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Single-blinded, randomized, parallel-controlled study evaluating the effects of multiple doses of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Author Contributions:

BXK and LBX conceived the study while XX, CXG, SZ, JZ, JX, STS, and YHM designed the study. The study protocol was drafted by BXK and LBX. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: This clinical trial was designed to observe the effect of multiple doses use of tranexamic acid on perioperative hidden blood loss (HBL) in patients with rheumatoid osteoarthritis (RA) and to verify the effectiveness and safety of multiple doses of tranexamic acid on reducing the amount of bleeding during the perioperative period, which can accelerate patient recovery after surgery. This study provides a new clinical evidence for perioperative blood management for total knee arthroplasty (TKA) in

patients with RA.

Methods and analysis: We will use a randomized, single-blinded, parallel-controlled study design to evaluate the efficacy of multiple doses use of tranexamic acid during the perioperative period. Before the patient is enrolled, the patient is fully informed of the condition and drug use plan, and the informed consent form is signed to fully inform the benefits and risks that may be obtained by using tranexamic acid multiple doses during the perioperative period. This study will include RA patients (age 50-75 years) with a unilateral primary end-stage TKA who will be randomly divided into group A or group B. The two groups will be given an IV infusion of 1 g of tranexamic acid before the operation, and 1.5 g of tranexamic acid will be administered by intra-articular injection during the surgery. Group A will be intravenously administered with 1 g of tranexamic acid at 3 hours after surgery. Group B will be intravenously administered 1 g of tranexamic acid at the 3rd, 6th, and 12th hours after surgery. The primary outcomes are postoperative hidden blood loss (calculated according to Nadle and Gross's formula), and the amount of change in perioperative haemoglobin. The secondary outcome measures include whole blood inflammatory factors (erythrocyte sedimentation rate and C-reactive protein), serum inflammatory factors (IL-6, IL-12 and TNF-α), and coagulation parameters (D dimer, thrombin time).The knee function indicators include the knee swelling rates and knee joint range of motion. The adverse events include deep vein thrombosis (DVT), pulmonary embolism (PE), and other complications.

Ethics and dissemination：This trial has been approved by the Ethics Committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine, and subsequent modifications of the protocol will be reported and approved by it.

Ethical number: 2019-K-02 .

Trial registration number: ChiCTR1900025013

Patient and Public Involvement: Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive written information about this trial, and the content includes the benefits, risks and discomforts that may be brought after participating in the study. Patients can also discuss with relatives, friends, or ask the doctor to explain and help them make a decision. However, they will not be involved in the recruitment and conduct of the study. Besides, the burden of the intervention will be assessed by patients themselves. After signing an informed consent by the participant, they will be assessed for eligibility and data collection will begin. Dissemination of the general results (no personal data) will be made on demand.

Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, hidden blood loss, clinical trial protocol

Article Summary

Strengths and limitations of this trial

This trial is the first trial to use a single-blinded, randomized, parallel-controlled design in China to observe the efficacy and safety of multiple doses of tranexamic acid in the perioperative period of TKA in patients with RA.

The study use a rigorously study designed , which includes proper randomization, allocation concealment, an adequate sample size and objective clinical test indicators ,and reduces the selectivity bias.

However, due to some geographical reasons, long-term follow-ups of some patients can only be conducted by phone.

Introduction

Total knee arthroplasty （TKA）was developed in the 1970s. TKA is an effective treatment for various knee arthritis end-stage lesions causing severe pain, deformity and dysfunction of the knee joint.[1] The US epidemiological survey shows that the number of patients undergoing TKA will increase each year.[2] There are 230 million surgeries each year worldwide; joint replacement surgery accounts for the majority for these surgeries, and haemorrhage is one of the major complications in the perioperative period.[3] Excessive blood loss may require an allogeneic blood transfusion. Allogeneic blood transfusion can spread blood diseases, cause immune complications, prolong hospitalization time and increase the infection rate.[4-5] The incidence of anaemia in rheumatoid osteoarthritis (RA) patients is high. Anaemia is negatively associated with rheumatoid arthritis and increase the progression of osteoarthritis damage observed by imaging.[6-7] Therefore, we believe that perioperative blood management in patients with RA is particularly important.

Hidden blood loss (HBL) is the blood lost during intraoperative and postoperative infiltration into the tissue, residual blood in the knee joint cavity and haemolysis, accounting for 50% of the total blood loss.[8] HBL is not involved in the blood circulation;

it can cause systemic blood cells, decreases in haemoglobin decrease, local tissue haematoma, poor wound healing, and even wound infections.

Surgical tourniquet use, can reduce intraoperative bleeding,[8-9] providing a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[10] However, after the release of the tourniquet, local tissue ischemia reperfusion injury and activation of the fibrinolytic system can occur.[11-12] Peripheral blood circulation accelerates, plasma fibrinolysis becomes enhanced, and postoperative HBL increases.[11] Thus reducing the dissolution of fibrin, can reduce postoperative HBL.[13]

Tranexamic acid is a synthetic lysine derivative that can competitively inhibit the binding of plasminogen and fibrin, prevents the activation of plasminogen, and protects fibrin from degradation and dissolution by plasmin. Tranexamic acid was initially used in obstetrics and gynaecology and was then gradually applied in surgeries such as cardiothoracic surgery, trauma, joint replacement, and spine surgery to reduce bleeding and blood transfusion rates.[14-16] The CRASH-2 trial has demonstrated the effectiveness and safety of tranexamic acid in reducing blood loss.[17] Currently, tranexamic acid has been recommended as a guideline drug for perioperative blood management during TKA.[18]

The methods of administering tranexamic acid includes oral administration, intravenous administration , single large dose intravenous administration, intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, and combination therapy.[19-23] Howver, there is no consensus on the optimal dose of and time of

administring tranexamic acid during the TKA perioperative period.[14,24-25]

Studies have shown that fibrinolysis peaks at 6 hours postoperatively and continues occur for approximately 18 hours after TKA with tourniquets.[26] The half-life of tranexamic acid in plasma is 2 hours, and the maximum concentration can be reached by intravenous administration for 1 hour.[27] Thus, we suspect that a single dose of tranexamic acid may not be sufficient for an anti-fibrinolytic effect during the perioperative period of TKA. There are also studies suggesting that for patients with osteoarthritis, higher doses of tranexamic acid during the perioperative period can increase the efficacy of the drug until the dosage reaches a certain upper limit.[16,28-29] The purpose of this clinical trial is to verify the effectiveness and safety of multiple doses of tranexamic acid in reducing blood loss in patients with RA during the perioperative period, improving the enhanced recovery after surgery (ERAS), and providing a new evidence for perioperative blood management for TKA. We will use a large sample size to ensure a credible conclusion.

Methods and analysis

Study context

This clinical trial will be conducted at the inpatient ward of Shanghai University of Traditional Chinese Medicine Guanghua Hospital in Shanghai, China on September 1, 2019, and there will be 11 investigators, including 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM and QS), 2 date collectors and who are also statisticians (B-xK and HX) and a nurse(X-rX). Give patients informed consent before the start of clinical trials. The perioperative ERAS blood management programme and the trial flow chart are shown in

Table 1 and Figure 1. The schedule is shown in Table 2.

Sample size calculation

This trial uses a completely randomized design, and multiple sample sizes are estimated by a previous clinical research review. The the main outcome measure is the amount of HBL. The overall mean estimate is $\sigma = 320$, and the overall standard deviation is $\mu = 79$, using the statistical formula $n = \psi^2\left(\sum_{i=1}^{k}\sigma^2/k\right)/\left[\sum_{i=1}^{k}(\mu_i-\mu)^2/(k-1)\right]$.Considering a dropout rate of 20%, 76 subjects were required to yield a power of 90% with a significance level of 0.05.

Randomisation and allocation concealment

Patients are randomly assigned to two groups according to a 1:1 ratio; SPSS 25.0 is used to generate a random sequence containing 76 random numbers, that are placed into an opaque envelope and input in a computer by encryption, and the group data is saved by the data collector who is a statiscian. Only the nurse will be allowed to check the enrollment and give the corresponding treatment.

Single-blinded design

The nurse will know the patients' enrolment and give the corresponding treatment. All participants in this trial, including the orthopaedic surgeons and data collectors who are statisticians, are all blinded to the treatment conditions. The outcome assessor will not be aware of the patient's enrolment and will objectively records the patients' test information. When performing the statistical analyses, the independent biostatistician will also be blinded to the conditions.

Eligibility criteria

The eligibility criteria are in accordance with the " Classification of Rheumatoid Arthritis" from the American Journal of Rheumatism revised in 1978,[30] and the 2010 American College of Rheumatology and the European League Against Rheumatism.[31] (1)The patient is diagnosed with RA and the Kellgren-Lawrence[32] classification is Stage III or IV; (2) The patient is aged 55 to 75 years old; (3) The patient will undergo the unilateral primary TKA; (4) The patients received perioperative anti-fibrinolytic tranexamic acid therapy; and (5)The patient did not have preoperative anaemia, and the blood clotting function was normal.

Exclusion criteria

The exclusion criteria were as follows:(1) Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2) Bilateral knee arthroplasty in patients with RA; (3) Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral haemorrhage);and (4) Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

The elimination criteria were as follows: (1) Patients with acquired colour vision disorder; (2) Active intravascular coagulation patients; and (3) Patients with a history of convulsions.

Termination criteria

The termination criteria were as follows: (1) Shock: once a shock occurs, appropriate therapy is administered to terminate it; (2) Allergic symptoms: such as itching and a rash; (3) Digestive disorders such as nausea, vomiting, loss of appetite, and diarrhoea after

medication; (4) Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, visual impairment, and others; and (5) Adverse events such as intracranial thrombosis and intracranial haemorrhage after medication.

Surgery and anesthesia

Surgery is performed by senior surgeons (LBX and WTZ).The operations are conducted under general anaesthesia. The median incision of the knee joint, the medial paramedian support band approach, and the length of the incision are approximately 14-17cm. Positioning is within the femoral and tibial bone marrow external positions. All patients will use a tourniquet during the operation, and the pressure will be controlled at approximately 230-250mmHg. During the operation，controlled hypotension ,a reduction in blood pressure to 20% of the basal blood pressure, will be administered with a postoperative suction drainage tube, and limb surgery will be conducted with an elastic bandage. In the perioperative period, conventional anti-infective, combined analgesic, anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments will be administered according to the "Chinese hip and total knee arthroplasty surgery perioperative anti-fibrinolytic drug sequential anticoagulant application programme expert consensus". Ten min before the incision, 1 g of tranexamic acid + 100mL intravenous saline and 1.5 g of tranexamic acid + 50 mL articular injection of saline will be administered preoperatively in the sutured joint cavity.

Tranexamic acid is produced by Hunan Dongting Pharmaceutical Co., Ltd., and the implementation standards are found in the following resources: second edition of 2015

Chinese Pharmacopoeia and drug supplement application approval (2013B02016), YBH07372010; the approval number is National Drug Standard H43020565.

Study interventions

Group A: At the 3rd hour after the operation, 1 g of tranexamic acid + 100 mL of physiological saline is administered intravenously. Group B: 1 g of tranexamic acid + 100 mL of physiological saline is intravenously instilled at 3, 6, and 12 hours after the operation.

Pain management and rehabilitation

A cocktail injection is given during the operation, and 0.2 g of oral celecoxib is given after surgery for analgesia. Anesthesia is given to the athlete's foot after anaesthesia The maximum angle of flexion and extension of the ankle is maintained for 6 seconds, the foot is relaxed for 5 seconds; and the quadriceps contractions are equal between the two sides. On the first postoperative day, the patients will be perform a straight leg raise exercise, a supine knee flexion exercise and a sitting flexion and extension knee exercise; the machine-assisted exercises will begin on the third day after surgery, such as continued passive motion.

Antibiotics

Cefazolin sodium perioperative antibiotics as prophylaxis are administered 30 min before surgery, and the incision 24-48 hours after the postoperative intravenous infusion.

Prevention of lower extremity venous thrombosis

Six hours after the perioperative injection, low molecular weight heparin is injected for the prevention of deep vein thrombosis.

Outcomes

Primary outcome

Hidden blood lose（HBL），haemoglobin

The amount of HBL is calculated according to the formula by Nadle[33] and Gross formula[34]: Patient's blood volume (PBV)= K1×height(m)+ K2×weight(kg)+ K3(Male:K1=0.3669,K2=0.03219, K3=0.6041. Female: K1=0.3561, K2=0.03308, K3=0.1833). HBL=PBV×(Hct $_{pre}$- Hct $_{post}$）/Hct$_{ave}$.

Preoperatively , on the 1st, 3rd, 7th and 14th days after surgery, we will calculate the HBL based on the value of haematocrit and recorded the amount of haemoglobin.

Second outcome indicator

Inflammatory index, Inflammatory factor, Coagulation index

Preoperatively, on the 1st, 3rd, 7th and 14th days after surgery, we will record the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole blood and interleukin 6 (IL-6), interleukin 12 (IL-12),and tumor necrosis factor α (TNF-α) in the plasma.

Whole blood test indicators and plasma inflammatory factors will be assessed in the Department of Clinical Laboratory of Guanghua Hospital. The indicators and factors will be tested by an inspector who is not involved in this clinical trial.

Knee function score and swelling rate

Knee function will be measured using the American Keen Society Score (AKSS) at one day before surgery and on the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully understand the questionnaire and how to assess their knee function in order to complete the questionnaire. The rate of swelling is defined as the postoperative circumference of the upper tibia divided by the preoperative circumference of the upper tibia.

Adverse events

Adverse events include the follow: Deep vein thrombosis[35]: (1)Acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg; (2) Extensive swelling on the affected limb; (3) The skin of the affected limb has a dull red colour and a rise in temperature ; (4) Generalized shallow venous tension on the affected limb; (5) Homan's sign and Neuhof's sign are positive; and (6)Doppler ultrasound for venous blood flow and venography are used to confirm the diagnosis and Pulmonary embolism: Clinical manifestations (cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling or pulsation, etc.) and computed tomography are used to identify the occurrence of a pulmonary embolism.

The wound healing process and complications[36] (wound bleeding, haematoma, wound infection, and deep infection)will be observed and recording during hospitalization and follow-ups. Wound exudation is defined as the exudation of the wound up to 48 hours after surgery.

Adverse event processing

Adverse events that occur during the use of medication are not necessarily related to drug use, but the content recorded in the CRFs is used to evaluate the relevance of drugs to the follow-up observations. The classification of adverse events will be recorded in accordance with the five-level scoring systems in the 5.0 version of the CTCAE.

Serious adverse events are defined as those that cause cancer, defects, teratogenicity, danger to the statement, death, and permanent damage to organ function, permanent or significant disability, and prolonged hospital stay. In the event of the above mentioned incidents, the researcher should immediately take appropriate measures with the subjects and report to the hospital sponsors and ethics committees within 24 hours.

Data management

Date entry will be conducted by two independent trained research assistants who are trained to use the paper CRFs. Computer data is entered with a strict specifications , double-entry input method. The hospital's independent investigators will monitor and audit the data periodically.

Statistical analysis

The analyses are as follows: (1) Descriptive analysis of the characteristics of the study participants; (2) Balance analysis of the baselines values among groups; (3) Comparison of the balance among groups of the primary outcome indicators; and (4) Comparison of secondary outcome indicators and safety indicators among groups.

The three groups' incidence and the total rate of adverse events are tested by bidirectional disordered R*C list chi-square test. The association between the occurrence of adverse events and the dose of tranexamic acid used is described.

Ethics and dissemination

This clinical trial has been approved by the ethics committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine (approval number: 2019-K-02). Data will be kept strictly confidential. The results of the trial will be published on the website of the China Clinical Trials Registry and published in peer-reviewed journals.

Discussion

Blood management is an important part of the ERAS programme, which is an evidence-based treatment programme that uses multiple strategies for treating TKA to reduce complications, improve the prognosis and promote rapid recovery after surgery.

In this trial, we will exclude patients with a large number of intravenous infusions to reduce the effect of blood dilution on the results. We will use a tourniquet and will not

conducted blood cell return during the operation, and the amount of intraoperative blood loss we will negligible.[37] It has been reported that intravenous infusion combined with intra-articular injection of tranexamic acid may be the optimal therapeutic scheme.[38-39] Previous studies have shown that swelling of the knee joint after TKA is associated with HBL in the joint cavity. Tranexamic acid reduces the degree of swelling around the joint by reducing postoperative HBL.[40] Animal experiments also indicate that plasminogen activators play an important role in the development of inflammation in RA, and the dissolution of fibrin will causes an inflammatory response.[41] Therefore, we suspect that the use of multiple doses of transxamic during the peroperative period may have an auxiliary anti-inflammatory effect.

In this study, is the sample size is sufficient to obtain true and reliable results. This study will provide new evidence for blood management during the perioperative period of TKA in RA patients.

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Table 1 Enhanced recovery after surgery blood management

Preoperative
Treatment of hemorrhagic primary disease

Nutritional guidance, balanced diet
Iron application
rHuEPO application
Intraoperative
Minimally invasive surgery
Tourniquet optimization
Controlled buck
Autologous blood return
Use of tranexamic acid
Postoperative
Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)
Nutritional support, iron supplementation, use of rHuEPO

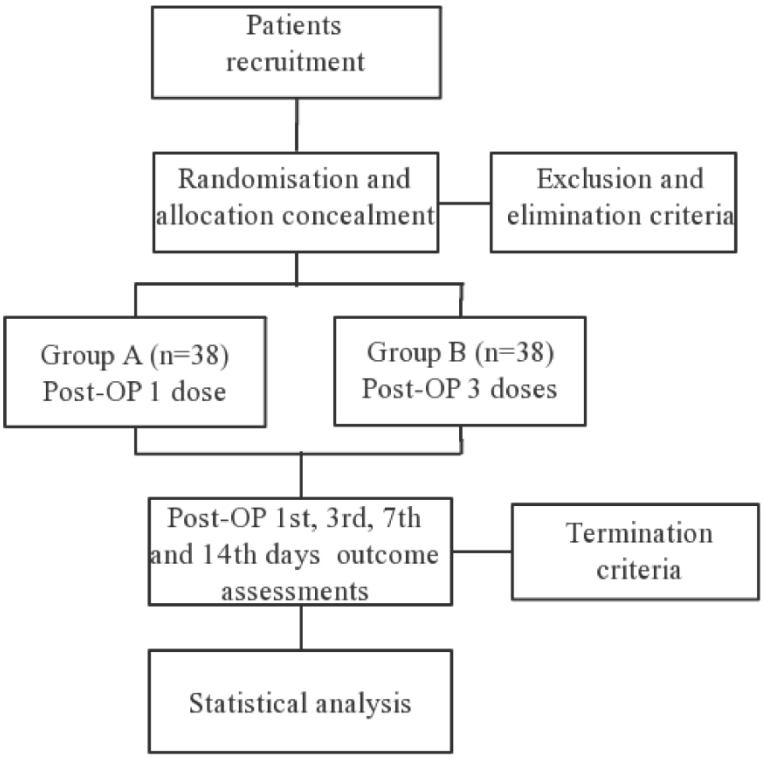
RHuEPO, Human recombinant erythropoietin.

Table 2. The schedule of trial enrolment, interventions and assessments

Patients recruitment	Time period for collecting data				
	Pre-OP	D1	D3	D7	D14
Enrolment	●				
Assessment of eligibility	●				
Randomisation	●				
Group A Post-OP 1 dose	●	●	●	●	●
Group B Post-OP 3 doses	●	●	●	●	●
HBL		●	●	●	●
Hb	●	●	●	●	●
Inflammatory index	●	●	●	●	●
inflammatory factor	●	●	●	●	●
coagulation index	●	●	●	●	●
Swelling rate		●	●	●	●
DVP		●	●	●	●
PE		●	●	●	●
Postoperative complications and adverse events		●	●	●	●

OP, operation; HBL, hidden blood lose; Hb, Hemoglobin; DVP, deep vein thrombosis; PE, pulmonary embolism

463



The flow chart of this test

232x214mm (300 x 300 DPI)

BMJ Open

The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Secondary Subject Heading:	Surgery
Keywords:	Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, Knee < ORTHOPAEDIC & TRAUMA

	SURGERY, Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Author Contributions:

BXK, HX and LBX conceived the study while CXG, SZ, JZ, JX, STS, YHM, and WTZ designed the study. The study protocol was drafted by BXK and HX. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: This clinical trial is designed to evaluate the effect of multiple-dose tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with rheumatoid osteoarthritis (RA).

Methods and analysis: A randomized, single-blinded, parallel-controlled study design will be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage TKA will be randomly divided into Group A or Group B. Group A will be treated with one dose of TXA (1g; intravenous injection at the 3rdhour) and Group B with three doses (at the 3rd, 6th, and 12th hours; intravenous injection) after surgery. The primary outcomes will be evaluated with hidden blood loss and haemoglobin level and the secondary outcomes with blood inflammatory factors, serum

inflammatory factors, and coagulation parameters.

Ethics and dissemination：This trial has been approved by the Ethics Committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine.

Ethical number: 2019-K-13.

Trial registration number: ChiCTR1900025013

Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, hidden blood loss, clinical trial protocol.

Article Summary

Strengths and limitations of this trial

(1)This is the first single-blinded, randomized, parallel-controlled study in China to evaluate the efficacy and safety of perioperative multiple-dose regimen of tranexamic acid after TKA in patients with RA.

(2)The study has its bias largely reduced by rigorously study designs, including proper randomization, allocation concealment, an adequate sample size and objective indicators.

(3)Long-term follow-ups of some patients can only be conducted by phone. And the results can only be extrapolated to Chinese RA population.

Introduction

Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like

anemia.[1]The overall prevalence of RA is 0.5-1% in Europe and North America, 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.[2-3] Total knee arthroplasty (TKA) is effective in treating flexion contracture and maintaining the stability of RA knee.[4] About 0.005% of RA patients receive TKA, a rate that has gradually decreased over the past decades. Even though, surgery remains the first choice for articular deformity and pain, despite that disease-modifying antirheumatic drugs(DEMARDs) and biologics angents can manage synovitis-related symptoms in RA patients.[5] The haemorrhage is a major perioperative complications of TKA.[6] Excessive blood loss should be replenished with allogeneic blood transfusion, but it may cause immune complications, prolong hospitalization time and increase the infection rate.[7-8] Haemoglobin has an obviously negative correlation with disease activity in RA.[9] Therefore, we believe that perioperative blood management is need for patients with RA.

Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in the knee joint cavity and gets haemolyzed.[10] As this blood is not involved in the blood circulation, HBL often leads to the postoperative pain, lower limb swelling, poor wound healing, postoperative inflammation, and even wound infections.

Surgical tourniquet use, can reduce intraoperative bleeding,[11] provide a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[12] However, after the release of the tourniquet, local tissue may be damaged by ischemia reperfusion injury, and fibrinolytic system

activated.[13-14] As a consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced, and postoperative HBL increased.[13] Therefore, reducing the dissolution of fibrin can reduce postoperative HBL.[15] Tranexamic acid (TXA) is a synthetic lysine derivative that can competitively inhibit the binding between plasminogen and fibrin, prevent the activation of plasminogen, and protect fibrin from degradation and dissolution by plasmin. TXA is initially used in obstetrics and gynaecology, then gradually replicated in surgeries to reduce bleeding and avoid blood transfusion rates.[16-17] The CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.[18] A large amount of literature has reported that TXA can significantly reduce peri-TKA blood loss.[19-23] Currently, TXA is recommended for perioperative blood management of TKA.[24] But, its efficacy and safety in RA patients undergoing TKA has been rarely reported.[25] TXA can be administered through oral intake, single large-dose intravenous injection, intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, and combination use.[23,26-29] There is no consensus on the optimal dose and time of TXA administration during perioperative TKA.[16,30-31] Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKA with tourniquets.[32] The half-life of TXA in plasma is 2 hours, and its concentration peaks at 1 hour after injection.[33] Thus, we suspect that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic. There are also studies suggesting that for patients with osteoarthritis, higher doses (within a limit) during the perioperative period can increase the efficacy of TXA.[34-36] The purpose of this clinical trial is to

verify the effectiveness and safety of multiple doses of TXA in reducing perioperative blood loss in RA patients treated with TKA, hoping to find a new modeof perioperative blood management for TKA.

Methods and analysis

Study context

This clinical trial will start on September 1, 2019 at the wards of Shanghai University of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China).The annual surgical number of TKA for RA patients was about 300 in 2018. Eleven investigators include 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM and SZ), 2 date collectors and who are also statisticians (B-xK and HX) and a nurse(X-rX). Informed consent will be obtained. The perioperative ERAS blood management programme and the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table 2.

Sample size calculation

This trial uses a completely randomized design, and multiple sample sizes are estimated by a previous clinical research review. The main outcome is measured with the amount of HBL. The overall mean estimate is σ = 320, and the overall standard deviation is μ = 79, both estimated by the statistical formula $n = \psi^2\left(\sum_{i=1}^{k}\sigma^2/k\right)/\left[\sum_{i=1}^{k}(\mu_i-\mu)^2/(k-1)\right]$. Considering a dropout rate of 20%, 76 subjects are required to yield a power of 90% with a significance level of 0.05.

Randomization and allocation concealment

Patients are randomly assigned to two groups according to at 1:1 ratio; SPSS version25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence containing 76 random numbers, which are placed into an opaque envelope and put in a computer by encryption. The group data is saved by the statistician. Only the nurse is allowed to check the enrollment and give the corresponding treatment.

Single-blinded design

Only the nurse will be allowed to know the patients' enrollment and give them corresponding treatment. The outcome evaluators will objectively record the patients' test results.

Eligibility criteria

The eligibility criteria are set in accordance with the "AMERICAN RHEUMATISM ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS" from the American Journal of Rheumatism (revised in 1978),[37] and the 2010 "ACR/EULAR classification criteria for rheumatoid arthritis"[38] (1)The patient is diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence[39] classification; (2)The patient is 55 to 75 years old; (3)The patient will undergo the unilateral primary TKA; (4)The patients will receive perioperative anti-fibrinolytic TXA therapy; and (5)The patient will show normal blood-clotting function and no preoperative anaemia.

Exclusion criteria

Excluded are those with: (1)Other types of arthritis (such as primary arthritis,

post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2)Bilateral knee arthroplasty (RA patients); (3)Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral haemorrhage);and (4)Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

Eliminated are those with: (1)Acquired colour vision disorder; (2)Active intravascular coagulation patients; and (3)a history of convulsions.

Termination criteria

The study on one patient will be terminated if he/she shows the following events: (1)Shock; (2)Allergic symptoms, such as itching and a rash; (3)Digestive disorders, such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4)Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, visual impairment, and others; and (5)Adverse events, such as intracranial thrombosis and intracranial haemorrhage after medication.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued at one week before surgery. Use of other disease-modifying antirheumatic drugs (DEMARDs) will be discontinued two days before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The use of newer biologic agents targeting tumor necrosis (TNF-α) will be discontinued

for 4 to 5 half-lives before surgery and restarted after wound healing and infection elimination.[40-41]

Surgery and anesthesia

Surgery will be performed by two senior surgeons (LBX and WTZ). The operations will be conducted under general anaesthesia. A median incision (14-17 cm long) is cut in the knee join with a medial paramedian support band. Internal positioning is used for femoral bone marrow and external positioning for tibial bone marrow. All patients will use a tourniquet with a pressure of 230-250 mmHg. During the operation, blood pressure will be reduced to 20% of the basal level through a suction drainage tube, and limb surgery will be conducted with an elastic bandage. During the operation, conventional anti-infective, combined analgesic, anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments will be administered according to the "Chinese Hip and Total Knee Arthroplasty Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert Consensus". Ten minutes before the incision, 1 g of TXA + 100 mL of intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be administered preoperatively in the sutured joint cavity.

TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according to the second edition of 2015 Chinese Pharmacopoeia and Drug Supplement Application Approval (2013B02016), YBH07372010; the approval number is National Drug Standard H43020565.

Intraoperative blood loss

The amount of postoperative blood loss= the total volume of fluid in the negative pressure drain－the volume of normal saline.

Study interventions

Group A: 1 g of TXA + 100 mL of physiological saline will be injected intravenously at the 3rd hour after the operation. Group B: 1 g of TX + 100 mL of physiological saline is intravenously instilled at the 3rd, 6th, and 12th hours after the operation.

Pain management and rehabilitation

A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib after surgery for analgesia. After anaesthesia the maximum angles of flexion and extension of the ankle will be maintained for 6 seconds, and the foot is relaxed for 5 seconds; the quadriceps contractions are equal between the two sides. At the first postoperative day, the patients will exercise straight-leg-raise, supine-knee-flexion and knee flexion and extension in sitting; the machine-assisted exercises will begin on the third day after surgery, such as continuous passive motion.

Antibiotics

For perioperative prophylaxis, cefazolin sodium antibiotics are administered at 30 minutes before surgery, and 24-48 hours after surgery.

Prevention of lower extremity venous thrombosis

Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day for 14 days) is injected for preventing deep vein thrombosis.

The Patient and Public Involvement

Any non-investigator will not be involved in the design of the study and

related questions. Patients will receive written information about this trial, pertaining to the benefits, risks and discomforts that they may get from the study. Patients can also discuss with their relatives, friends, or doctors to help them make a decision. Besides, the benefits and risks of the intervention will be assessed by patients themselves. After signing an informed consent, they will be assessed for eligibility and data will be collected. Dissemination of the general results (no personal data) will be made on demand.

Outcomes

Primary outcomes

Hidden blood lose（HBL），haemoglobin level

HBL is calculated according to the formula by Nadle[42] and Gross formula:[43] Patient's blood volume (PBV)= K1×height(m)+ K2×weight(kg)+ K3(Male:K1=0.3669,K2=0.03219, K3=0.6041. Female: K1=0.3561, K2=0.03308, K3=0.1833). HBL=PBV×(Hct_{pre}- Hct_{post}）/Hct_{ave}.

Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will calculate the HBL based on the value of haematocrit and recorded the count of haemoglobin.

Secondary outcomes

Inflammatory index, inflammatory factor and coagulation index

Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF-α in the plasma.

Whole blood test indicators and plasma inflammatory factors will be assessed in the Department of Clinical Laboratory of Guanghua Hospital. The indicators and factors will be tested by an inspector who is not involved in this clinical trial.

Knee function and swelling

Knee function will be measured using the American Keen Society Score (AKSS) at one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully know how to assess their knee function through the questionnaires. The rate of swelling is defined as the postoperative circumference of the upper tibia ÷ the preoperative circumference of the upper tibia.

Adverse events

Adverse events include (1)Deep vein thrombosis[44] (acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg); (2)Extensive swelling on the affected limb; (3)A dull red colour and a rise in the skin of the affected limb; (4)Generalized shallow venous tension on the affected limb; (5)In the skin of the affected limb; (6)Pulmonary embolism diagnosed by Doppler ultrasound and venography (clinical manifestations: cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism diagnosed by CT.

The wound healing process and complications[45] (wound bleeding, haematoma, wound infection, and deep infection) will be observed and recorded in the patient's

case report forms (CRFs) during hospitalization and follow-ups. Wound exudation is defined as the presence of exudation from the wound even 48 hours after surgery.

Adverse event treatment

Adverse events during the follow-up will be recorded in the CRFs, and their relevance to drug use will be evaluated. All the adverse events will be classified in accordance with the five-level scoring systems (5.0) of the CTCAE.

Serious adverse events are defined as those that may cause cancer, defects, teratogenicity, death, and permanent damage to organ function, permanent or significant disability, and prolonged hospital stay. In any event, the researcher should immediately take appropriate measures and report it to the hospital and ethics committees within 24 hours.

Data management

Data on the CRFs will be put in the computer by two independent trained research assistants with a double-entry method. The hospital's independent investigators will check the data periodically.

Statistical analysis

The analyses are as follows: (1)Descriptive analysis on the characteristics of the study participants; (2)Balance analysis on the baseline values in groups; (3)Comparison of the balance between groups of primary outcomes; and (4)Comparison of secondary outcomes and safety between groups.

The total rate of adverse events of the two groups are tested by bidirectional disordered R*C list chi-square test. The association between the incidence of adverse events and the dose of TXA used is described.

Ethics and dissemination

This clinical trial has been approved by the ethics committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. The data sets can be obtained from appropriate authors upon reasonable request. Data will be kept strictly confidential and published on the website of the China Clinical Trials Registry and in peer-reviewed journals.

Discussion

Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical studies have shown that high dose of TXA can reduce blood loss after TKA in patients with osteoarthritis.[25,45-46] In this trial, we will exclude patients with a large number of intravenous infusions to eliminate the effect of blood dilution on the results. We will use a tourniquet to minimize the blood loss during the operation. Therefore, what we will observed is the blood loss after the removal of tourniquet.[10] It has been reported that intravenous infusion combined with intra-articular injection of TXA may be the optimal bleeding-control scheme.[47-48] Previous studies have shown that knee joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the swelling around the joint.[49] Given that plasminogen activators play an important role in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory response.[50] Therefore, we suspect that multiple doses of TXA in the peroperative period may exert an auxiliary anti-inflammatory effect.

This study will provide new evidence for managing perioperative HBL in TKA

in Chinese RA patients.

Acknowledgment:

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Table 1 Enhanced recovery after surgery blood management

Preoperative
1 Treatment of hemorrhagic primary disease
2 Nutritional guidance, balanced diet
3 Iron application
4 rHuEPO application
Intraoperative
5 Minimally invasive surgery
6 Tourniquet optimization
7 Controlled buck
8 Autologous blood return
9 Use of tranexamic acid
Postoperative
10 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)
11 Nutritional support, iron supplementation, use of rHuEPO

rHuEPO, recombinant human erythropoietin.

Table 2 The schedule of trial enrolment, interventions and assessments

	Outcome assessment				
	Pre-OP	**D1**	**D3**	**D7**	**D14**
Enrolment	•				
Assessment of eligibility	•				
Randomisation	•				
Group A Post-OP 1 dose of TXA	•	•	•	•	•
Group B Post-OP 3 doses of TXA	•	•	•	•	•
HBL		•	•	•	•
haemoglobin level	•	•	•	•	•
Inflammatory index	•	•	•	•	•
inflammatory factor	•	•	•	•	•
coagulation index	•	•	•	•	•
swelling rate		•	•	•	•
DVP		•	•	•	•
PE		•	•	•	•
Postoperative complications and adverse events		•	•	•	•

OP, operative; TXA, tranexamic acid; HBL, hidden blood lose; DVP, deep vein thrombosis; PE, pulmonary embolism; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA,tranexamic acid.

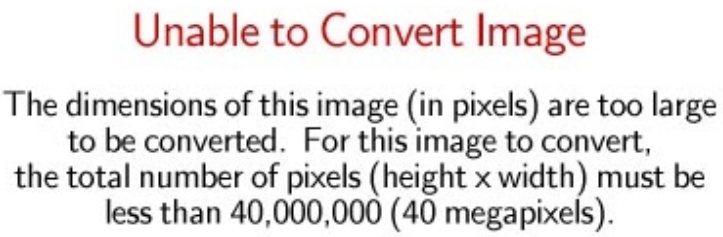

Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA,tranexamic acid.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Line Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1-3
	2b	All items from the World Health Organization Trial Registration Data Set	71
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	49
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	7-36;44-47
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	87-132
	6b	Explanation for choice of comparators	
Objectives	7	Specific objectives or hypotheses	133-135
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	1-3; 79-80.
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	68; 139-141; 248-249.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	165-182
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	223-227
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	186-192
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	228-235
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	253-275;

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	259;263;271 and Figure1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	146-154
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	141
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	155-160
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	155-160
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	142-145
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	159-164
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	159-160;
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	286-288; 290-298
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	300-302
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	303-310
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	53-55
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	185-191

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	186-192; 276-289
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	68-71
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	142-143 162-164
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	244-249
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	242-247
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	249-250
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	49-54
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	246-249 313-316;
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	313-316

	31b	Authorship eligibility guidelines and any intended use of professional writers	332-333
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	244-248
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	262-268

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Keywords:	Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, Knee < ORTHOPAEDIC & TRAUMA

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The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Author Contributions:

B-xK, HX and L-bX conceived the study while B-xK and HX drafted the study protocol, B-xK and HX contributed equally to this work and should be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX, S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Abstract:

Introduction: This clinical trial is designed to evaluate the effect of multiple-dose tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with rheumatoid osteoarthritis (RA).

Methods and analysis: A randomized, single-blinded, parallel-controlled study design will be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage total knee arthroplasty (TKA) will be randomly divided into Group A or Group B. Group A will be treated with one dose of TXA (1g; intravenous injection at the 3rdhour) and Group B with three doses (at the 3rd, 6th, and 12th hours; intravenous injection) after surgery. The primary outcomes will be evaluated with blood loss and haemoglobin level and the secondary outcomes with blood inflammatory factors,

serum inflammatory factors, and coagulation parameters.

Ethics and dissemination: This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. All of the participants or their authorised agents will give written informed consent before the study.

Ethical number: 2019-K-13.

Trial registration number: ChiCTR1900025013

Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, blood loss, clinical trial protocol.

Article Summary

Strengths and limitations of this trial

(1)This is the first study in China to evaluate the efficacy and safety of perioperative multiple-dose regimen of TXA after TKA in RA patients.

(2)The bias of this study reduced dramatically by extensive study design which includes proper randomization, allocation concealment and objective indicator.

(3)Long-term follow-ups of some patients can only be conducted by phone.

(4)The results can only be extrapolated to Chinese RA population.

Introduction

Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like anemia.[1] The overall prevalence of RA is 0.5-1% in Europe and North America,

0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.[2-3] Total knee arthroplasty(TKA) is effective in treating flexion contracture and maintaining the stability of RA knee.[4] About 0.005% of RA patients receive TKA, a rate that has gradually decreased over the past decades. Even though, surgery remains the first choice for articular deformity and pain, despite that disease-modifying antirheumatic drugs(DEMARDs) and biologics angents can manage synovitis-related symptoms in RA patients.[5] The haemorrhage is a major perioperative complications of TKA.[6] Excessive blood loss should be replenished with allogeneic blood transfusion, but it may cause immune complications, prolong hospitalization time and increase the infection rate.[7-8] Haemoglobin has an obviously negative correlation with disease activity in RA.[9] Therefore, we believe that perioperative blood management is need for patients with RA.

Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in the knee joint cavity and gets haemolyzed.[10] As this blood is not involved in the blood circulation, HBL often leads to the joint swell, postoperative inflammation and pain.[11-12]

Surgical tourniquet use, can reduce intraoperative bleeding,[13] provide a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[14] However, after the release of the tourniquet, local tissue may be damaged by ischemia reperfusion injury, and fibrinolytic system activated.[15-16] As a consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced,

and postoperative HBL increased.[15] Therefore, reducing the dissolution of fibrin can reduce postoperative HBL.[17] Tranexamic acid (TXA) is a synthetic lysine derivative that can competitively inhibit the binding between plasminogen and fibrin, prevent the activation of plasminogen, and protect fibrin from degradation and dissolution by plasmin. TXA is initially used in obstetrics and gynaecology, then gradually replicated in surgeries to reduce bleeding and avoid blood transfusion rates.[18-19] The CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.[20] A large amount of literature has reported that TXA can significantly reduce peri-TKA blood loss.[21-25] Currently, TXA is recommended for perioperative blood management of TKA.[26] But, its efficacy and safety in RA patients undergoing TKA has been rarely reported.[27] TXA can be administered through oral intake, single large-dose intravenous injection, intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, and combination use.[25,28-31] There is no consensus on the optimal dose and time of TXA administration during perioperative TKA.[18,32-33] Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKA with tourniquets.[34] The half-life of TXA in plasma is 2 hours, and its concentration peaks at 1 hour after injection.[35] Thus, we suspect that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic. There are also studies suggesting that for patients with osteoarthritis, higher doses (within a limit) during the perioperative period can increase the efficacy of TXA.[36-38] The purpose of this clinical trial is to verify the effectiveness and safety of multiple doses of TXA in reducing perioperative blood loss in RA patients treated with TKA, hoping

to find a new mode of perioperative blood management for TKA.

Methods and analysis

Study context

This clinical trial will start on September 1, 2019 at the wards of Shanghai University of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China).The annual surgical number of TKA for RA patients was about 300 in 2018. Eleven investigators include 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM and SZ), 2 date collectors and who are also statisticians (B-xK and HX) and a nurse (X-rX). Informed consent will be obtained. The perioperative ERAS blood management programme and the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table 2.

Sample size calculation

This trial uses a completely randomized design, and multiple sample sizes are estimated by a previous clinical research review. The main outcome is measured with the amount of HBL. The overall mean estimate is $\sigma = 320$, and the overall standard deviation is $\mu = 79$, both estimated by the statistical formula $n = \psi^2\left(\sum_{i=1}^{k}\sigma^2/k\right)/\left[\sum_{i=1}^{k}(\mu_i-\mu)^2/(k-1)\right]$. Considering a dropout rate of 20%, 76 subjects are required to yield a power of 90% with a significance level of 0.05.

Randomization and allocation concealment

Patients are randomly assigned to two groups according to at 1:1 ratio; SPSS version25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence containing 76 random numbers, which are placed into an opaque envelope and put in a computer by encryption. The group data is saved by the statistician. Only the nurse is allowed to check the enrollment and give the corresponding treatment.

Single-blinded design

Only the nurse will be allowed to know the patients' enrollment and give them corresponding treatment. The outcome evaluators will objectively record the patients' test results.

Eligibility criteria

The eligibility criteria are set in accordance with the "AMERICAN RHEUMATISM ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS" from the American Journal of Rheumatism (revised in 1978),[39] and the 2010 "ACR/EULAR classification criteria for rheumatoid arthritis"[40] (1)The patient is diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence[41] classification; (2)The patient is 50 to 75 years old; (3)The patient will undergo the unilateral primary TKA; (4)The patients will receive perioperative anti-fibrinolytic TXA therapy; and (5)The patient will show normal blood-clotting function and no preoperative anaemia.

Exclusion criteria

Excluded are those with: (1)Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and

tuberculous arthritis); (2)Bilateral knee arthroplasty (RA patients); (3)Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral haemorrhage);and (4)Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

Eliminated are those with: (1)Acquired color vision disorder; (2)Active intravascular coagulation patients; and (3)a history of convulsions.

Termination criteria

The study on one patient will be terminated if he/she shows the following events: (1)Shock; (2)Allergic symptoms, such as itching and a rash; (3)Digestive disorders, such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4)Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, visual impairment, and others; and (5)Adverse events, such as intracranial thrombosis and intracranial haemorrhage after medication.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued at one week before surgery. Use of other disease-modifying antirheumatic drugs (DEMARDs) will be discontinued two days before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The use of newer biologic agents targeting tumor necrosis (TNF-α) will be discontinued for 4 to 5 half-lives before surgery and restarted after wound healing and infection

elimination.[42-43]

Surgery and anesthesia

Surgery will be performed by two senior surgeons (L-bX and W-tZ). The operations will be conducted under general anaesthesia. A median incision (14-17 cm long) is cut in the knee join with a medial paramedian support band. Internal positioning is used for femoral bone marrow and external positioning for tibial bone marrow. All patients will use a tourniquet with a pressure of 230-250 mmHg. During the operation, blood pressure will be reduced to 20% of the basal level through a suction drainage tube, and limb surgery will be conducted with an elastic bandage. During the operation, conventional anti-infective, combined analgesic, anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments will be administered according to the "Chinese Hip and Total Knee Arthroplasty Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert Consensus". Ten minutes before the incision, 1 g of TXA + 100 mL of intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be administered preoperatively in the sutured joint cavity.

TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according to the second edition of 2015 Chinese Pharmacopoeia and Drug Supplement Application Approval (2013B02016), YBH07372010; the approval number is National Drug Standard H43020565.

Intraoperative blood loss

The amount of intropeative blood loss= the total volume of fluid in the

negative pressure drain—the volume of normal saline.

Study interventions

Group A: 1 g of TXA + 100 mL of physiological saline will be injected intravenously at the 3rd hour after the operation. Group B: 1 g of TXA + 100 mL of physiological saline is intravenously instilled at the 3rd, 6th, and 12th hours after the operation.

Pain management and rehabilitation

A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib after surgery for analgesia. After anaesthesia the maximum angles of flexion and extension of the ankle will be maintained for 6 seconds, and the foot is relaxed for 5 seconds; the quadriceps contractions are equal between the two sides. At the first postoperative day, the patients will exercise straight-leg-raise, supine-knee-flexion and knee flexion and extension in sitting; the machine-assisted exercises will begin on the third day after surgery, such as continuous passive motion.

Antibiotics

For perioperative prophylaxis, cefazolin sodium antibiotics are administered at 30 minutes before surgery, and 24-48 hours after surgery.

Prevention of lower extremity venous thrombosis

Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day for 14 days) is injected for preventing deep vein thrombosis.

Outcomes

Primary outcomes

The blood lose，haemoglobin level

The blood loss is calculated according to the formula by Nadle[44] and Gross formula:[45] Patient's blood volume (PBV)= K1×height^3(m^3)+ K2×weight(kg)+ K3(Male:K1=0.3669,K2=0.03219, K3=0.6041. Female: K1=0.3561, K2=0.03308, K3=0.1833). Total blood loss (TBL)=PBV×(Hct_{pre}- Hct_{post}).HBL=PBV×(Hct_{pre}- Hct_{post}）/Hct_{ave}.

Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will calculate the HBL based on the value of haematocrit and recorded the count of haemoglobin.

Secondary outcomes

Inflammatory index, inflammatory factor and coagulation index

Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF-α in the plasma. Whole blood test indicators and plasma inflammatory factors will be assessed in the participating hospital (Department of Clinical Laboratory of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine). The indicators and factors will be tested by an inspector who is not involved in this clinical trial.

Knee function and swelling

Knee function will be measured using the American Keen Society Score (AKSS) at one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully know how to assess their knee function through the questionnaires. The rate of swelling is defined as the

postoperative circumference of the upper tibia ÷ the preoperative circumference of the upper tibia.

Adverse events

Adverse events include (1)Deep vein thrombosis[46] (acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg); (2)Extensive swelling on the affected limb; (3)A dull red color and a rise in the skin of the affected limb; (4)Generalized shallow venous tension on the affected limb; (5)In the skin of the affected limb; (6)Pulmonary embolism diagnosed by Doppler ultrasound and venography (clinical manifestations: cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism diagnosed by CT.

The wound healing process and complications[47] (wound bleeding, haematoma, wound infection, and deep infection) will be observed and recorded in the patient's case report forms (CRFs) during hospitalization and follow-ups. Wound exudation is defined as the presence of exudation from the wound even 48 hours after surgery.

Adverse event treatment

Adverse events during the follow-up will be recorded in the CRFs, and their relevance to drug use will be evaluated. All the adverse events will be classified in accordance with the five-level scoring systems (5.0) of the CTCAE.

Serious adverse events are defined as those that may cause cancer, defects, teratogenicity, death, and permanent damage to organ function, permanent or significant disability, and prolonged hospital stay. In any event, the researcher should

immediately take appropriate measures and report it to the hospital and ethics committees within 24 hours.

Data management

Data on the CRFs will be put in the computer by two independent trained research assistants with a double-entry method. The hospital's independent investigators will check the data periodically.

Statistical analysis

The analyses are as follows: (1)Descriptive analysis on the characteristics of the study participants; (2)Balance analysis on the baseline values in groups; (3)Comparison of the balance between groups of primary outcomes; and (4)Comparison of secondary outcomes and safety between groups.

The total rate of adverse events of the two groups are tested by bidirectional disordered R*C list chi-square test. The association between the incidence of adverse events and the dose of TXA used is described.

Ethics and dissemination

Written inform consent will be obtained from all participants or their authorised agents before the study. All TXA treatments will be free. Research data will be kept strictly confidential and obtained from appropriate authors upon reasonable request .Results of the trial will be published on the website of the China Clinical Trials Registry and in peer-reviewed journals.

The Patient and Public Involvement

Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written

information about this trial, pertaining to the benefits, risks and discomforts that they may get from the study. They will not be involved in the recruitment and conduct of the study. Besides, the burden of the intervention will be assessed by patients themselves. After signing an informed consent, they will be assessed for eligibility and data will be collected. Dissemination of the general results (no personal data) will be made on demand.

Discussion

Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical studies have shown that high dose of TXA can reduce blood loss after TKA in patients with osteoarthritis.[27,47-48] In this trial, we will exclude patients with a large number of intravenous infusions to eliminate the effect of blood dilution on the results. We will use a tourniquet to minimize the blood loss during the operation. Therefore, what we will observed is the blood loss after the removal of tourniquet.[10] It has been reported that intravenous infusion combined with intra-articular injection of TXA may be the optimal bleeding-control scheme.[49-50] Previous studies have shown that knee joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the swelling around the joint.[51] Given that plasminogen activators play an important role in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory response.[52] Therefore, we suspect that multiple doses of TXA in the peroperative period may exert an auxiliary anti-inflammatory effect.

This study will provide new evidence for managing perioperative HBL in TKA in Chinese RA patients.

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Table 1 Enhanced recovery after surgery blood management

Preoperative
1 Treatment of hemorrhagic primary disease
2 Nutritional guidance, balanced diet
3 Iron application
4 rHuEPO application
Intraoperative
5 Minimally invasive surgery
6 Tourniquet optimization
7 Controlled buck
8 Autologous blood return
9 Use of tranexamic acid
Postoperative
10 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)
11 Nutritional support, iron supplementation, use of rHuEPO

rHuEPO, recombinant human erythropoietin.

Table 2 The schedule of trial enrolment, interventions and assessments

	Outcome assessment				
	Pre-OP	**D1**	**D3**	**D7**	**D14**
Enrolment	•				
Assessment of eligibility	•				
Randomisation	•				
Group A Post-OP 1 dose of TXA	•	•	•	•	•
Group B Post-OP 3 doses of TXA	•	•	•	•	•
HBL		•	•	•	•
haemoglobin level	•	•	•	•	•
Inflammatory index	•	•	•	•	•
inflammatory factor	•	•	•	•	•
coagulation index	•	•	•	•	•
swelling rate		•	•	•	•
DVP		•	•	•	•
PE		•	•	•	•
Postoperative complications and adverse events		•	•	•	•

OP, operative; TXA, tranexamic acid; HBL, hidden blood lose; DVP, deep vein thrombosis; PE, pulmonary embolism; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA,tranexamic acid.

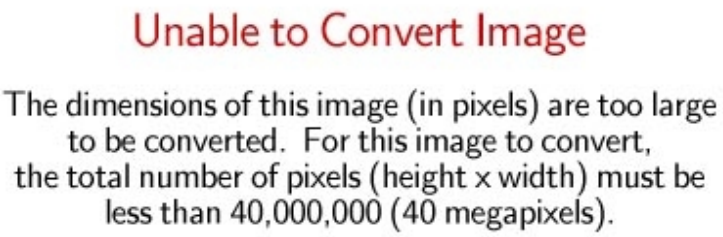

Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA,tranexamic acid.

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The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Surgery
Keywords:	Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, Knee < ORTHOPAEDIC & TRAUMA

	SURGERY, Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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The protocol of a single-blinded, randomized, parallel-controlled study to evaluate the effects of multiple-dose of tranexamic acid on perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis

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ASBTRACT:

Introduction This clinical trial is designed to evaluate the effect of multiple-dose tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with rheumatoid osteoarthritis (RA).

Methods and analysis A randomized, single-blinded, parallel-controlled study will be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage total knee arthroplasty (TKA) will be randomly divided into Group A or Group B. Group A will be treated with one dose of TXA (1g; intravenous injection at the 3rd hour) and Group B with three doses (at the 3rd, 6th, and 12th hours; intravenous injection) after surgery. The primary outcomes will be evaluated with blood loss and haemoglobin level and the secondary outcomes with blood inflammatory factors, serum inflammatory factors, and coagulation parameters.

Ethics and dissemination This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. All of the participants or their authorised agents will give written informed consent before the study.

Trial registration number ChiCTR1900025013; Pre-results.

Article Summary

Strengths and limitations of this trial

(1) This is the first study in China to evaluate the efficacy and safety of perioperative multiple-dose regimen of TXA after TKA in RA patients.

(2) The bias of this study reduced dramatically by extensive study design which includes proper randomization, allocation concealment and objective indicator.

(3) Long-term follow-ups of some patients can only be conducted by phone.

(4) The results can only be extrapolated to Chinese RA population.

INTRODUCTION

Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like anemia.[1] The overall prevalence of RA is 0.5-1% in Europe and North America, 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.[2 3] Total knee arthroplasty (TKA) is effective in treating flexion contracture and maintaining the stability of RA knee.[4] About 0.005% of RA patients receive TKA, a rate that has gradually decreased over the past decades. Even though, surgery remains the first choice for articular deformity and pain, despite that disease-modifying antirheumatic drugs (DEMARDs) and biologics angents can manage synovitis-related symptoms in RA patients.[5] The haemorrhage is a major perioperative complications of TKA.[6] Excessive blood loss should be replenished with allogeneic blood transfusion, but it may cause immune complications, prolong hospitalization time and increase the infection rate.[7 8] Haemoglobin has an obviously negative correlation with disease activity in RA.[9] Therefore, we believe that perioperative blood management is need for patients with RA.

Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in

the knee joint cavity and gets haemolyzed.[10] As this blood is not involved in the blood circulation, HBL often leads to the joint swell, postoperative inflammation and pain.[11 12]

Surgical tourniquet use, can reduce intraoperative bleeding,[13] provide a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[14] However, after the release of the tourniquet, local tissue may be damaged by ischemia reperfusion injury, and fibrinolytic system activated.[15 16] As a consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced, and postoperative HBL increased.[15] Therefore, reducing the dissolution of fibrin can reduce postoperative HBL.[17]

Tranexamic acid (TXA) is a synthetic lysine derivative that can competitively inhibit the binding between plasminogen and fibrin, prevent the activation of plasminogen, and protect fibrin from degradation and dissolution by plasmin. TXA is initially used in obstetrics and gynaecology, then gradually replicated in surgeries to reduce bleeding and avoid blood transfusion rates.[18 19] The CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.[20] A large amount of literature has reported that TXA can significantly reduce peri-TKA blood loss.[21-25] Currently, TXA is recommended for perioperative blood management of TKA.[26] But, its efficacy and safety in RA patients undergoing TKA has been rarely reported.[27] TXA can be administered through oral intake, single large-dose intravenous injection, intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, and combination use.[25 28-31] There is no consensus on the

optimal dose and time of TXA administration during perioperative TKA.[18 32 33] Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKA with tourniquets.[34] The half-life of TXA in plasma is 2 hours, and its concentration peaks at 1 hour after injection.[35] Thus, we suspect that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic. There are also studies suggesting that for patients with osteoarthritis, higher doses (within a limit) during the perioperative period can increase the efficacy of TXA.[36-38] The purpose of this clinical trial is to verify the effectiveness and safety of multiple doses of TXA in reducing perioperative blood loss in RA patients treated with TKA, hoping to find a new mode of perioperative blood management for TKA.

METHODS AND ANALYSIS

Study context

This clinical trial will start on September 1, 2019 at the wards of Shanghai University of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China). The annual surgical number of TKA for RA patients was about 300 in 2018. Eleven investigators include 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM and SZ), 2 date collectors and who are also statisticians (B-xK and HX) and a nurse (X-rX). Informed consent will be obtained. The perioperative ERAS blood management programme and the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table

2.

Sample size calculation

This trial uses a completely randomized design, and multiple sample sizes are estimated by a previous clinical research review.[25] The main outcome is measured with the amount of HBL. The the overall standard deviation is $\sigma = 250$, and allowable error estimate is $\delta = 200$, both estimated by the statistical formula $n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2} + Z_{\beta})/\sigma}{\delta} \right]^2$. Considering a dropout rate of 10%, 104 subjects are required to yield a power of 90% with a significance level of 0.05.

Randomization and allocation concealment

Patients will be randomly assigned to two groups according to at 1:1 ratio; SPSS version 25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence containing 104 random numbers, which will be placed into an opaque envelope and put in a computer by encryption. The group data is saved by the statistician. Only the nurse is allowed to check the enrollment and give the corresponding treatment.

Single-blinded design

Only the nurse will be allowed to know the patients' enrollment and give them corresponding treatment. The outcome evaluators will objectively record the patients' test results.

Eligibility criteria

The eligibility criteria are set in accordance with the "AMERICAN RHEUMATISM ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS" from the American Journal of Rheumatism (revised in 1978),[39] and the 2010 "ACR/EULAR classification criteria for rheumatoid arthritis".[40] (1) The patient is diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence[41] classification; (2) The patient is 50 to 75 years old; (3) The patient will undergo the unilateral primary TKA; (4) The patient will receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient will show normal blood-clotting function and no preoperative anaemia.

Exclusion criteria

(1) Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2) Bilateral knee arthroplasty (RA patients); (3) Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral haemorrhage); and (4) Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

(1) Acquired color vision disorder; (2) Active intravascular coagulation patients; and (3) a history of convulsions.

Termination criteria

(1) Shock; (2) Allergic symptoms, such as itching and a rash; (3) Digestive disorders, such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4) Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, visual impairment, and others; and (5) Adverse events, such as intracranial thrombosis and intracranial haemorrhage after medication.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued at one week before surgery. Use of other disease-modifying antirheumatic drugs (DEMARDs) will be discontinued two days before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The use of newer biologic agents targeting tumor necrosis (TNF-α) will be discontinued for 4 to 5 half-lives before surgery and restarted after wound healing and infection elimination.[42 43]

Surgery and anesthesia

Surgery will be performed by two senior surgeons (L-bX and W-tZ). The operations will be conducted under general anaesthesia. A median incision (14-17 cm long) is cut in the knee join with a medial paramedian support band. Internal positioning is used for femoral bone marrow and external positioning for tibial bone marrow. All patients will use a tourniquet with a pressure of 230-250 mmHg. During the operation, blood

pressure will be reduced to 20% of the basal level through a suction drainage tube, and limb surgery will be conducted with an elastic bandage. During the operation, conventional anti-infective, combined analgesic, anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments will be administered according to the "Chinese Hip and Total Knee Arthroplasty Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert Consensus". Ten minutes before the incision, 1 g of TXA + 100 mL of intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be administered preoperatively in the sutured joint cavity.

TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according to the second edition of 2015 Chinese Pharmacopoeia and Drug Supplement Application Approval (2013B02016), YBH07372010; the approval number is National Drug Standard H43020565.

Intraoperative blood loss

The amount of introperative blood loss = the total volume of fluid in the negative pressure drain - the volume of normal saline.

Study interventions

Group A: 1 g of TXA + 100 mL of physiological saline will be injected intravenously at the 3rd hour after the operation. Group B: 1 g of TXA + 100 mL of physiological saline is intravenously instilled at the 3rd, 6th, and 12th hours after the operation.

Pain management and rehabilitation

A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib after surgery for analgesia. After anaesthesia the maximum angles of flexion and extension of the ankle will be maintained for 6 seconds, and the foot is relaxed for 5 seconds; the quadriceps contractions are equal between the two sides. At the first postoperative day, the patients will exercise straight-leg-raise, supine-knee-flexion and knee flexion and extension in sitting; the machine-assisted exercises will begin on the third day after surgery, such as continuous passive motion.

Antibiotics

For perioperative prophylaxis, cefazolin sodium antibiotics are administered at 30 minutes before surgery, and 24-48 hours after surgery.

Prevention of lower extremity venous thrombosis

Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day for 14 days) is injected for preventing deep vein thrombosis.

Outcomes

Primary outcomes

The blood lose, haemoglobin level

The blood loss is calculated according to the formula by Nadle[44] and Gross formula:[45]

Patient's blood volume (PBV) = K1 × height^3 (m^3) + K2 × weight (kg) + K3 (Male:

K1 = 0.3669, K2 = 0.03219, K3 = 0.6041. Female: K1 = 0.3561, K2 = 0.03308, K3 = 0.1833). Total blood loss (TBL) = PBV × (Hct_{pre} - Hct_{post}). HBL = PBV × (Hct_{pre} - Hct_{post}) / Hct_{ave}. Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will calculate the HBL based on the value of haematocrit and recorded the count of haemoglobin.

Secondary outcomes

Inflammatory index, inflammatory factor and coagulation index

Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF-α in the plasma. Whole blood test indicators and plasma inflammatory factors will be assessed in the participating hospital (Department of Clinical Laboratory of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine). The indicators and factors will be tested by an inspector who is not involved in this clinical trial.

Knee function and swelling

Knee function will be measured using the American Keen Society Score (AKSS) at one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully know how to assess their knee function through the questionnaires. The rate of swelling is defined as the postoperative circumference of the upper tibia divide by the preoperative

circumference of the upper tibia.

Adverse events

Adverse events include (1) Deep vein thrombosis[46] (acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg); (2) Extensive swelling on the affected limb; (3) A dull red color and a rise in the skin of the affected limb; (4) Generalized shallow venous tension on the affected limb; (5) In the skin of the affected limb; (6) Pulmonary embolism diagnosed by Doppler ultrasound and venography (clinical manifestations: cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism diagnosed by CT. The wound healing process and complications[47] (wound bleeding, haematoma, wound infection, and deep infection) will be observed and recorded in the patient's case report forms (CRFs) during hospitalization and follow-ups. Wound exudation is defined as the presence of exudation from the wound even 48 hours after surgery.

Adverse event treatment

Adverse events during the follow-up will be recorded in the CRFs, and their relevance to drug use will be evaluated. All the adverse events will be classified in accordance with the five-level scoring systems (5.0) of the CTCAE. Serious adverse events are defined as those that may cause cancer, defects, teratogenicity, death, and permanent damage to organ function, permanent or significant disability, and prolonged hospital

stay. In any event, the researcher should immediately take appropriate measures and report it to the hospital and ethics committees within 24 hours.

Data management

Data on the CRFs will be put in the computer by two independent trained research assistants with a double-entry method. The hospital's independent investigators will check the data periodically.

Statistical analysis

(1) Descriptive analysis on the characteristics of the study participants; (2) Balance analysis on the baseline values in groups; (3) Comparison of the balance between groups of primary outcomes; and (4) Comparison of secondary outcomes and safety between groups. The total rate of adverse events of the two groups are tested by bidirectional disordered R*C list chi-square test. The association between the incidence of adverse events and the dose of TXA used is described.

Ethics and dissemination

Written inform consent will be obtained from all participants or their authorised agents before the study. All TXA treatments will be free. Research data will be kept strictly confidential and obtained from appropriate authors upon reasonable request. Results of the trial will be published on the website of the China Clinical Trials Registry and in peer-reviewed journals.

The Patient and public involvement

Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial, pertaining to the benefits, risks and discomforts that they may get from the study. Besides, the burden of the intervention will be assessed by patients themselves. Dissemination of the general results (no personal data) will be made on demand.

DISCUSSION

Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical studies have shown that high dose of TXA can reduce blood loss after TKA in patients with osteoarthritis.[25 47 48] Based on previous research,[25] we will set the patient's age between 50-75 to improve the quality of study. In this trial, we will exclude patients with a large number of intravenous infusions to eliminate the effect of blood dilution on the results. We will use a tourniquet to minimize the blood loss during the operation. Therefore, what we will observed is the blood loss after the removal of tourniquet.[10] It has been reported that intravenous infusion combined with intra-articular injection of TXA may be the optimal bleeding-control scheme.[49 50] Previous studies have shown that knee joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the swelling around the joint.[51] Given that plasminogen activators play an important role in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory

response.[52] Therefore, we suspect that multiple doses of TXA in the peroperative period may exert an auxiliary anti-inflammatory effect.

This study will provide new evidence for managing perioperative HBL in TKA in Chinese RA patients.

Author Contributions B-xK, HX and L-bX conceived the study while B-xK and HX drafted the study protocol, B-xK and HX contributed equally to this work and should be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX, S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Patient consent for publication Obtained.

Ethics approval This study has been approved by the ethics committee Shanghai Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine (approval NO. 2019-K-13), and any modification of the protocol will be reported and approved by it.

Provenance and peer review Not commissioned; externally peer reviewed.

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Table 1 Enhanced recovery after surgery blood management

Preoperative	
1	Treatment of hemorrhagic primary disease
2	Nutritional guidance, balanced diet
3	Iron application
4	Rhu-Epo application
Intraoperative	
5	Minimally invasive surgery
6	Tourniquet optimization
7	Controlled buck
8	Autologous blood return
9	Use of tranexamic acid

Postoperative	
10	Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)
11	Nutritional support, iron supplementation, use of Rhu-Epo

Rhu-Epo, recombinant human erythropoietin.

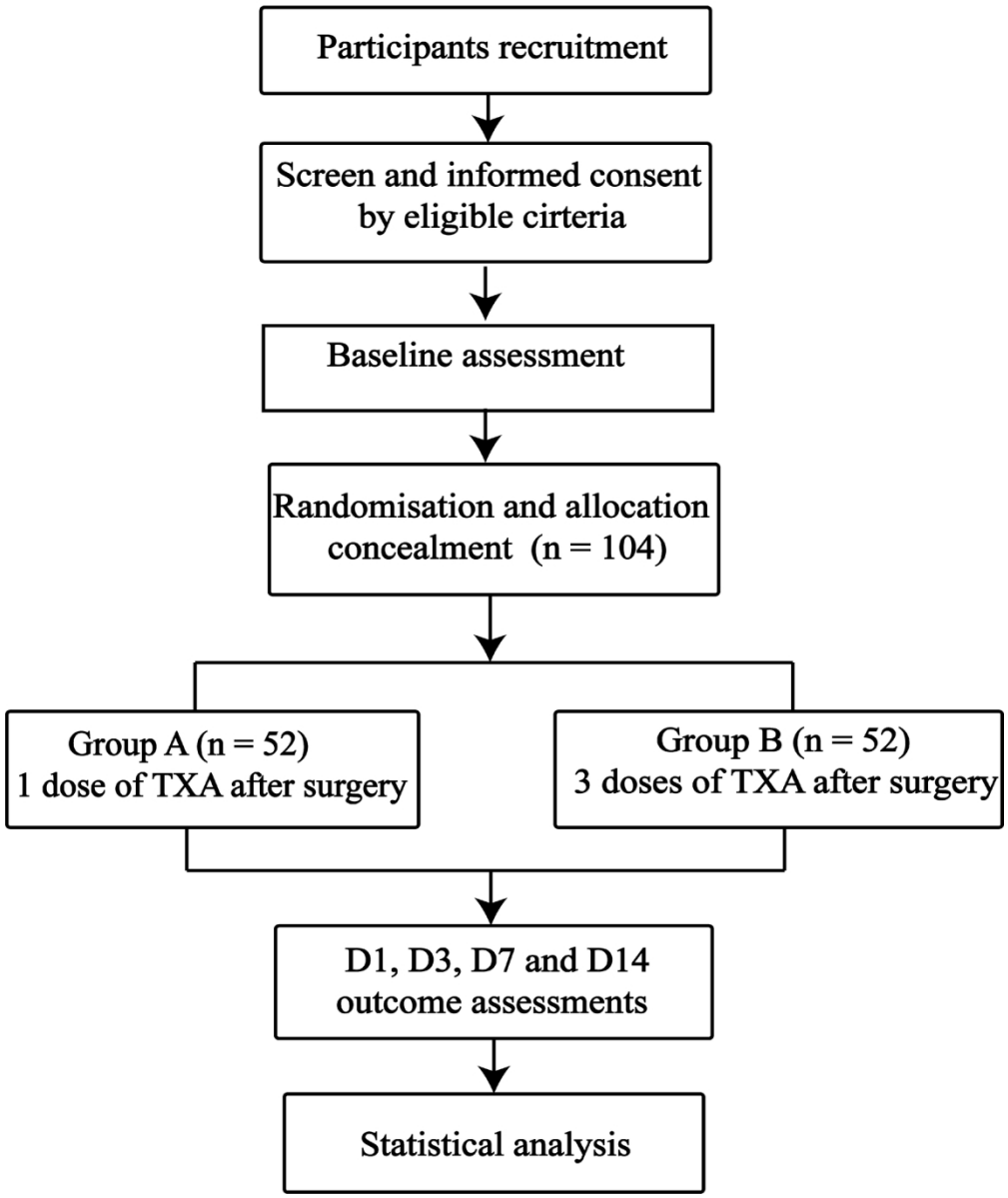
Table 2 The schedule of trial enrolment, interventions and assessments

	Outcome assessment				
	Pre-OP	**D1**	**D3**	**D7**	**D14**
Enrolment	•				
Assessment of eligibility	•				
Randomisation	•				
Group A Post-OP 1 dose of TXA	•	•	•	•	•
Group B Post-OP 3 doses of TXA	•	•	•	•	•
HBL		•	•	•	•
Haemoglobin level	•	•	•	•	•
Inflammatory index	•	•	•	•	•
Inflammatory factor	•	•	•	•	•
Coagulation index	•	•	•	•	•
Swelling rate		•	•	•	•
DVT		•	•	•	•
PE		•	•	•	•
Postoperative complications and adverse events		•	•	•	•

OP, operative; TXA, tranexamic acid; HBL, hidden blood lose; DVT, deep vein thrombosis; PE, pulmonary embolism; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA,

tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.



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163x195mm (300 x 300 DPI)

BMJ Open

Multiple-dose tranexamic acid for perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis : A single-blinded, randomized, parallel-controlled study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034431.R4
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Multiple-dose tranexamic acid for perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis : A single-blinded, randomized, parallel-controlled study protocol

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ABSTRACT

Introduction This clinical trial is designed to evaluate the effect of multiple-dose tranexamic acid (TXA) on perioperative blood loss in patients with rheumatoid arthritis (RA).

Methods and analysis A randomized, single-blinded, parallel-controlled study will be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage total knee arthroplasty will be randomly divided into Group A or Group B. Group A will be treated with one dose of TXA (1 g; intravenous injection 3 hours post-surgery) and Group B with three doses (1 g; intravenous injection at 3, 6, and 12 hours post-surgery) after surgery. The primary outcomes will be evaluated with blood loss, maximum haemoglobin drop, and transfusion rate. The secondary outcomes will be evaluated with knee function and complications.

Ethics and dissemination This study has been approved by the ethics committee, and subsequent modifications of the protocol will be reported and approved by it. All of the participants or their authorised agents will give written informed consent before the study.

Trial registration number ChiCTR1900025013; Pre-results.

Article Summary

Strengths and limitations of this trial

(1) This is the first study in China to evaluate the efficacy and safety of a perioperative multiple-dose regimen of tranexamic acid during total knee arthroplasty in rheumatoid arthritis patients.

(2) The bias of this study was reduced dramatically by the extensive study design, which included proper randomization, allocation concealment, and objective indications.

(3) The short follow-up time, may be insufficient in fully assessing the risk of complications in a multiple-dose regimen of tranexamic acid during total knee arthroplasty in rheumatoid arthritis patients.

INTRODUCTION

Rheumatoid arthritis (RA) may be accompanied by haematological diseases such as anaemia.[1] The overall prevalence of RA is 0.5-1% in Europe and North America, 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.[2,3] Total knee arthroplasty (TKA) is effective in treating flexion contractures and maintaining the stability of knees effected by RA.[4] About 0.005% of RA patients receive TKA, a rate that has gradually decreased over the past decades. However, surgery remains the first choice for articular deformity and pain, despite the fact that disease-modifying antirheumatic drugs and biologics agents can manage synovitis-related symptoms in RA patients.[5] Haemorrhage is a major perioperative complication of TKA.[6] Excessive blood loss should be treated with an allogeneic blood transfusion, but this has adverse effects such as immune complications, prolong hospitalization time, and increased infection rate.[7,8] Haemoglobin has a negative correlation with disease activity in RA.[9] Therefore, we believe that perioperative blood loss management is

needed for patients with RA.

Accounting for approximately 50% of the total blood loss, hidden blood loss (HBL) is the blood lost as infiltrates into the tissue intraoperatively and postoperatively. This blood resides in the knee joint cavity before being haemolyzed.[10] HBL often leads to the joint swelling, postoperative inflammation, and pain.[11,12]

Use of a surgical tourniquet can reduce intraoperative bleeding,[13] provide a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[14] However, after the release of the tourniquet, local tissue may be damaged by ischemic reperfusion injury, and the fibrinolytic system may be activated.[15,16] As a consequence, peripheral blood circulation can be accelerated, plasma fibrinolysis enhanced, and postoperative HBL increased.[15] Therefore, reducing the dissolution of fibrin can reduce postoperative HBL.[17]

Tranexamic acid (TXA) is a synthetic lysine derivative that competitively inhibits the binding between plasminogen and fibrin, prevents the activation of plasminogen, and protects fibrin from degradation and dissolution by plasmin. TXA was initially used in obstetric and gynaecologic surgery, and its use was then gradually replicated in other surgeries to reduce bleeding and blood transfusion rates.[18,19] The CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.[20] A large amount of literature has reported that TXA can significantly reduce peri-TKA blood loss.[21-25] Currently, TXA is recommended for perioperative management of blood loss during TKA.[26] However, its efficacy and safety in RA patients undergoing TKA has rarely been reported.[27] TXA can be administered through oral intake, a

single large-dose intravenous injection, an intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, or through a combination of these methods.[25,28-30] There is no consensus on the optimal dosage and timing of perioperative TXA administration for TKA.[18,31,32] Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKAs that were performed with tourniquets.[33] The half-life of TXA in the plasma is 2 hours, and its concentration peaks at 1 hour after injection.[34] Thus, we suspect that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic effect. There are also studies suggesting that, for patients with osteoarthritis, higher doses (within the normal range) during the perioperative period can increase the efficacy of TXA.[35,36] The purpose of this clinical trial is to verify the effectiveness and safety of multiple doses of TXA in reducing perioperative blood loss in RA patients treated with TKA, in order to determine a new strategy for management of perioperative blood loss during TKA.

METHODS AND ANALYSIS

Study context

This clinical trial was initiated on 1 September 2019 in the wards of Shanghai University of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China). The annual number of TKA cases performed in RA patients was about 300 in 2018. Eleven investigators will be involved in this study including 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience, 6 orthopaedic physicians

(C-xG, JZ, JX, S-sT, Y-hM, and SZ), 2 data collectors who are also statisticians (B-xK and HX), and a nurse (X-rX). Informed consent will be obtained from all patients. The perioperative ERAS blood management programme and the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table 2.

Table 1 Enhanced recovery after surgery blood management

Preoperative
1 Treatment of haemorrhagic primary disease
2 Nutritional guidance, balanced diet
3 Iron application
4 Rhu-Epo application
Intraoperative
5 Minimally invasive surgery
6 Tourniquet optimization
7 Controlled buck
8 Autologous blood return
9 Use of tranexamic acid
Postoperative
10 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)
11 Nutritional support, iron supplementation, use of Rhu-Epo

Rhu-Epo, recombinant human erythropoietin.

Table 2 The schedule of trial enrolment, interventions, and assessments

	Outcome assessment				
	Pre-OP	**D1**	**D3**	**D7**	**D14**
Enrolment	●				
Assessment of eligibility	●				
Randomisation	●				

Group A Post-OP 1 dose of TXA	●	●	●	●	●
Group B Post-OP 3 doses of TXA	●	●	●	●	●
HBL		●	●	●	●
Haemoglobin level	●	●	●	●	●
Inflammatory index	●	●	●	●	●
Inflammatory factor	●	●	●	●	●
Coagulation index	●	●	●	●	●
Swelling rate		●	●	●	●
DVT		●	●	●	●
PE		●	●	●	●
Postoperative complications and adverse events		●	●	●	●

OP, operative; TXA, tranexamic acid; HBL, hidden blood loss; DVT, deep vein thrombosis; PE, pulmonary embolism; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

Sample size calculation

This study uses a completely randomized trial design. Multiple sample sizes will evaluated by a review of previously conducted clinical research.[25] The primary outcome will be measured with the amount of HBL, dependent on TXA therapy. The overall standard deviation is $\sigma = 250$, and the allowable error estimate is $\delta = 200$. These values were estimated using the statistical formula $n_1 = n_2 = 2\times\left[\frac{(Z_{\alpha/2}+Z_{\beta})\sigma}{\delta}\right]^2$. Predicting an estimated dropout rate of 10%, 104 subjects will be required to yield a

power of 90% with a significance level of 0.05.

Randomization and allocation concealment

Patients will be randomly assigned to two groups (1:1 ratio). This will be done by assigning each patient a number from 1 to 104. SPSS version 25.0 (IBM Corporation, Armonk, NY) will be used to generate a random sequence containing the numbers 1 to 104, dividing these numbers in two groups. These group lists will be placed in an opaque envelope and put into a computer by encryption. The group data will be saved by the statistician. Only the nurse will be allowed to check the enrolment and give the corresponding treatment.

Single-blinded design

Only the nurse will be allowed to know the patients' enrolment and give them the corresponding treatment. The outcome evaluators will objectively record the patients' test results.

Eligibility criteria

The eligibility criteria have been set in accordance with the 'American Rheumatism Association criteria for rheumatoid arthritis'[37] and the 2010 'ACR/EULAR classification criteria for rheumatoid arthritis'.[38] The eligibility criteria are as follows: (1) The patient must have been diagnosed with RA in Stage III or IV according to the

Kellgren-Lawrence classification;[39] (2) The patient must be 50 to 75 years old; (3) The patient must be willing to undergo the unilateral primary TKA; (4) The patient must receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient must show normal blood-clotting function and must not have preoperative anaemia.

Exclusion criteria

The exclusion criteria are as follows: (1) Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2) Bilateral knee arthroplasty (RA patients); (3) Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and cardiac failure) or cerebrovascular disease (such as cerebral infarction and cerebral haemorrhage); and (4) Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

The elimination criteria are as follows: (1) Acquired colour vision disorder; (2) Active intravascular coagulation patients; and (3) A history of seizures.

Termination criteria

The termination criteria are as follows: (1) Shock; (2) Allergic symptoms such as itching and a rash; (3) Digestive disorders such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4) Symptoms such as reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, and visual impairment; and (5)

Adverse events such as intracranial thrombosis and intracranial haemorrhage after medication.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued one week before surgery. Use of other disease-modifying antirheumatic drugs will be discontinued two days before surgery, and restarted 1-2 days after gastrointestinal function recovery. The use of newer biologic agents such as tumour necrosis factor alpha will be discontinued 4 to 5 half-lives before surgery and restarted after wound healing and infection elimination.[40,41]

Surgery and anesthesia

Surgery will be performed by two senior surgeons (L-bX and W-tZ). During each surgery, a standard midline incision will be followed by a medial parapatellar capsular incision to expose the knee joint. A tourniquet will be used for all patients at a pressure of 200-250 mmHg. The operations will be conducted under general anaesthesia and blood pressure will be controlled within a range of 80 to 100 mmHg / 60 to 70 mmHg by anaesthetists throughout the surgical procedure. During the operation, conventional anti-infective, combined analgesic, anti-inflammatory, anti-coagulation treatment, and other symptomatic treatments will be administered according to the 'Chinese Hip and Total Knee Arthroplasty Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert

Consensus'.[26] Ten minutes prior to skin incision, 1 g of TXA + 100 mL of intravenous-saline will be administered, and then 1.5 g of TXA + 50 mL articular-injection saline will be administered post-operatively into the sutured joint cavity. Group A and B will then receive additional TXA therapy according to the treatment regime devised for each group.

TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according to the second edition of the 2015 Chinese Pharmacopoeia and Drug Supplement Application Approval (2013B02016), YBH07372010; the National Drug Standard approval number is H43020565.

Study interventions

Group A: 1 g of TXA + 100 mL of physiological saline will be administered intravenously 3 hours after the operation. Group B: 1 g of TXA + 100 mL of physiological saline will be administered intravenously 3, 6, and 12 hours after the operation.

Pain management and rehabilitation

A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib will be given after surgery for analgesia. After the anaesthesia, the maximum angles of flexion and extension of the ankle will be maintained for 6 seconds, and the foot will then be allowed to relax for 5 seconds. This exercise will be performed on both limbs in order to ensure the quadriceps contractions are equal. On the first postoperative day, the patients will be encouraged to exercise using straight-leg-raises,

supine-knee-flexion, and knee flexion and extension in sitting. Machine-assisted exercises, such as continuous passive motion, will begin on the third day after surgery.

Antibiotics

For perioperative infection prophylaxis, cefazolin (40 mg) will be administered 30 minutes before surgery and 24-48 hours after surgery.[42]

Prevention of lower extremity venous thrombosis

Six hours after the surgery, enoxaparin sodium injections (60 mg) will be initiated and continued daily for 14 days to prevent formation of a deep vein thrombosis.[26]

Outcomes

Complete blood count, hepatic function, renal function, and coagulation function will be tested before surgery routinely. Complete blood count, inflammatory index, inflammatory factor and coagulation index will be tested at the 1st, 3rd, 7th and 14th days after surgery. All the blood test will be assessed in our hospital (Department of Clinical Laboratory of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine) by an inspector who is not involved in this clinical trial.

Primary outcomes

The blood lose, haemoglobin level, and transfusion rate

The blood loss is calculated according to the formulae by Nadle[43] and Gross:[44] Patient's blood volume (PBV) = K1 × height^3 (m^3) + K2 × weight (kg) + K3. Male: K1 = 0.3669, K2 = 0.03219, K3 = 0.6041; Female: K1 = 0.3561, K2 = 0.03308, K3 = 0.1833. Total blood loss (TBL) = PBV × (Hct_{pre} - Hct_{post}) / $Hct_{ave.}$ Hct_{pre} = the initial pre-operative Hct level; Hct_{post} = the lowest Hct post-operative; Hct_{ave} = the average of the Hct_{pre} and Hct_{post}. The amount of intraoperative blood loss = the total volume of fluid in the negative pressure drain - the volume of normal saline. HBL volume = TBL volume - intra-operative blood loss volume.

The maximum haemoglobin decline will be defined as the difference between the pre-operative Hb level and the minimal Hb level drawn post-operatively during the hospitalization and prior to any blood transfusion. The transfusion rate for patients requiring a transfusion will be determined post-operatively during the inpatient hospital stay.

Secondary outcomes

Knee function and swelling

Knee function will be measured using the American Knee Society Score (AKSS) one day before surgery and on the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully understand how to assess their knee function using the questionnaires. The degree of swelling is defined as the postoperative circumference of the upper tibia divided by the preoperative circumference of the upper tibia.

Adverse events

Potential adverse events include deep vein thrombosis (clinical manifestations: acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg) and pulmonary embolism (clinical manifestations: cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling, or pulsation, etc.). Deep vein thrombosis and pulmonary embolism will be diagnosed by Doppler ultrasound and computer tomography, respectively. The wound healing process and complications (wound bleeding, haematoma, wound infection, and deep infection) will be observed and recorded in the patient's case report forms (CRFs) during hospitalization and follow-ups.

Adverse event treatment

Adverse events during the follow-up period will be recorded in the CRFs, and their relevance to drug use will be evaluated. All the adverse events will be classified in accordance with the five-level scoring systems (5.0) of the CTCAE. Serious adverse events are defined as those that may cause cancer, teratogenicity, death, permanent damage to organ function, permanent or significant disability, and prolonged hospital stay. In the case of adverse events occurring, the researcher should immediately take appropriate measures and report these events to the hospital and ethics committees within 24 hours.

Data management

Data on the CRFs will be put into the computer by two independent trained research assistants with a double-entry method. The hospital's independent investigators will check the data periodically.

Statistical analysis

(1) Descriptive analysis on the characteristics of the study participants; (2) Balance analysis on the baseline values in groups; (3) Comparison of the balance of primary outcomes between groups; and (4) Comparison of secondary outcomes and safety between groups. The total rate of adverse events in the two groups will be tested by the bidirectional disordered R*C list chi-square test. The association between the incidence of adverse events and the dose of TXA use will be described.

Ethics and dissemination

Written inform consent will be obtained from all participants or their authorised agents before the study. All TXA treatments will be free. Research data will be kept strictly confidential and obtained from appropriate authors upon reasonable request. Results of the trial will be published on the website of the China Clinical Trials Registry and in peer-reviewed journals.

The Patient and public involvement

Patients and public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial, pertaining to the benefits, risks and discomforts that they may get from the study. Besides, the burden of the intervention will be assessed by patients themselves.

Dissemination of the general results (no personal data) will be made on demand.

DISCUSSION

Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical studies have shown that high doses of TXA can reduce blood loss after TKA in patients with osteoarthritis.[25,45,46] It has been reported that an intravenous infusion of TXA, combined with intra-articular injection may be the optimal bleeding-control scheme.[47,48] Previous studies have shown that knee joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the swelling around the joint.[11] Given that plasminogen activators play an important role in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory response.[49] Therefore, we suspect that multiple doses of TXA in the perioperative period may exert an auxiliary anti-inflammatory effect.

Enhanced recovery after surgery is strongly advocated, and the management of perioperative blood loss is an essential component. The RA patients aged 50-80 years undergoing TKA have a lower risk of requiring a revision, and are likely to obtain higher knee function and present with fewer complications.[50,51] In order to reduce bias caused by a wide age range, patients aged 50-75 will be selected. This study will provide new evidence for managing perioperative blood loss in TKA in Chinese RA patients if the results indicate that the administration of the additional three doses of

TXA therapy after surgery is beneficial over a single dose.

Author Contributions B-xK, HX and L-bX conceived the study while B-xK and HX drafted the study protocol, B-xK and HX contributed equally to this work and should be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX, S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study protocol.

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Conflicts of Interests The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Patient consent for publication Written informed consent will be obtained.

Ethics approval This study has been approved by the ethics committee Shanghai Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine (approval NO. 2019-K-13), and any modification of the protocol will be reported and approved by it.

Provenance and peer review Not commissioned; externally peer reviewed.

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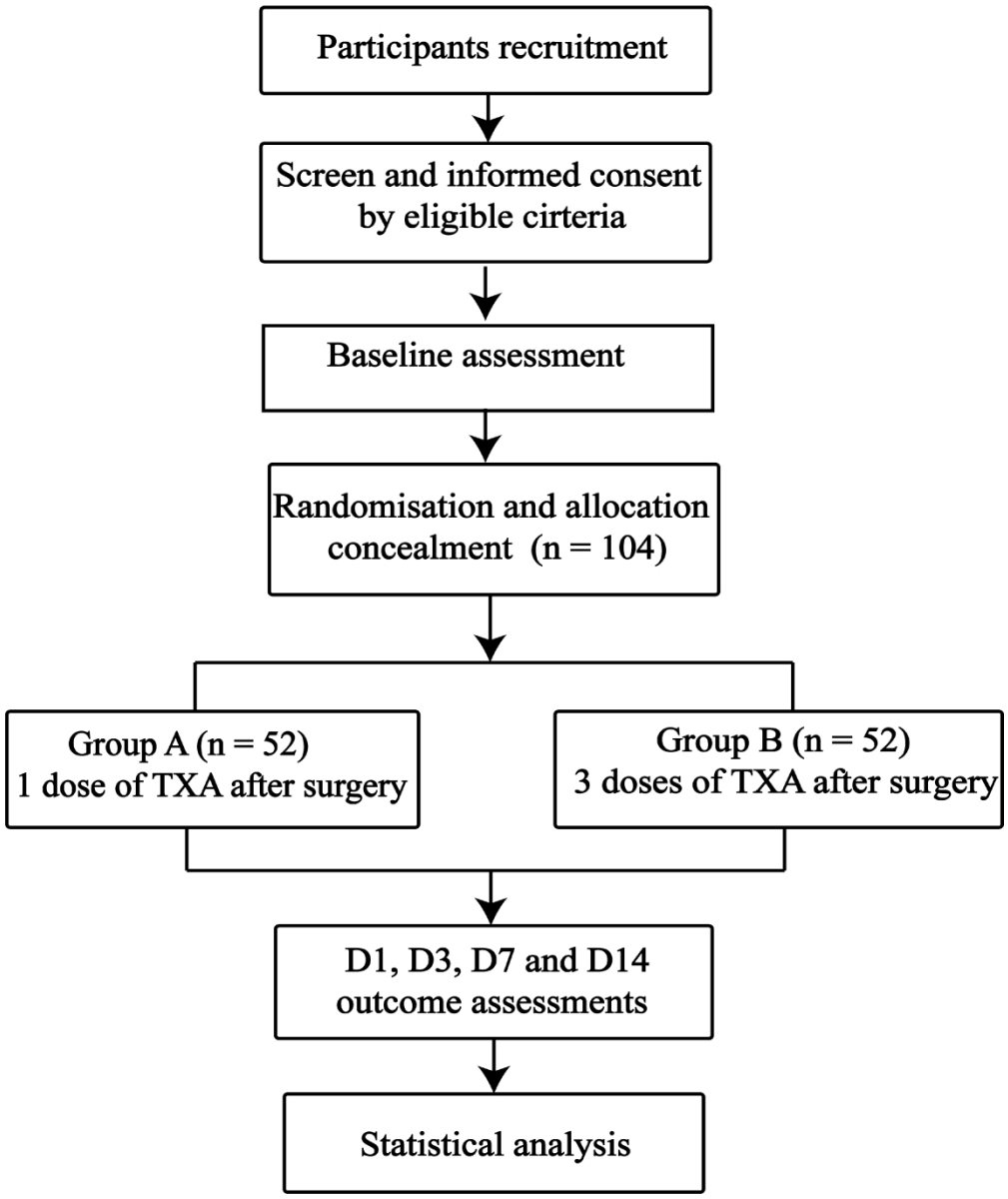
Figure 1: The study flow diagram, including participants recruitment, eligibility,

screening, randomisation, allocation concealment and outcome assessments. TXA, tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.



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Multiple-dose tranexamic acid for perioperative blood loss in total knee arthroplasty in patients with rheumatoid arthritis : A single-blinded, randomized, parallel-controlled study protocol in China

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ABSTRACT

Introduction This clinical trial is designed to evaluate the effect of multiple-dose tranexamic acid (TXA) on perioperative blood loss in patients with rheumatoid arthritis (RA).

Methods and analysis A randomized, single-blinded, parallel-controlled study will be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage total knee arthroplasty will be randomly divided into Group A or Group B. Group A will be treated with one dose of TXA (1 g; intravenous injection 3 hours post-surgery) and Group B with three doses (1 g; intravenous injection at 3, 6, and 12 hours post-surgery) after surgery. The primary outcomes will be evaluated with blood loss, maximum haemoglobin drop, and transfusion rate. The secondary outcomes will be evaluated with knee function and complications.

Ethics and dissemination The Shanghai Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Ethics Committee approved in this study in July 2019. Informed consent will be obtained from all participants. Results of the trial will be published in the Dryad and repository in a peer-reviewed journal. Additionally, deidentified data collected and analysed for this study will be available for review from the corresponding author on reasonable request.

Trial registration number ChiCTR1900025013; Pre-results.

Article Summary

Strengths and limitations of this trial

(1) This is the first study in China to evaluate the efficacy and safety of a perioperative multiple-dose regimen of tranexamic acid during total knee arthroplasty in rheumatoid arthritis patients.

(2) The bias of this study was reduced dramatically by the extensive study design, which included proper randomization, allocation concealment, and objective indications.

(3) If multiple-dose TXA after surgery can reduce postoperative blood loss in rheumatoid arthritis patients without adverse events, this medication regimen may reduce the occurrence of postoperative anaemia in rheumatoid arthritis patients.

(4) The short follow-up time may be insufficient in fully assessing the risk of complications in a multiple-dose regimen of tranexamic acid during total knee arthroplasty in rheumatoid arthritis patients.

INTRODUCTION

Rheumatoid arthritis (RA) may be accompanied by haematological diseases such as anaemia.[1] The overall prevalence of RA is 0.5-1% in Europe and North America, 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.[2,3] Total knee arthroplasty (TKA) is effective in treating flexion contractures and maintaining the stability of knees effected by RA.[4] About 0.005% of RA patients receive TKA, a rate that has gradually decreased over the past decades. However, surgery remains the first choice for articular deformity and pain, despite the fact that disease-modifying

antirheumatic drugs and biologics agents can manage synovitis-related symptoms in RA patients.[5] Haemorrhage is a major perioperative complication of TKA.[6] Excessive blood loss should be treated with an allogeneic blood transfusion, but this has adverse effects such as immune complications, prolong hospitalization time, and increased infection rate.[7,8] Haemoglobin has a negative correlation with disease activity in RA.[9] Therefore, we believe that perioperative blood loss management is needed for patients with RA.

Accounting for approximately 50% of the total blood loss, hidden blood loss (HBL) is the blood lost as infiltrates into the tissue intraoperatively and postoperatively. This blood resides in the knee joint cavity before being haemolyzed.[10] HBL often leads to the joint swelling, postoperative inflammation, and pain.[11,12]

Use of a surgical tourniquet can reduce intraoperative bleeding,[13] provide a clear view during the surgery, and facilitate the connection between the cement, bone and joint prostheses.[14] However, after the release of the tourniquet, local tissue may be damaged by ischemic reperfusion injury, and the fibrinolytic system may be activated.[15,16] As a consequence, peripheral blood circulation can be accelerated, plasma fibrinolysis enhanced, and postoperative HBL increased.[15] Therefore, reducing the dissolution of fibrin can reduce postoperative HBL.[17]

Tranexamic acid (TXA) is a synthetic lysine derivative that competitively inhibits the binding between plasminogen and fibrin, prevents the activation of plasminogen, and protects fibrin from degradation and dissolution by plasmin. TXA was initially used in obstetric and gynaecologic surgery, and its use was then gradually replicated

in other surgeries to reduce bleeding and blood transfusion rates.[18,19] The CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.[20] A large amount of literature has reported that TXA can significantly reduce peri-TKA blood loss.[21-25] Currently, TXA is recommended for perioperative management of blood loss during TKA.[26] However, its efficacy and safety in RA patients undergoing TKA has rarely been reported.[27] TXA can be administered through oral intake, a single large-dose intravenous injection, an intra-articular injection, joint cavity irrigation, postoperative drainage tube injection, or through a combination of these methods.[25,28-30] There is no consensus on the optimal dosage and timing of perioperative TXA administration for TKA.[18,31,32] Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKAs that were performed with tourniquets.[33] The half-life of TXA in the plasma is 2 hours, and its concentration peaks at 1 hour after injection.[34] Thus, we suspect that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic effect. There are also studies suggesting that, for patients with osteoarthritis, higher doses (within the normal range) during the perioperative period can increase the efficacy of TXA.[35,36] The purpose of this clinical trial is to verify the effectiveness and safety of multiple doses of TXA in reducing perioperative blood loss in RA patients treated with TKA, in order to determine a new strategy for management of perioperative blood loss during TKA.

METHODS AND ANALYSIS

Study context

This clinical trial was initiated on 1 September 2019 in the wards of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai University of Traditional Chinese Medicine (Shanghai, China). The annual number of TKA cases performed in RA patients was about 300 in 2018. Eleven investigators will be involved in this study including 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical experience, 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM, and SZ), 2 data collectors who are also statisticians (B-xK and HX), and a nurse (X-rX). Informed consent will be obtained from all patients. The perioperative ERAS blood management programme and the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table 2.

Table 1 Enhanced recovery after surgery blood management

Preoperative	
1	Treatment of haemorrhagic primary disease
2	Nutritional guidance, balanced diet
3	Iron application
4	Rhu-Epo application
Intraoperative	
5	Minimally invasive surgery
6	Tourniquet optimization
7	Controlled buck
8	Autologous blood return
9	Use of tranexamic acid
Postoperative	
10	Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)

11	Nutritional support, iron supplementation, use of Rhu-Epo

Rhu-Epo, recombinant human erythropoietin.

Table 2 The schedule of trial enrolment, interventions, and assessments

	Outcome assessment				
	Pre-OP	**D1**	**D3**	**D7**	**D14**
Enrolment	●				
Assessment of eligibility	●				
Randomisation	●				
Group A Post-OP 1 dose of TXA	●	●	●	●	●
Group B Post-OP 3 doses of TXA	●	●	●	●	●
HBL		●	●	●	●
Haemoglobin level	●	●	●	●	●
Inflammatory index	●	●	●	●	●
Inflammatory factor	●	●	●	●	●
Coagulation index	●	●	●	●	●
Swelling rate		●	●	●	●
DVT		●	●	●	●
PE		●	●	●	●
Postoperative complications and adverse events		●	●	●	●

OP, operative; TXA, tranexamic acid; HBL, hidden blood loss; DVT, deep vein thrombosis; PE, pulmonary embolism; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

Sample size calculation

This study uses a completely randomized trial design. Multiple sample sizes will evaluated by a review of previously conducted clinical research.[25] The primary outcome will be measured with the amount of HBL, dependent on TXA therapy. The overall standard deviation is $\sigma = 250$, and the allowable error estimate is $\delta = 200$. These values were estimated using the statistical formula $n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2}+Z_{\beta})/\sigma}{\delta}\right]^2$. Predicting an estimated dropout rate of 10%, 104 subjects will be required to yield a power of 90% with a significance level of 0.05.

Randomization and allocation concealment

Patients will be randomly assigned to two groups (1:1 ratio). This will be done by assigning each patient a number from 1 to 104. SPSS version 25.0 (IBM Corporation, Armonk, NY) will be used to generate a random sequence containing the numbers 1 to 104, dividing these numbers in two groups. These group lists will be placed in an opaque envelope and put into a computer by encryption. The group data will be saved by the statistician. Only the nurse will be allowed to check the enrolment and give the corresponding treatment.

Single-blinded design

Only the nurse will be allowed to know the patients' enrolment and give them the corresponding treatment. The outcome evaluators will objectively record the patients'

test results.

Eligibility criteria

The eligibility criteria have been set in accordance with the 'American Rheumatism Association criteria for rheumatoid arthritis'[37] and the 2010 'ACR/EULAR classification criteria for rheumatoid arthritis'.[38] The eligibility criteria are as follows: (1) The patient must have been diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence classification;[39] (2) The patient must be 50 to 75 years old; (3) The patient must be willing to undergo the unilateral primary TKA; (4) The patient must receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient must show normal blood-clotting function and must not have preoperative anaemia.

Exclusion criteria

The exclusion criteria are as follows: (1) Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2) Bilateral knee arthroplasty (RA patients); (3) Severe cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris, and cardiac failure) or cerebrovascular disease (such as cerebral infarction and cerebral haemorrhage); and (4) Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).

Elimination criteria

The elimination criteria are as follows: (1) Acquired colour vision disorder; (2) Active

intravascular coagulation patients; and (3) A history of seizures.

Termination criteria

The termination criteria are as follows: (1) Shock; (2) Allergic symptoms such as itching and a rash; (3) Digestive disorders such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4) Symptoms such as reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions, and visual impairment; and (5) Adverse events such as intracranial thrombosis and intracranial haemorrhage after medication.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine will be used during the perioperative period. Leflunomide will be discontinued one week before surgery. Use of other disease-modifying antirheumatic drugs will be discontinued two days before surgery, and restarted 1-2 days after gastrointestinal function recovery. The use of newer biologic agents such as tumour necrosis factor alpha will be discontinued 4 to 5 half-lives before surgery and restarted after wound healing and infection elimination.[40,41]

Surgery and anaesthesia

Surgery will be performed by two senior surgeons (L-bX and W-tZ). During each surgery, a standard midline incision will be followed by a medial parapatellar capsular incision to expose the knee joint. A tourniquet will be used for all patients at a

pressure of 200-250 mmHg. The operations will be conducted under general anaesthesia and blood pressure will be controlled within a range of 80 to 100 mmHg / 60 to 70 mmHg by anaesthetists throughout the surgical procedure. During the operation, conventional anti-infective, combined analgesic, anti-inflammatory, anti-coagulation treatment, and other symptomatic treatments will be administered according to the 'Chinese Hip and Total Knee Arthroplasty Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert Consensus'.[26] Ten minutes prior to skin incision, 1 g of TXA + 100 mL of intravenous-saline will be administered, and then 1.5 g of TXA + 50 mL articular-injection saline will be administered post-operatively into the sutured joint cavity. Group A and B will then receive additional TXA therapy according to the treatment regime devised for each group.

TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according to the second edition of the 2015 Chinese Pharmacopoeia and Drug Supplement Application Approval (2013B02016), YBH07372010; the National Drug Standard approval number is H43020565.

Study interventions

Group A: 1 g of TXA + 100 mL of physiological saline will be administered intravenously 3 hours after the operation. Group B: 1 g of TXA + 100 mL of physiological saline will be administered intravenously 3, 6, and 12 hours after the operation.

Pain management and rehabilitation

A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib will be given after surgery for analgesia. After the anaesthesia, the maximum angles of flexion and extension of the ankle will be maintained for 6 seconds, and the foot will then be allowed to relax for 5 seconds. This exercise will be performed on both limbs in order to ensure the quadriceps contractions are equal. On the first postoperative day, the patients will be encouraged to exercise using straight-leg-raises, supine-knee-flexion, and knee flexion and extension in sitting. Machine-assisted exercises, such as continuous passive motion, will begin on the third day after surgery.

Antibiotics

For perioperative infection prophylaxis, cefazolin (40 mg) will be administered 30 minutes before surgery and 24-48 hours after surgery.[42]

Prevention of lower extremity venous thrombosis

Six hours after the surgery, enoxaparin sodium injections (60 mg) will be initiated and continued daily for 14 days to prevent formation of a deep vein thrombosis.[26]

Outcome measures

Complete blood count, hepatic function, renal function, and coagulation function will be routinely tested before surgery. Complete blood count, inflammatory index, inflammatory factor and coagulation index will be tested on the 1st, 3rd, 7th and 14th

days after surgery. All the blood tests will be assessed in our hospital (Department of Clinical Laboratory of Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai University of Traditional Chinese Medicine) by an inspector who is not involved in this clinical trial.

Primary outcome measures

Blood loss, haemoglobin level, and transfusion rate

Blood loss is calculated according to the formulae by Nadle[43] and Gross:[44] Patient's blood volume (PBV) = K1 × height^3 (m^3) + K2 × weight (kg) + K3. Male: K1 = 0.3669, K2 = 0.03219, K3 = 0.6041; Female: K1 = 0.3561, K2 = 0.03308, K3 = 0.1833. Total blood loss (TBL) = PBV × (Hct_{pre} − Hct_{post}) / $Hct_{ave.}$ Hct_{pre} = the initial pre-operative Hct level; Hct_{post} = the lowest Hct post-operative; Hct_{ave} = the average of the Hct_{pre} and Hct_{post}. The amount of intraoperative blood loss = the total volume of fluid in the negative pressure drain − the volume of normal saline. HBL volume = TBL volume − intra-operative blood loss volume.

The maximum haemoglobin decline will be defined as the difference between the pre-operative Hb level and the minimal Hb level drawn post-operatively during the hospitalization and prior to any blood transfusion. The transfusion rate for patients requiring a transfusion will be determined post-operatively during the inpatient hospital stay.

Secondary outcome measures

Knee function and swelling

Knee function will be measured using the American Knee Society Score (AKSS) one day before surgery and on the 3rd, 7th and 14th days after surgery. A trained researcher will educate all patients until they fully understand how to assess their knee function using the questionnaires. The degree of swelling is defined as the postoperative circumference of the upper tibia divided by the preoperative circumference of the upper tibia.

Adverse event measures

Potential adverse events include deep vein thrombosis (clinical manifestations: acute onset, affected limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg) and pulmonary embolism (clinical manifestations: cough, chest tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous filling, or pulsation, etc.). Deep vein thrombosis and pulmonary embolism will be diagnosed by Doppler ultrasound and computed tomography, respectively. The wound healing process and complications (wound bleeding, haematoma, wound infection, and deep infection) will be observed and recorded in the patient's case report forms (CRFs) during hospitalization and follow-ups.

Adverse event treatment

Adverse events during the follow-up period will be recorded in the CRFs, and their relevance to drug use will be evaluated. All the adverse events will be classified in

accordance with the five-level scoring systems (5.0) of the CTCAE. Serious adverse events are defined as those that may cause cancer, teratogenicity, death, permanent damage to organ function, permanent or significant disability, and prolonged hospital stay. In the case of adverse events occurring, the researcher should immediately take appropriate measures and report these events to the hospital and ethics committees within 24 hours.

Data management

Data on the CRFs will be put into the computer by two independent trained research assistants with a double-entry method. The hospital's independent investigators will check the data periodically.

Statistical analysis

(1) Descriptive analysis on the characteristics of the study participants; (2) Balance analysis on the baseline values in groups; (3) Comparison of the balance of primary outcomes between groups; and (4) Comparison of secondary outcomes and safety between groups. The total rate of adverse events in the two groups will be tested by the bidirectional disordered R*C list chi-square test. The association between the incidence of adverse events and the dose of TXA use will be described.

The Patient and public involvement

Patients and the public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial, pertaining to the benefits, risks and discomforts that they

may experience during the study. Further, the burden of the intervention will be assessed by patients themselves. Dissemination of the general results (no personal data) will be made available on reasonable request.

ETHICS AND DISSEMINATION

Ethics approval has been granted by the Shanghai Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Ethics Committee. Written inform consent will be obtained from all participants or their authorised agents before initiation of the study. All TXA treatments will be free. Personal data of participants will be kept strictly confidential and obtained from appropriate authors upon reasonable request. Results of the trial will be published on the Dryad website and in a peer-reviewed journal.

DISCUSSION

Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical studies have shown that high doses of TXA can reduce blood loss after TKA in patients with osteoarthritis.[25,45,46] It has been reported that an intravenous infusion of TXA, combined with intra-articular injection may be the optimal bleeding-control

scheme.[47,48] Previous studies have shown that knee joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the swelling around the joint.[11] Given that plasminogen activators play an important role in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory response.[49] Therefore, we suspect that multiple doses of TXA in the perioperative period may exert an auxiliary anti-inflammatory effect.

Enhanced recovery after surgery is strongly advocated, and the management of perioperative blood loss is an essential component. The RA patients aged 50-80 years undergoing TKA have a lower risk of requiring a revision, and are likely to obtain higher knee function and present with fewer complications.[50,51] In order to reduce bias caused by a wide age range, patients aged 50-75 will be selected. This study will provide new evidence for managing perioperative blood loss in TKA in Chinese RA patients if the results indicate that the administration of the additional three doses of TXA therapy after surgery is beneficial over a single dose.

Author Contributions B-xK, HX and L-bX conceived the study while B-xK and HX drafted the study protocol, B-xK and HX contributed equally to this work and should be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX, S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study protocol.

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planning Commission of Shanghai (Grant NO. ZY (2018-2020)-FWTX-6023).

Conflicts of Interests The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

Patient consent for publication Written informed consent will be obtained.

Ethics approval This study has been approved by the Shanghai Guanghua Hospital of Integrated Traditional Chinese Medicine and Western Medicine Ethics Committee (NO. 2019-K-13). And any modification of the protocol will be reported to and approved by this ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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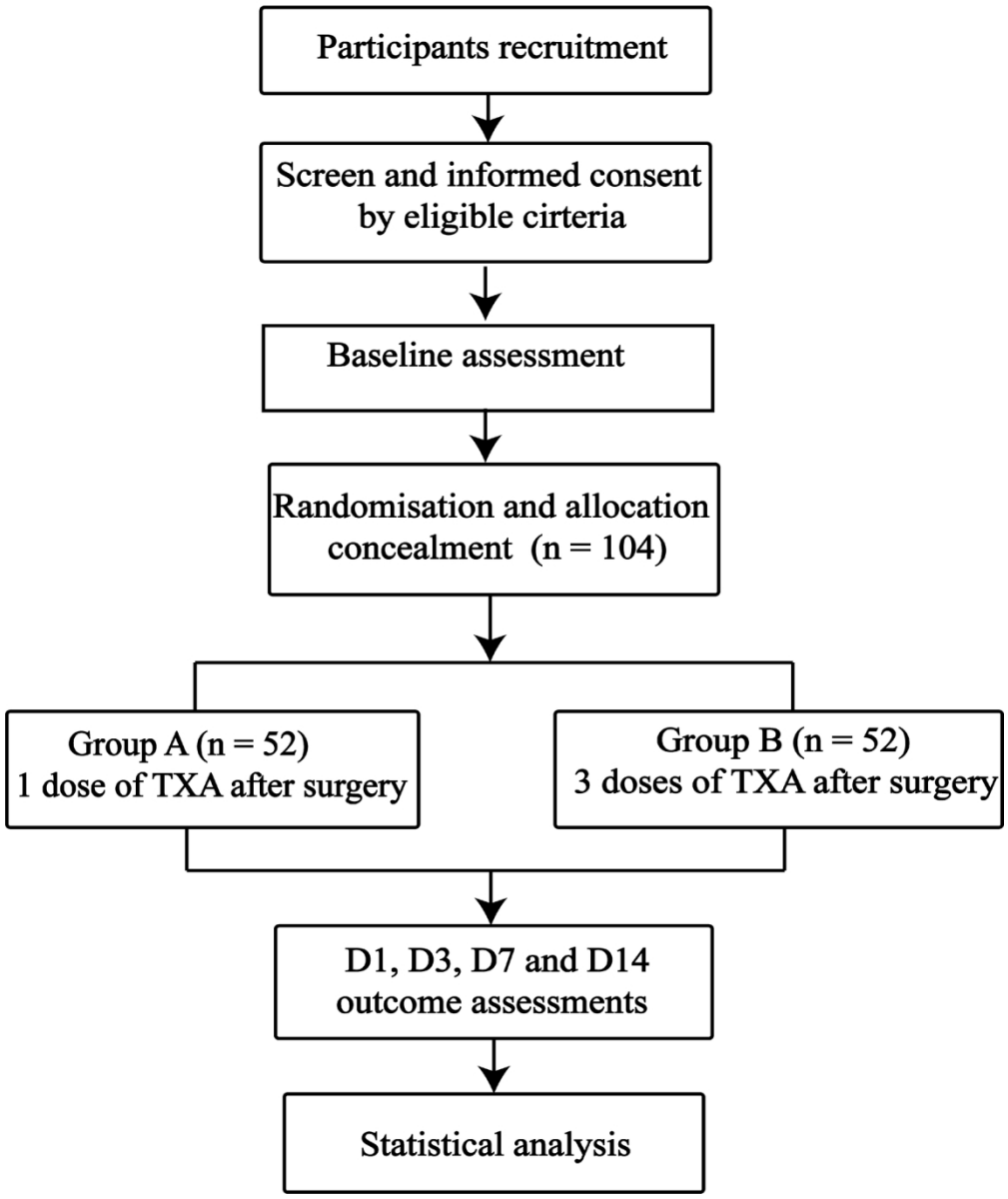
Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA, tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.



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163x195mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Line Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Line 1-3.
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Line 63.
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	Line 371-372.
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Line 7-37; 139-143
	5b	Name and contact information for the trial sponsor	Line 39-42.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Line 142-143; 366-370.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Line 83-131.
	6b	Explanation for choice of comparators	Line 116-131.
Objectives	7	Specific objectives or hypotheses	Line 360-363.
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Line 2-3; 157-169.
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Line 136-138; 63.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Line 171-188.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Line 232-236.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Line 194-200.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Line 265-310.

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Line 258-259 and see Figure1.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Line 149-155.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Line 138-139.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Line 158-161.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Line 161-164.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Line 167-169.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Line 313-315.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Line 161-163; 313-315.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Line 317-323.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Line 335-342
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Line 375.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Line 327-332.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Line 371-374.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Line 341-342.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Line 305-310
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Line 339-342.

	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Line 339-342.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.