use of a tourniquet during TKA can significantly reduce intraoperative blood loss, with an average TBL of 1474 mL and hidden blood loss of 735 mL, which accounts for 50% of TBL. However, releasing the tourniquet may lead to an imbalance of fibrinolysis-coagulation, causing an excessive activation of the fibrinolysis system. In addition, tourniquet use can cause lower limb ischaemia, microcirculation disorders and distal ischaemia-reperfusion injury, leading to the further exacerbation of the fibrinolytic response.[2]

Tranexamic acid (TXA) is a lysine derivative that can effectively block the interaction between lysine residues and the heavy chain of plasmin, preventing plasmin from binding to fibrin monomers and inhibiting the lysis of fibrin clots. This mechanism provides the basis for the use of TXA, often used to reduce perioperative bleeding and postoperative blood transfusion.

In 1987, Benoni *et al*[3] first applied TXA to postoperative bleeding control in TKA. The methods for using TXA include intravenous infusion, local application and oral administration. Intravenous infusion of TXA can achieve maximum blood drug concentration in 5–15 min, rapidly diffusing into synovial tissue and synovial fluid, achieving a concentration similar to the maximum plasma concentration, and with a half-life in the synovial fluid of up to 3 hours. Alshryda *et al*[4] analysed a randomised controlled trial of intravenous infusion of TXA during TKA and found that the use of TXA could reduce the average TBL by 591 mL, and shorten the average length of hospital stay by 0.76 days. The therapeutic effect is related to the dose of the drug, and an overdose can cause systemic complications, while an insufficient dose can lead to an ineffective local concentration of TXA in the joints. Additionally, for patients using tourniquets during TKA, the therapeutic effect of intravenous TXA is related to the timing of administration during the procedure; typically, TXA should be administered intravenously 15 min before the tourniquet is released, but mistakes may happen in practice, which may impact the effectiveness of intravenous TXA infusion.

Since TXA can quickly penetrate into tissues in the joint cavity and reach the maximum drug activity in the target organs, local application can limit the systemic accumulation of TXA and broaden the indications for TXA. Seo *et al*[5] conducted a randomised controlled trial on patients undergoing TKA and reported that local application of TXA could reduce blood loss by about 400 mL, reduce the postoperative decrease in haemoglobin (Hb) by about 13 g/L, and have relatively fewer systemic complications. Ishida *et al*[6] found that local application of TXA during TKA not only reduced TBL but also reduced the degree of swelling on the operated limb. Wind *et al*[7] compared the effects of intravenous infusion and local application of TXA on intraoperative blood loss in TKA. They found that none of the patients in the local application group required blood transfusion, while the transfusion rate in the intravenous infusion group was 0.3%. Hamlin *et al*[8] compared the efficacy of 1.0 g of TXA administered via intravenous infusion before the procedure and 3 g of TXA diluted in 100 mL of saline and locally injected into the joint cavity through a drainage tube. The local application group had a significantly lower Hb decline (2.2 g vs 2.8 g) and transfusion rate (0% vs 2.4%) compared with the intravenous infusion group, but there was no difference in hospital stay or incidence of venous thromboembolism (VTE) between the two groups.

However, there is still uncertainty about the optimal dosage of TXA. Currently, favoured options include a single dose of 10 mg/kg, 15 mg/kg or 20 mg/kg, or a standardised dose of 1.0 g. In a randomised controlled trial conducted by Levine *et al*,[9] the difference in TBL between the standardised dose group (1.0 g) and personalised dose group (20 mg/kg) was investigated. The results showed that the TBL for the standardised dose group and the personalised dose group was (293.75±77.96) mL and (356.5±77.61) mL, respectively, with no significant statistical difference between the two groups.

Intraosseous infusion (IO), a drug delivery approach, uses the rich vascular network of the medullary canal in long bones to deliver drugs and fluids into the bloodstream. The medullary canal is composed of a network of venous sinuses and spaces that communicate with the circulatory system through the central canal, nutrient veins and emissary veins. Therefore, drugs and fluids administered into the medullary canal can enter the circulatory system quickly and effectively. The medullary canal is surrounded by a bony structure, which provides anatomical basis for the delivery of drugs and fluids into the bone marrow and is unaffected by blood volume changes and has a high degree of permeability. IO can achieve similar pharmacokinetic and pharmacodynamic effects as intravascular administration and has the advantage of not increasing systemic complications, which has historically been used in the treatment of haematological malignancies. It can also be used in patients who are not suitable for intravascular drug administration. Recently, orthopaedic surgeons have focused on the use of IO, primarily in periprosthetic joint infection. Young *et al*[10] demonstrated in animal experiments that using intraosseous regional administration (IORA) to deliver equipotent doses of cefazolin or low doses of vancomycin can achieve better antibacterial effects and reduce the amount of bacterial colony formation compared with an intravenous infusion of equipotent doses of cefazolin or high doses of vancomycin. Young *et al*[11] administered 500 mg of vancomycin via IORA or 1000 mg of vancomycin intravenously to patients undergoing revision TKA. They found that the vancomycin concentration in the IORA group was 5.3 times than that of the intravenous infusion group. Symonds *et al*[12] suggested that administering antibiotics via IORA during TKA might reduce the incidence of periprosthetic joint infections. These studies suggest the feasibility of using IORA to deliver TXA in TKA.

However, there is currently a lack of study on IORA of TXA. As the femur medullary canal needs to be opened during conventional TKA, a natural pathway for IORA

can be created and a sufficient amount of TXA can be delivered. Furthermore, hidden blood loss is mainly sourced from blood extravasation in the tissue spaces and blood accumulation in the joint cavity, as well as the loss of Hb due to its haemolytic activity. Intraoperative and postoperative bleeding from the medullary canals is also a significant source of hidden blood loss due to the need for invasive procedures that disrupt the medullary canals during TKA. Han *et al*[13] reported a meta-analysis showing that the utilisation of navigation technology during surgical procedures could significantly increase postoperative Hb levels, and reduce TBL by avoiding damage to the medullary canals. Thus, IORA of TXA combined with medullary canal blocking can theoretically increase the local concentration of TXA and reduce intraoperative blood loss. Also, as the infusion site is located at the far end of the tourniquet, there may be reduced restriction of tourniquet timing when administering TXA compared with intravenous infusion.

Given the potential benefits of IORA of TXA, it is essential to investigate its feasibility and efficacy, and the resulting data will shed light on the alternative use of TXA during TKA. This study aims to provide a comprehensive exploration of the effectiveness and safety of IORA of TXA in TKA and to compare differences in perioperative blood loss between IORA of TXA, intravenous infusion of TXA, and combined IORA and intravenous infusion of TXA. We hypothesise that IORA of TXA combined with medullary canal blocking can reduce medullary canal bleeding and ensure local concentration of TXA, leading to reduce TBL of TKA. In comparison to traditional intravenous infusion, IORA of TXA has comparable safety and does not increase systemic complications. If the hypothesis is confirmed, this technique might eventually become an effective choice for reducing perioperative blood loss, promoting postoperative recovery and improving the overall efficacy of TKA.

METHODS AND ANALYSIS

This study is a randomised controlled trial that enrolled 105 patients with osteoarthritis who met the inclusion criteria for unilateral TKA from the Joint Surgery Center of Peking Union Medical College Hospital. Patients were randomly divided into three groups using the random number table method 30 min prior to the procedure. Specially, the number table was generated using a random number generator, consisting of a sequence of 46 numbers (1, 2 or 3) representing the 46 beds in our centre. The patients' bed numbers were matched with the numbers in the random number table, where 1, 2 and 3 corresponded to groups A, B and C, respectively. Group A received 1.0 g of TXA via IORA from intraoperative femoral canal, group B received 1.0 g of TXA via intravenous infusion 15 min prior to the tourniquet release and group C received both intraoperative femoral canal infusion of 1.0 g of TXA and intravenous infusion of 1.0 g of TXA 15 min prior to the tourniquet release. A detailed schema of the trial is presented in figure 1.

Eligibility criteria

Inclusion criteria were as follows: (1) with knee osteoarthritis; (2) receive primary unilateral TKA; (3) age between 20 and 80 years old; and (4) voluntary signature of informed consent form.

Exclusion criteria were as follows: (1) allergy to TXA; (2) high-risk factors for thrombosis, including a history of VTE, myocardial infarction, or stroke, concomitant malignant tumours, hypercoagulable state and prior thrombotic events; (3) concomitant severe organ diseases such as heart, brain, lung, kidney or haematological disorders; (4) preoperative Hb level below 11 g/L; (5) underwent open orthopaedic surgery within 3 weeks before the current procedure; (6) use of aspirin or other antiplatelet agents within 1 week before procedure; and (7) diseases requiring anticoagulant therapy or history of regular anticoagulant therapy.

Treatment protocol

All the TKA procedure is performed under tourniquet. The proximal tibia cut is performed with an extramedullary guide. The distal femoral cut is performed with an intramedullary guide and femoral canal is opened. The anterior, posterior, anterior chamfer and posterior chamfer are prepared with a conventional cutting jig. Posterior stabilised (PS) prosthesis is used for all the patients and the intercondylar box is prepared with a cutting jig. The femur component with an open box design is used for the femur side (Weigao, Shandong, China). All the components are fixed with cement. Before final implantation, the opening of the femoral canal is filled with gelatine sponge and completely sealed with compaction autogenous bone from the anterior chamfer cut.

For the IORA group, the effusion from the femoral medullary canal is aspirated with suction, the opening of the femoral canal is sealed as previously described, and 1.0 g (10 mL) of TXA is injected into the distal femur from the opening of the femoral canal with a 14 gauge needle and 20 mL syringe. For the intravenous group, 1.0 g of TXA is administrated via intravenous infusion 15 min prior to the tourniquet release. After final implantation and completely fixing the component, the tourniquet is released and careful haemostasis is performed before wound closure for all the patients. No drainage is placed in this study. All the patients accepted extra 1.0 g of TXA intravenous treatment at 3 hours after the surgery.

A uniform cocktail injection formula (40 mg of ropivacaine, 0.25 mg of epinephrine, 50 mg of flurbiprofen, 2 mg of betamethasone and 30 mL of 0.9% normal saline) is used for periarticular injection for analgesia. Postoperative treatment follows expert consensus in enhanced recovery after TKA in China, which includes anti-infection, analgesia and anticoagulation therapy.[14] Ten mg rivaroxaban is used for VTE prevention within 24

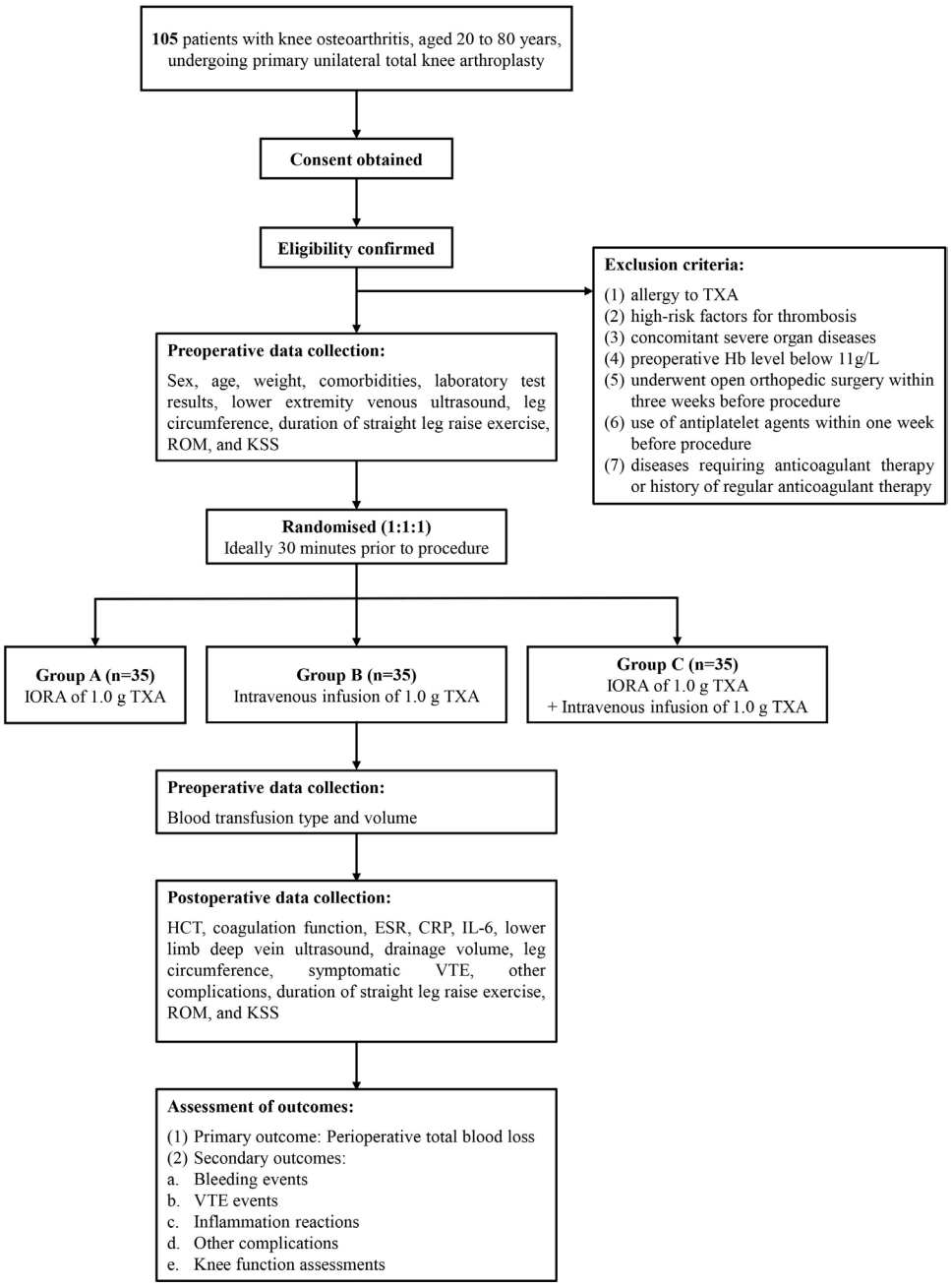

Figure 1 Trial schema. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HCT, haematocrit; IORA, intraosseous regional administration; KSS, Knee Society Score; ROM, range of motion; TXA, tranexamic acid; VTE, venous thromboembolism.

hours after the procedure and is continued for 14 days. All patients received physical thromboprophylaxis with lower limb gradient compression pump during hospitalisation. A uniform postoperative joint rehabilitation programme and blood management strategies are adopted during the perioperative period. For red blood cell mobilisation, 10 000 IU of erythropoietin (EPO) is injected and 100 mg of iron agent is intravenously infused for postoperative 3 days.

Data collection

The patients are followed until postoperative 3 months. The following medical data of patients will be collected during the investigation: sex; age; weight; comorbidities including primary hypertension, coronary atherosclerotic heart disease, hyperlipidaemia, diabetes, and other cardiovascular and cerebrovascular diseases; laboratory test results including blood routine test, liver and kidney function test, coagulation function test (including D-dimer), C reactive protein (CRP), and erythrocyte sedimentation rate (ESR); bilateral lower extremity venous ultrasound; leg circumference; complications including lower limb symptomatic VTE, cardiovascular and cerebrovascular events, bruising, TXA-related allergic reactions, allogeneic blood transfusion, etc.

Assessment of outcomes

Primary outcome

The primary outcome measure in this study is perioperative TBL, calculated by changes between the preoperative and postoperative haematocrit (HCT). The calculation method is as follows:

1. Measurements of HCT are taken preoperatively, and on postoperative day (POD) 3.
2. Information on intraoperative and postoperative blood transfusion type and volume is recorded. Patients require blood transfusions in the following scenarios: (1) Hb<75 g/L; (2) Hb<90 g/L, in combination with circulatory disorders caused by low Hb, such as unstable circulation and ischaemic heart disease. The TBL is calculated using the following formula:

$$TBL = PBV \times (HCT_{pre\text{-}op} - HCT_{post\text{-}op}) \times 2 / (HCT_{pre\text{-}op} - HCT_{post\text{-}op}) + Vt$$

$$PBV = k1 \times height^3\ (m^3) + k2 \times weight\ (kg) + k3$$

PBV: patient blood volume

Vt: volume of allogeneic or autologous blood transfusion

Male: k1=0.3669, k2=0.03219 and k3=0.6041

Female: k1=0.3561, k2=0.03308 and k3=0.1833

Secondary outcomes

1. Bleeding events:
   - The onset, location, extent, duration and evolution of postoperative bleeding events are recorded, including gastrointestinal bleeding, melena and cutaneous mucosal bleeding (including ecchymosis and petechia).
2. VTE events:
   - Measurements of coagulation function and CRP levels are taken preoperatively and on POD 1 and POD 3.
   - Lower limb deep vein ultrasound is performed preoperatively. Postoperative deep vein ultrasound is performed from POD 14 to POD 28.
   - Postoperative symptomatic VTE is recorded including lower limb swelling and pain caused by deep vein thrombosis, as well as symptomatic pulmonary embolism.
   - Inflammation reactions: Measurements of ESR, CRP and IL-6 levels are taken preoperatively and on POD 1, POD 3 and POD 14.
3. Other complications:
   - The relevant information on postoperative discomfort symptoms is recorded, including gastrointestinal symptoms, central nervous system symptoms, allergic reactions, fever, etc.
   - Preoperative and postoperative measurements of the circumference of both legs at 10 cm above the patella and 10 cm below the tibial tuberosity are taken, and the healing progress of the incision is recorded.
   - Cardiovascular and cerebrovascular complications during medication management are recorded, such as cerebral infarction, cerebral haemorrhage, myocardial infarction, heart failure, arrhythmia, shock, etc.
   - Knee function assessments: Measurements of the duration of straight leg raise exercise, knee range of motion and Knee Society Score are taken preoperatively, and on POD 14 and 3-month follow-up.

Data evaluation and sample size

The sample size was calculated using the TBL of unilateral TKA in previous studies, and a difference in postoperative Hb of 10 g/L or more was considered significant. With α=0.05, β=0.2, and a follow-up loss rate of 10%, 35 cases were required per group.

Statistical analysis is performed using SPSS V.16.0 software. For qualitative data, the χ^2 test for independent R×C contingency table data should be used. For quantitative data, expressed as mean±SD in this study, the t-test for paired design data or two independent samples should be used. A test level of α=0.05 is adopted, and $p<0.05$ is considered to be statistically significant.

Safety evaluation and risk minimisation measures

Exclusion criteria for this study include patients with a hypercoagulable state. We actively encourage and monitor lower extremity functional exercise and early ambulation for patients after procedure. Routine postoperative use of rivaroxaban, compression stockings and continuous passive motion are employed to prevent VTE. For potential cardiovascular events, postoperative monitoring of vital signs such as ECG and blood oxygen levels is regularly conducted. We closely monitor patients' complaints and proactively prevent and manage any potential risks. Internal medicine specialists are involved as necessary for diagnosis and treatment. Potential risk factors for this study include TXA-related hypersensitivity reactions and thromboembolic risks.

Clinical specimen management and data preservation

We retain all the information related to this study, including records of drug dosages and timings administered to study participants, all signed informed consent forms, and all the data collected throughout the study process. The retention period is 5 years.

Patient and public involvement

The development of the research question and outcome measures is not influenced by patients' priorities, experiences and preferences. Participants and the public are not involved in the design, recruitment or conduct of the study.

ETHICS AND DISSEMINATION

This study has been authorised by the Ethics Committee of Peking Union Medical College Hospital (approval number: K2371) and the Chinese Clinical Trial Registry (trial registration number: ChiCTR2200066293), and is being conducted in accordance with the Helsinki Declaration. Prior to participating, all participants provided

signed informed consent. Participation in the study does not interfere with hospital care, and the participants have the right to withdraw consent at any time without experiencing any negative consequences. Authorship is granted to investigators who have contributed to the project's design, conduct, statistical analysis, interpretation and reporting. The findings of this study will be published in a peer-reviewed academic journal.

Contributors This study was designed by BF and XW. This manuscript was written by ZW, MY, YX and BF. All authors approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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