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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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4 **1 Single-blinded, randomized, parallel-controlled study evaluating the effects of**
5 **2 multiple doses of tranexamic acid on perioperative blood loss in total knee**
6 **3 arthroplasty in patients with rheumatoid arthritis**
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16
17 30 BXK and LBX conceived the study while XX, CXG, SZ, JZ, JX, STS, and YHM
18
19 31 designed the study. The study protocol was drafted by BXK and LBX. All authors
20
21 32 approved the final manuscript of this study protocol.
22
23

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26

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28

29
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31
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33
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35 **37 Conflicts of Interests**
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37
38 38 The authors declared that there are no potential conflicts of interest with respect to
39
40 39 the research, authorship, and/or publication of this study.
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43 **40 Abstract:**
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45
46 41 Introduction: This clinical trial was designed to observe the effect of multiple doses use
47
48 42 of tranexamic acid on perioperative hidden blood loss (HBL) in patients with rheumatoid
49
50 43 osteoarthritis (RA) and to verify the effectiveness and safety of multiple doses of
51
52 44 tranexamic acid on reducing the amount of bleeding during the perioperative period,
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54 45 which can accelerate patient recovery after surgery. This study provides a new clinical
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56 46 evidence for perioperative blood management for total knee arthroplasty (TKA) in
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4 47 patients with RA.
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6 48 Methods and analysis: We will use a randomized, single-blinded, parallel-controlled
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8
9 49 study design to evaluate the efficacy of multiple doses use of tranexamic acid during the
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11
12 50 perioperative period. Before the patient is enrolled, the patient is fully informed of the
13
14
15 51 condition and drug use plan, and the informed consent form is signed to fully inform the
16
17
18 52 benefits and risks that may be obtained by using tranexamic acid multiple doses during
19
20
21 53 the perioperative period. This study will include RA patients (age 50-75 years) with a
22
23
24 54 unilateral primary end-stage TKA who will be randomly divided into group A or group
25
26
27 55 B. The two groups will be given an IV infusion of 1 g of tranexamic acid before the
28
29
30 56 operation, and 1.5 g of tranexamic acid will be administered by intra-articular injection
31
32
33 57 during the surgery. Group A will be intravenously administered with 1 g of tranexamic
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35
36 58 acid at 3 hours after surgery. Group B will be intravenously administered 1 g of
37
38
39 59 tranexamic acid at the 3rd, 6th, and 12th hours after surgery. The primary outcomes are
40
41
42 60 postoperative hidden blood loss (calculated according to Nadle and Gross's formula), and
43
44
45 61 the amount of change in perioperative haemoglobin. The secondary outcome measures
46
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48 62 include whole blood inflammatory factors (erythrocyte sedimentation rate and C-reactive
49
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51 63 protein), serum inflammatory factors (IL-6, IL-12 and TNF- α), and coagulation
52
53
54 64 parameters (D dimer, thrombin time).The knee function indicators include the knee
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56
57 65 swelling rates and knee joint range of motion. The adverse events include deep vein
58
59
60 66 thrombosis (DVT), pulmonary embolism (PE), and other complications.

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4 67 Ethics and dissemination: This trial has been approved by the Ethics Committee of
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6 68 Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine,
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9 69 and subsequent modifications of the protocol will be reported and approved by it.
10

11 70 Ethical number: 2019-K-02 .
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13
14 71 Trial registration number: ChiCTR1900025013
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17 72 Patient and Public Involvement: Patients and public will not be involved in the
18
19 73 development of the research question or in the design of the study. Patients will receive
20
21 74 written information about this trial, and the content includes the benefits, risks and
22
23 75 discomforts that may be brought after participating in the study. Patients can also discuss
24
25 76 with relatives, friends, or ask the doctor to explain and help them make a decision.
26
27 77 However, they will not be involved in the recruitment and conduct of the study. Besides,
28
29 78 the burden of the intervention will be assessed by patients themselves. After signing an
30
31 79 informed consent by the participant, they will be assessed for eligibility and data
32
33 80 collection will begin. Dissemination of the general results (no personal data) will be
34
35 81 made on demand.
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43 82 Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative
44
45 83 blood management, hidden blood loss, clinical trial protocol
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47

48 84 **Article Summary**

49 85 *Strengths and limitations of this trial*

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52
53 86 This trial is the first trial to use a single-blinded, randomized, parallel-controlled
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56 87 design in China to observe the efficacy and safety of multiple doses of tranexamic acid in
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58 88 the perioperative period of TKA in patients with RA.
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4 89 The study use a rigorously study designed , which includes proper randomization,
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6 90 allocation concealment, an adequate sample size and objective clinical test indicators ,and
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9 91 reduces the selectivity bias.

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11 92 However, due to some geographical reasons, long-term follow-ups of some patients
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13
14 93 can only be conducted by phone.

17 94 **Introduction**

18
19 95 Total knee arthroplasty (TKA) was developed in the 1970s. TKA is an effective
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21
22 96 treatment for various knee arthritis end-stage lesions causing severe pain, deformity and
23
24
25 97 dysfunction of the knee joint.¹ The US epidemiological survey shows that the number of
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28 98 patients undergoing TKA will increase each year.² There are 230 million surgeries each
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31 99 year worldwide; joint replacement surgery accounts for the majority for these surgeries,
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34 100 and haemorrhage is one of the major complications in the perioperative period.³
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37 101 Excessive blood loss may require an allogeneic blood transfusion. Allogeneic blood
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40 102 transfusion can spread blood diseases, cause immune complications, prolong
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43 103 hospitalization time and increase the infection rate.⁴⁻⁵ The incidence of anaemia in
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46 104 rheumatoid osteoarthritis (RA) patients is high. Anaemia is negatively associated with
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49 105 rheumatoid arthritis and increase the progression of osteoarthritis damage observed by
50
51
52 106 imaging.⁶⁻⁷ Therefore, we believe that perioperative blood management in patients with
53
54
55 107 RA is particularly important.

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57
58 108 Hidden blood loss (HBL) is the blood lost during intraoperative and postoperative
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61 109 infiltration into the tissue, residual blood in the knee joint cavity and haemolysis,
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64 110 accounting for 50% of the total blood loss.⁸ HBL is not involved in the blood circulation;

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4 111 it can cause systemic blood cells, decreases in haemoglobin decrease, local tissue
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7 112 haematoma, poor wound healing, and even wound infections.

8
9 113 Surgical tourniquet use, can reduce intraoperative bleeding,⁸⁻⁹ providing a clear view
10
11 114 during the surgery, and facilitate the connection between the cement, bone and joint
12
13
14 115 prostheses.¹⁰ However, after the release of the tourniquet, local tissue ischemia
15
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17 116 reperfusion injury and activation of the fibrinolytic system can occur.¹¹⁻¹² Peripheral
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20 117 blood circulation accelerates, plasma fibrinolysis becomes enhanced, and postoperative
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22 118 HBL increases.¹¹ Thus reducing the dissolution of fibrin, can reduce postoperative
23
24
25 119 HBL.¹³

26
27 120 Tranexamic acid is a synthetic lysine derivative that can competitively inhibit the
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29
30 121 binding of plasminogen and fibrin, prevents the activation of plasminogen, and protects
31
32
33 122 fibrin from degradation and dissolution by plasmin. Tranexamic acid was initially used in
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36 123 obstetrics and gynaecology and was then gradually applied in surgeries such as
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38
39 124 cardiothoracic surgery, trauma, joint replacement, and spine surgery to reduce bleeding
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41
42 125 and blood transfusion rates.¹⁴⁻¹⁶ The CRASH-2 trial has demonstrated the effectiveness
43
44
45 126 and safety of tranexamic acid in reducing blood loss.¹⁷ Currently, tranexamic acid has
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47
48 127 been recommended as a guideline drug for perioperative blood management during
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51 128 TKA.¹⁸

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54 129 The methods of administering tranexamic acid includes oral administration,
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57 130 intravenous administration , single large dose intravenous administration, intra-articular
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60 131 injection, joint cavity irrigation, postoperative drainage tube injection, and combination
132 132 therapy.¹⁹⁻²³ However, there is no consensus on the optimal dose of and time of

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4 133 administering tranexamic acid during the TKA perioperative period.^{14,24-25}
5

6 134 Studies have shown that fibrinolysis peaks at 6 hours postoperatively and continues
7
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9 135 occur for approximately 18 hours after TKA with tourniquets.²⁶ The half-life of
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11
12 136 tranexamic acid in plasma is 2 hours, and the maximum concentration can be reached by
13
14 137 intravenous administration for 1 hour.²⁷ Thus, we suspect that a single dose of tranexamic
15
16
17 138 acid may not be sufficient for an anti-fibrinolytic effect during the perioperative period of
18
19
20 139 TKA. There are also studies suggesting that for patients with osteoarthritis, higher doses
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23 140 of tranexamic acid during the perioperative period can increase the efficacy of the drug
24
25 141 until the dosage reaches a certain upper limit.^{16,28-29} The purpose of this clinical trial is to
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28 142 verify the effectiveness and safety of multiple doses of tranexamic acid in reducing blood
29
30 143 loss in patients with RA during the perioperative period, improving the enhanced
31
32
33 144 recovery after surgery (ERAS), and providing a new evidence for perioperative blood
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35 145 management for TKA. We will use a large sample size to ensure a credible conclusion.
36

37 146 **Methods and analysis**

38 147 *Study context*

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43 148 This clinical trial will be conducted at the inpatient ward of Shanghai University of
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46 149 Traditional Chinese Medicine Guanghai Hospital in Shanghai, China on September 1,
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48
49 150 2019, and there will be 11 investigators, including 2 senior orthopaedic surgeons (L-bX,
50
51
52 151 W-tZ) with 20 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX,
53
54 152 S-sT, Y-hM and QS), 2 data collectors and who are also statisticians (B-xK and HX) and
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56 153 a nurse(X-rX). Give patients informed consent before the start of clinical trials. The
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59 154 perioperative ERAS blood management programme and the trial flow chart are shown in
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4 155 Table 1 and Figure 1. The schedule is shown in Table 2.
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7 156 *Sample size calculation*
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9 157 This trial uses a completely randomized design, and multiple sample sizes are
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11 158 estimated by a previous clinical research review. The the main outcome measure is the
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13 159 amount of HBL. The overall mean estimate is $\sigma = 320$, and the overall standard deviation
14
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16
17 160 is $\mu = 79$, using the statistical formula $n = \frac{z^2 \left(\sum_{i=1}^k \sigma^2 / k \right) \left[\sum_{i=1}^k (\mu_i - \mu)^2 / (k-1) \right]}{d^2}$. Considering a dropout
18
19 161 rate of 20%, 76 subjects were required to yield a power of 90% with a significance level
20
21
22 162 of 0.05.
23

24 163 *Randomisation and allocation concealment*
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26
27 164 Patients are randomly assigned to two groups according to a 1:1 ratio; SPSS 25.0 is
28
29
30 165 used to generate a random sequence containing 76 random numbers, that are placed into
31
32 166 an opaque envelope and input in a computer by encryption, and the group data is saved
33
34
35 167 by the data collector who is a statistician. Only the nurse will be allowed to check the
36
37 168 enrollment and give the corresponding treatment.
38
39

40 169 *Single-blinded design*
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43 170 The nurse will know the patients' enrolment and give the corresponding treatment.
44
45
46 171 All participants in this trial, including the orthopaedic surgeons and data collectors who
47
48 172 are statisticians, are all blinded to the treatment conditions. The outcome assessor will not
49
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51 173 be aware of the patient's enrolment and will objectively records the patients' test
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53 174 information. When performing the statistical analyses, the independent biostatistician will
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56 175 also be blinded to the conditions.
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58 176 *Eligibility criteria*
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4 177 The eligibility criteria are in accordance with the " Classification of Rheumatoid
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6 178 Arthritis" from the American Journal of Rheumatism revised in 1978,³⁰ and the 2010
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9 179 American College of Rheumatology and the European League Against Rheumatism.³¹
10
11
12 180 (1)The patient is diagnosed with RA and the Kellgren-Lawrence³² classification is Stage
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14 181 III or IV; (2) The patient is aged 55 to 75 years old; (3) The patient will undergo the
15
16
17 182 unilateral primary TKA; (4) The patients received perioperative anti-fibrinolytic
18
19
20 183 tranexamic acid therapy; and (5)The patient did not have preoperative anaemia, and the
21
22 184 blood clotting function was normal.

23 24 25 185 *Exclusion criteria*

26
27 186 The exclusion criteria were as follows:(1) Other types of arthritis (such as primary
28
29 187 arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and
30
31 188 tuberculous arthritis); (2) Bilateral knee arthroplasty in patients with RA; (3) Severe
32
33 189 cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina pectoris,
34
35
36 190 and heart failure) or cerebrovascular disease (cerebral infarction and cerebral
37
38 191 haemorrhage);and (4) Prolonged use of oral anticoagulant drugs (such as aspirin,
39
40 192 warfarin, and clopidogrel).

41 42 43 193 *Elimination criteria*

44
45 194 The elimination criteria were as follows: (1) Patients with acquired colour vision
46
47 195 disorder; (2) Active intravascular coagulation patients; and (3) Patients with a history of
48
49 196 convulsions.

50 51 52 197 *Termination criteria*

53
54 198 The termination criteria were as follows: (1) Shock: once a shock occurs, appropriate
55
56 199 therapy is administered to terminate it; (2) Allergic symptoms: such as itching and a rash;
57
58
59 200 (3) Digestive disorders such as nausea, vomiting, loss of appetite, and diarrhoea after
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3 201 medication; (4) Reactive dermatitis, dizziness, hypotension, drowsiness, headache;
4
5 202 convulsions, visual impairment, and others; and (5) Adverse events such as intracranial
6
7 203 thrombosis and intracranial haemorrhage after medication.
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10
11 204 *Surgery and anaesthesia*
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13 205 Surgery is performed by senior surgeons (LBX and WTZ).The operations are
14
15
16 206 conducted under general anaesthesia. The median incision of the knee joint, the medial
17
18 207 paramedian support band approach, and the length of the incision are approximately
19
20
21 208 14-17cm. Positioning is within the femoral and tibial bone marrow external positions. All
22
23
24 209 patients will use a tourniquet during the operation, and the pressure will be controlled at
25
26 210 approximately 230-250mmHg. During the operation, controlled hypotension, a
27
28
29 211 reduction in blood pressure to 20% of the basal blood pressure, will be administered with
30
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32 212 a postoperative suction drainage tube, and limb surgery will be conducted with an elastic
33
34 213 bandage. In the perioperative period, conventional anti-infective, combined analgesic,
35
36
37 214 anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments will
38
39
40 215 be administered according to the "Chinese hip and total knee arthroplasty surgery
41
42 216 perioperative anti-fibrinolytic drug sequential anticoagulant application programme
43
44
45 217 expert consensus". Ten min before the incision, 1 g of tranexamic acid + 100mL
46
47 218 intravenous saline and 1.5 g of tranexamic acid + 50 mL articular injection of saline will
48
49
50 219 be administered preoperatively in the sutured joint cavity.
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52 220 Tranexamic acid is produced by Hunan Dongting Pharmaceutical Co., Ltd., and the
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55 221 implementation standards are found in the following resources: second edition of 2015
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4 222 Chinese Pharmacopoeia and drug supplement application approval (2013B02016),

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7 223 YBH07372010; the approval number is National Drug Standard H43020565.

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9 224 *Study interventions*

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11 225 Group A: At the 3rd hour after the operation, 1 g of tranexamic acid + 100 mL of
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13 226 physiological saline is administered intravenously. Group B: 1 g of tranexamic acid + 100
14
15 227 mL of physiological saline is intravenously instilled at 3, 6, and 12 hours after the
16
17
18 228 operation.

19
20 229 *Pain management and rehabilitation*

21
22 230 A cocktail injection is given during the operation, and 0.2 g of oral celecoxib is
23
24 231 given after surgery for analgesia. Anesthesia is given to the athlete's foot after anaesthesia
25
26
27 232 The maximum angle of flexion and extension of the ankle is maintained for 6 seconds,
28
29 233 the foot is relaxed for 5 seconds; and the quadriceps contractions are equal between the
30
31 234 two sides. On the first postoperative day, the patients will be perform a straight leg raise
32
33 235 exercise, a supine knee flexion exercise and a sitting flexion and extension knee exercise;
34
35 236 the machine-assisted exercises will begin on the third day after surgery, such as continued
36
37
38 237 passive motion.

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41 238 *Antibiotics*

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43 239 Cefazolin sodium perioperative antibiotics as prophylaxis are administered 30 min
44
45 240 before surgery, and the incision 24-48 hours after the postoperative intravenous infusion.

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47 241 *Prevention of lower extremity venous thrombosis*

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49 242 Six hours after the perioperative injection, low molecular weight heparin is injected
50
51 243 for the prevention of deep vein thrombosis.

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53 244 *Outcomes*

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55 245 *Primary outcome*

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59 246 *Hidden blood lose (HBL) , haemoglobin*

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4 247 The amount of HBL is calculated according to the formula by Nadle³³ and Gross
5
6 248 formula³⁴: Patient's blood volume (PBV)= $K1 \times \text{height(m)} + K2 \times \text{weight(kg)} +$
7
8
9 249 $K3$ (Male: $K1=0.3669, K2=0.03219, K3=0.6041$. Female: $K1=0.3561, K2=0.03308,$
10
11 250 $K3=0.1833$). $\text{HBL} = \text{PBV} \times (\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}) / \text{Hct}_{\text{ave}}$.

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13
14 251 Preoperatively, on the 1st, 3rd, 7th and 14th days after surgery, we will calculate the
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16 252 HBL based on the value of haematocrit and recorded the amount of haemoglobin.

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18 253 *Second outcome indicator*

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20 254 *Inflammatory index, Inflammatory factor, Coagulation index*

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24 255 Preoperatively, on the 1st, 3rd, 7th and 14th days after surgery, we will record the
25
26 256 erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole blood
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28 257 and interleukin 6 (IL-6), interleukin 12 (IL-12), and tumor necrosis factor α (TNF- α) in
29
30 258 the plasma.

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33
34 259 Whole blood test indicators and plasma inflammatory factors will be assessed in the
35
36 260 Department of Clinical Laboratory of Guanghua Hospital. The indicators and factors will
37
38 261 be tested by an inspector who is not involved in this clinical trial.

39
40 262 *Knee function score and swelling rate*

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42
43 263 Knee function will be measured using the American Keen Society Score (AKSS) at
44
45 264 one day before surgery and on the 3rd, 7th and 14th days after surgery. A trained
46
47 265 researcher will educate all patients until they fully understand the questionnaire and how
48
49 266 to assess their knee function in order to complete the questionnaire. The rate of swelling
50
51 267 is defined as the postoperative circumference of the upper tibia divided by the
52
53 268 preoperative circumference of the upper tibia.

54
55
56 269 *Adverse events*

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2
3 270 Adverse events include the follow: Deep vein thrombosis³⁵: (1)Acute onset, affected
4
5 271 limb swelling, sever pain, or significant tenderness at the femoral triangle or/and leg; (2)
6
7 272 Extensive swelling on the affected limb; (3) The skin of the affected limb has a dull red
8
9 273 colour and a rise in temperature ; (4) Generalized shallow venous tension on the affected
10
11 274 limb; (5) Homan’s sign and Neuhof’s sign are positive; and (6)Doppler ultrasound for
12
13 275 venous blood flow and venography are used to confirm the diagnosis and Pulmonary
14
15 276 embolism: Clinical manifestations (cough, chest tightness, palpitations, haemoptysis,
16
17 277 shortness of breath, dizziness, shock, cyanosis, increased respiratory rate, arteriovenous
18
19 278 filling or pulsation, etc.) and computed tomography are used to identify the occurrence of
20
21 279 a pulmonary embolism.
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26 280 The wound healing process and complications³⁶ (wound bleeding, haematoma,
27
28 281 wound infection, and deep infection)will be observed and recording during
29
30 282 hospitalization and follow-ups. Wound exudation is defined as the exudation of the
31
32 283 wound up to 48 hours after surgery.
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35 284 *Adverse event processing*

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37 285 Adverse events that occur during the use of medication are not necessarily related to
38
39 286 drug use, but the content recorded in the CRFs is used to evaluate the relevance of drugs
40
41 287 to the follow-up observations. The classification of adverse events will be recorded in
42
43 288 accordance with the five-level scoring systems in the 5.0 version of the CTCAE.
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46 289 Serious adverse events are defined as those that cause cancer, defects, teratogenicity,
47
48 290 danger to the statement, death, and permanent damage to organ function, permanent or
49
50 291 significant disability, and prolonged hospital stay. In the event of the above mentioned
51
52 292 incidents, the researcher should immediately take appropriate measures with the subjects
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54 293 and report to the hospital sponsors and ethics committees within 24 hours.
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56

57 294 *Data management*

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3 295 Date entry will be conducted by two independent trained research assistants who are
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5 296 trained to use the paper CRFs. Computer data is entered with a strict specifications ,
6
7 297 double-entry input method. The hospital's independent investigators will monitor and
8
9 298 audit the data periodically.

12 299 *Statistical analysis*

14 300 The analyses are as follows: (1) Descriptive analysis of the characteristics of the
15
16 301 study participants; (2) Balance analysis of the baselines values among groups; (3)
17
18 302 Comparison of the balance among groups of the primary outcome indicators; and (4)
19
20 303 Comparison of secondary outcome indicators and safety indicators among groups.

23 304 The three groups' incidence and the total rate of adverse events are tested by bidirectional
24
25 305 disordered R*C list chi-square test. The association between the occurrence of adverse
26
27 306 events and the dose of tranexamic acid used is described.

32 307 *Ethics and dissemination*

34 308 This clinical trial has been approved by the ethics committee of Shanghai Guanghua
35
36 309 Hospital of Integrated Traditional Chinese and Western Medicine (approval number:
37
38 310 2019-K-02). Data will be kept strictly confidential. The results of the trial will be
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40 311 published on the website of the China Clinical Trials Registry and published in
41
42 312 peer-reviewed journals.

48 313 *Discussion*

50 314 Blood management is an important part of the ERAS programme, which is an
51
52 315 evidence-based treatment programme that uses multiple strategies for treating TKA to
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54 316 reduce complications, improve the prognosis and promote rapid recovery after surgery.

57 317 In this trial, we will exclude patients with a large number of intravenous infusions to
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59 318 reduce the effect of blood dilution on the results. We will use a tourniquet and will not

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3 319 conducted blood cell return during the operation, and the amount of intraoperative blood
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5 320 loss we will negligible.³⁷ It has been reported that intravenous infusion combined with
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7 321 intra-articular injection of tranexamic acid may be the optimal therapeutic scheme.³⁸⁻³⁹
8
9 322 Previous studies have shown that swelling of the knee joint after TKA is associated with
10
11 323 HBL in the joint cavity. Tranexamic acid reduces the degree of swelling around the joint
12
13 324 by reducing postoperative HBL.⁴⁰ Animal experiments also indicate that plasminogen
14
15 325 activators play an important role in the development of inflammation in RA, and the
16
17 326 dissolution of fibrin will causes an inflammatory response.⁴¹ Therefore, we suspect that
18
19 327 the use of multiple doses of transxamic during the peroperative period may have an
20
21 328 auxiliary anti-inflammatory effect.
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26 329 In this study, is the sample size is sufficient to obtain true and reliable results. This
27
28 330 study will provide new evidence for blood management during the perioperative period
29
30 331 of TKA in RA patients.
31
32

33 332 **Acknowledgment:** The authors thank all the patient advisers for participating in this
34
35 333 study.
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39 335 References:

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Table 1 Enhanced recovery after surgery blood management

Preoperative

Treatment of hemorrhagic primary disease

1
2
3 Nutritional guidance, balanced diet

4 Iron application

5 rHuEPO application

6 Intraoperative

7 Minimally invasive surgery

8 Tourniquet optimization

9 Controlled buck

10 Autologous blood return

11 Use of tranexamic acid

12 Postoperative

13 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)

14 Nutritional support, iron supplementation, use of rHuEPO

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22 RHuEPO, Human recombinant erythropoietin.
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29 Table 2. The schedule of trial enrolment, interventions and assessments

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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		●	●	●	●

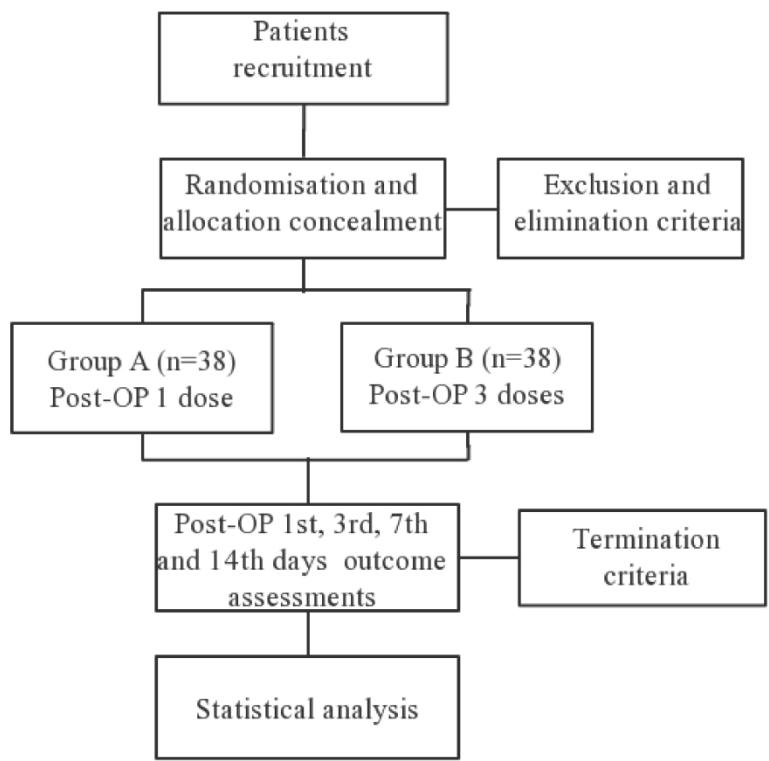
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OP, operation; HBL, hidden blood lose; Hb, Hemoglobin; DVP, deep vein thrombosis;
PE, pulmonary embolism

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For peer review only

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

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	SURGERY, Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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

4 Bing-xin Kang, Hui Xu, Chen-xin Gao, Sheng Zhong, Jing Zhang, Jun Xie, Song-tao
5 Sun, Ying-hui Ma, Wei-tao Zhai, Lian-bo Xiao

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41 37 Bing-xin Kang and Hui Xu contributed equally to this paper.
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58 44 **Author Contributions:**
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4 45 BXK, HX and LBX conceived the study while CXG, SZ, JZ, JX, STS, YHM,
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6 46 and WTZ designed the study. The study protocol was drafted by BXK and HX. All
7
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9 47 authors approved the final manuscript of this study protocol.
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18
19 51 commercial or not-for-profit sectors.
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22 52 **Conflicts of Interests**

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25 53 The authors declared that there are no potential conflicts of interest with respect
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27 54 to the research, authorship, and/or publication of this study.
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32 56 **Abstract:**

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35 57 Introduction: This clinical trial is designed to evaluate the effect of multiple-dose
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37 58 tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with
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39 59 rheumatoid osteoarthritis (RA).
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43 60 Methods and analysis: A randomized, single-blinded, parallel-controlled study design
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45 61 will be designed. RA patients (age 50-75 years) undergoing unilateral primary
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47 62 end-stage TKA will be randomly divided into Group A or Group B. Group A will be
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49 63 treated with one dose of TXA (1g; intravenous injection at the 3rdhour) and Group B
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51 64 with three doses (at the 3rd, 6th, and 12th hours; intravenous injection) after surgery.
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56 65 The primary outcomes will be evaluated with hidden blood loss and haemoglobin
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58 66 level and the secondary outcomes with blood inflammatory factors, serum
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4 67 inflammatory factors, and coagulation parameters.
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6 68 Ethics and dissemination: This trial has been approved by the Ethics Committee of
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9 69 Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western
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11 70 Medicine.
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14 71 Ethical number: 2019-K-13.
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17 72 Trial registration number: ChiCTR1900025013
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19 73 Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty,
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21 74 perioperative blood management, hidden blood loss, clinical trial protocol.
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27 76 **Article Summary**

28 29 77 *Strengths and limitations of this trial*

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32 78 (1)This is the first single-blinded, randomized, parallel-controlled study in China
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35 79 to evaluate the efficacy and safety of perioperative multiple-dose regimen of
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38 80 tranexamic acid after TKA in patients with RA.
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40 81 (2)The study has its bias largely reduced by rigorously study designs, including
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43 82 proper randomization, allocation concealment, an adequate sample size and
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46 83 objective indicators.
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48 84 (3)Long-term follow-ups of some patients can only be conducted by phone. And
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51 85 the results can only be extrapolated to Chinese RA population.
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55 56 87 **Introduction**

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58 88 Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like
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4 89 anemia.¹The overall prevalence of RA is 0.5-1% in Europe and North America,
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6 90 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.²⁻³ Total knee
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9 91 arthroplasty (TKA) is effective in treating flexion contracture and maintaining the
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11
12 92 stability of RA knee.⁴ About 0.005% of RA patients receive TKA, a rate that has
13
14 93 gradually decreased over the past decades. Even though, surgery remains the first
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17 94 choice for articular deformity and pain, despite that disease-modifying antirheumatic
18
19 95 drugs (DMARDs) and biologics agents can manage synovitis-related symptoms in
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21
22 96 RA patients.⁵ The haemorrhage is a major perioperative complications of TKA.⁶
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24
25 97 Excessive blood loss should be replenished with allogeneic blood transfusion, but it
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27
28 98 may cause immune complications, prolong hospitalization time and increase the
29
30 99 infection rate.⁷⁻⁸ Haemoglobin has an obviously negative correlation with disease
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32
33 100 activity in RA.⁹ Therefore, we believe that perioperative blood management is need
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35 101 for patients with RA.

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37
38 102 Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as
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40 103 the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in
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42
43 104 the knee joint cavity and gets haemolyzed.¹⁰ As this blood is not involved in the blood
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45
46 105 circulation, HBL often leads to the postoperative pain, lower limb swelling, poor
47
48 106 wound healing, postoperative inflammation, and even wound infections.

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51 107 Surgical tourniquet use, can reduce intraoperative bleeding,¹¹ provide a clear
52
53 108 view during the surgery, and facilitate the connection between the cement, bone and
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56 109 joint prostheses.¹² However, after the release of the tourniquet, local tissue
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59 110 may be damaged by ischemia reperfusion injury, and fibrinolytic system
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4 111 activated.¹³⁻¹⁴ As a consequence, peripheral blood circulation is accelerated, plasma
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6 112 fibrinolysis enhanced, and postoperative HBL increased.¹³ Therefore, reducing the
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9 113 dissolution of fibrin can reduce postoperative HBL.¹⁵ Tranexamic acid (TXA) is a
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11 114 synthetic lysine derivative that can competitively inhibit the binding between
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13
14 115 plasminogen and fibrin, prevent the activation of plasminogen, and protect fibrin from
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16
17 116 degradation and dissolution by plasmin. TXA is initially used in obstetrics and
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19
20 117 gynaecology, then gradually replicated in surgeries to reduce bleeding and avoid
21
22 118 blood transfusion rates.¹⁶⁻¹⁷ The CRASH-2 trial has demonstrated the effectiveness
23
24
25 119 and safety of TXA in reducing blood loss.¹⁸ A large amount of literature has reported
26
27 120 that TXA can significantly reduce peri-TKA blood loss.¹⁹⁻²³ Currently, TXA is
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29
30 121 recommended for perioperative blood management of TKA.²⁴ But, its efficacy and
31
32 122 safety in RA patients undergoing TKA has been rarely reported.²⁵ TXA can be
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35 123 administered through oral intake, single large-dose intravenous injection,
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38 124 intra-articular injection, joint cavity irrigation, postoperative drainage tube injection,
39
40
41 125 and combination use.^{23,26-29} There is no consensus on the optimal dose and time of
42
43 126 TXA administration during perioperative TKA.^{16,30-31} Studies have shown that
44
45 127 fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKA
46
47
48 128 with tourniquets.³² The half-life of TXA in plasma is 2 hours, and its concentration
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51 129 peaks at 1 hour after injection.³³ Thus, we suspect that a single dose of TXA may not
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54 130 be sufficient to exert an anti-fibrinolytic. There are also studies suggesting that for
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56 131 patients with osteoarthritis, higher doses (within a limit) during the perioperative
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59 132 period can increase the efficacy of TXA.³⁴⁻³⁶ The purpose of this clinical trial is to
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4 133 verify the effectiveness and safety of multiple doses of TXA in reducing perioperative
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6 134 blood loss in RA patients treated with TKA, hoping to find a new mode of
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9 135 perioperative blood management for TKA.
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12 136

137 **Methods and analysis**

138 *Study context*

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

148 *Sample size calculation*

149 This trial uses a completely randomized design, and multiple sample sizes are
150 estimated by a previous clinical research review. The main outcome is measured with
151 the amount of HBL. The overall mean estimate is $\sigma = 320$, and the overall standard
152 deviation is $\mu = 79$, both estimated by the statistical formula
153
$$n = \frac{z^2 \left(\sum_{i=1}^k \sigma_i^2 / k \right) / \left[\sum_{i=1}^k (\mu_i - \mu)^2 / (k-1) \right]}{1 - \text{power}}$$
. Considering a dropout rate of 20%, 76 subjects are
154 required to yield a power of 90% with a significance level of 0.05.

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4 155 *Randomization and allocation concealment*

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6 156 Patients are randomly assigned to two groups according to at 1:1 ratio; SPSS
7
8
9 157 version 25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence
10
11 158 containing 76 random numbers, which are placed into an opaque envelope and put in
12
13
14 159 a computer by encryption. The group data is saved by the statistician. Only the nurse
15
16
17 160 is allowed to check the enrollment and give the corresponding treatment.

18
19 161 *Single-blinded design*

20
21
22 162 Only the nurse will be allowed to know the patients' enrollment and give them
23
24 163 corresponding treatment. The outcome evaluators will objectively record the patients'
25
26
27 164 test results.

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29
30 165 *Eligibility criteria*

31
32 166 The eligibility criteria are set in accordance with the "AMERICAN
33
34 167 RHEUMATISM ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS"
35
36
37 168 from the American Journal of Rheumatism (revised in 1978),³⁷ and the 2010
38
39 169 "ACR/EULAR classification criteria for rheumatoid arthritis"³⁸ (1)The patient is
40
41
42 170 diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence³⁹
43
44 171 classification; (2)The patient is 55 to 75 years old; (3)The patient will undergo the
45
46
47 172 unilateral primary TKA; (4)The patients will receive perioperative anti-fibrinolytic
48
49 173 TXA therapy; and (5)The patient will show normal blood-clotting function and no
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52 174 preoperative anaemia.

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55 175 *Exclusion criteria*

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58 176 Excluded are those with: (1)Other types of arthritis (such as primary arthritis,
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4 177 post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis, and
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6 178 tuberculous arthritis); (2)Bilateral knee arthroplasty (RA patients); (3)Severe
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9 179 cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina
10
11 180 pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral
12
13
14 181 haemorrhage);and (4)Prolonged use of oral anticoagulant drugs (such as aspirin,
15
16
17 182 warfarin, and clopidogrel).

18
19
20 183 *Elimination criteria*

21
22 184 Eliminated are those with: (1)Acquired colour vision disorder; (2)Active
23
24 185 intravascular coagulation patients; and (3)a history of convulsions.

25
26
27 186 *Termination criteria*

28
29
30 187 The study on one patient will be terminated if he/she shows the following
31
32 188 events: (1)Shock; (2)Allergic symptoms, such as itching and a rash; (3)Digestive
33
34 189 disorders, such as nausea, vomiting, loss of appetite, and diarrhoea after medication;
35
36
37 190 (4)Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions,
38
39
40 191 visual impairment, and others; and (5)Adverse events, such as intracranial thrombosis
41
42
43 192 and intracranial haemorrhage after medication.

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45 193 *Perioperative anti-rheumatic treatment*

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48 194 Methotrexate and hydroxychloroquine will be used during the perioperative
49
50 195 period. Leflunomide will be discontinued at one week before surgery. Use of other
51
52 196 disease-modifying antirheumatic drugs (DMARDs) will be discontinued two days
53
54
55 197 before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The
56
57
58 198 use of newer biologic agents targeting tumor necrosis (TNF- α) will be discontinued
59
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4 199 for 4 to 5 half-lives before surgery and restarted after wound healing and infection
5
6 200 elimination.⁴⁰⁻⁴¹
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8

9 201 *Surgery and anesthesia*
10

11 202 Surgery will be performed by two senior surgeons (LBX and WTZ). The
12
13 203 operations will be conducted under general anaesthesia. A median incision (14-17 cm
14
15 204 long) is cut in the knee joint with a medial paramedian support band. Internal
16
17 205 positioning is used for femoral bone marrow and external positioning for tibial bone
18
19 206 marrow. All patients will use a tourniquet with a pressure of 230-250 mmHg. During
20
21 207 the operation, blood pressure will be reduced to 20% of the basal level through a
22
23 208 suction drainage tube, and limb surgery will be conducted with an elastic bandage.
24
25 209 During the operation, conventional anti-infective, combined analgesic,
26
27 210 anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments
28
29 211 will be administered according to the "Chinese Hip and Total Knee Arthroplasty
30
31 212 Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application
32
33 213 Programme Expert Consensus". Ten minutes before the incision, 1 g of TXA + 100
34
35 214 mL of intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be
36
37 215 administered preoperatively in the sutured joint cavity.
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47 216 TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used
48
49 217 according to the second edition of 2015 Chinese Pharmacopoeia and Drug
50
51 218 Supplement Application Approval (2013B02016), YBH07372010; the approval
52
53 219 number is National Drug Standard H43020565.
54
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58 220 *Intraoperative blood loss*
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4 221 The amount of postoperative blood loss= the total volume of fluid in the
5
6 222 negative pressure drain—the volume of normal saline.

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8
9 223 *Study interventions*

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11 224 Group A: 1 g of TXA + 100 mL of physiological saline will be injected
12
13
14 225 intravenously at the 3rd hour after the operation. Group B: 1 g of TX + 100 mL of
15
16
17 226 physiological saline is intravenously instilled at the 3rd, 6th, and 12th hours after the
18
19
20 227 operation.

21 228 *Pain management and rehabilitation*

22
23
24 229 A cocktail injection will be given during the operation, and 0.2 g of oral
25
26
27 230 celecoxib after surgery for analgesia. After anaesthesia the maximum angles of
28
29
30 231 flexion and extension of the ankle will be maintained for 6 seconds, and the foot is
31
32
33 232 relaxed for 5 seconds; the quadriceps contractions are equal between the two sides. At
34
35
36 233 the first postoperative day, the patients will exercise straight-leg-raise,
37
38 234 supine-knee-flexion and knee flexion and extension in sitting; the machine-assisted
39
40 235 exercises will begin on the third day after surgery, such as continuous passive motion.

41 236 *Antibiotics*

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43
44 237 For perioperative prophylaxis, cefazolin sodium antibiotics are administered at
45
46 238 30 minutes before surgery, and 24-48 hours after surgery.

47
48
49 239 *Prevention of lower extremity venous thrombosis*

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51
52 240 Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day
53
54 241 for 14 days) is injected for preventing deep vein thrombosis.

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56
57 242 *The Patient and Public Involvement*

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59 243 Any non-investigator will not be involved in the design of the study and
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4 244 related questions. Patients will receive written information about this trial, pertaining
5
6 245 to the benefits, risks and discomforts that they may get from the study. Patients can
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9 246 also discuss with their relatives, friends, or doctors to help them make a decision.
10
11 247 Besides, the benefits and risks of the intervention will be assessed by patients
12
13
14 248 themselves. After signing an informed consent, they will be assessed for eligibility
15
16
17 249 and data will be collected. Dissemination of the general results (no personal data) will
18
19
20 250 be made on demand.

21
22 251

23 252 *Outcomes*

24 253 *Primary outcomes*

25 254 *Hidden blood loss (HBL), haemoglobin level*

26 255 HBL is calculated according to the formula by Nadle⁴² and Gross formula:⁴³

27 256 Patient's blood volume (PBV)= $K_1 \times \text{height(m)} + K_2 \times \text{weight(kg)} +$

28 257 K_3 (Male: $K_1=0.3669, K_2=0.03219, K_3=0.6041$. Female: $K_1=0.3561, K_2=0.03308,$

29 258 $K_3=0.1833$). $\text{HBL} = \text{PBV} \times (\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}) / \text{Hct}_{\text{ave}}$.

30 259 Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will calculate the

31 260 HBL based on the value of haematocrit and recorded the count of haemoglobin.

32 261 *Secondary outcomes*

33 262 *Inflammatory index, inflammatory factor and coagulation index*

34 263 Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the

35 264 erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole

36 265 blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF- α in the plasma.

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4 266 Whole blood test indicators and plasma inflammatory factors will be assessed in
5
6 267 the Department of Clinical Laboratory of Guanghua Hospital. The indicators and
7
8
9 268 factors will be tested by an inspector who is not involved in this clinical trial.
10

11
12 269 *Knee function and swelling*
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14 270 Knee function will be measured using the American Keen Society Score (AKSS)
15
16
17 271 at one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained
18
19
20 272 researcher will educate all patients until they fully know how to assess their knee
21
22 273 function through the questionnaires. The rate of swelling is defined as the
23
24
25 274 postoperative circumference of the upper tibia ÷ the preoperative circumference of the
26
27 275 upper tibia.
28

29
30 276 *Adverse events*
31

32 277 Adverse events include (1)Deep vein thrombosis⁴⁴ (acute onset, affected limb
33
34
35 278 swelling, sever pain, or significant tenderness at the femoral triangle or/and leg);
36
37
38 279 (2)Extensive swelling on the affected limb; (3)A dull red colour and a rise in the skin
39
40
41 280 of the affected limb; (4)Generalized shallow venous tension on the affected limb;
42
43 281 (5)In the skin of the affected limb; (6)Pulmonary embolism diagnosed by Doppler
44
45
46 282 ultrasound and venography (clinical manifestations: cough, chest tightness,
47
48 283 palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased
49
50
51 284 respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism
52
53 285 diagnosed by CT.
54

55
56 286 The wound healing process and complications⁴⁵ (wound bleeding, haematoma,
57
58 287 wound infection, and deep infection) will be observed and recorded in the patient's
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4 288 case report forms (CRFs) during hospitalization and follow-ups. Wound exudation is
5
6 289 defined as the presence of exudation from the wound even 48 hours after surgery.
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8

9 290 *Adverse event treatment*

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11 291 Adverse events during the follow-up will be recorded in the CRFs, and their
12
13 292 relevance to drug use will be evaluated. All the adverse events will be classified in
14
15 293 accordance with the five-level scoring systems (5.0) of the CTCAE.
16
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18 294 Serious adverse events are defined as those that may cause cancer, defects,
19
20 295 teratogenicity, death, and permanent damage to organ function, permanent or
21
22 296 significant disability, and prolonged hospital stay. In any event, the researcher should
23
24 297 immediately take appropriate measures and report it to the hospital and ethics
25
26 298 committees within 24 hours.
27
28

29 299 *Data management*

30
31 300 Data on the CRFs will be put in the computer by two independent trained
32
33 301 research assistants with a double-entry method. The hospital's independent
34
35 302 investigators will check the data periodically.
36
37

38 303 *Statistical analysis*

39
40 304 The analyses are as follows: (1)Descriptive analysis on the characteristics of the
41
42 305 study participants; (2)Balance analysis on the baseline values in groups;
43
44 306 (3)Comparison of the balance between groups of primary outcomes; and
45
46 307 (4)Comparison of secondary outcomes and safety between groups.
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51 308 The total rate of adverse events of the two groups are tested by bidirectional
52
53 309 disordered R*C list chi-square test. The association between the incidence of adverse
54
55 310 events and the dose of TXA used is described.
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58 311 *Ethics and dissemination*
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4 312 This clinical trial has been approved by the ethics committee of Shanghai
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6 313 Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. The data
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8
9 314 sets can be obtained from appropriate authors upon reasonable request. Data will be
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11
12 315 kept strictly confidential and published on the website of the China Clinical Trials
13
14 316 Registry and in peer-reviewed journals.

17 317 **Discussion**

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21 318 Controlling blood loss can facilitate the recovery from TKA surgery. Previous
22
23 319 clinical studies have shown that high dose of TXA can reduce blood loss after TKA in
24
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26 320 patients with osteoarthritis.^{25,45-46} In this trial, we will exclude patients with a large
27
28 321 number of intravenous infusions to eliminate the effect of blood dilution on the results.
29
30
31 322 We will use a tourniquet to minimize the blood loss during the operation. Therefore,
32
33 323 what we will observed is the blood loss after the removal of tourniquet.¹⁰ It has been
34
35
36 324 reported that intravenous infusion combined with intra-articular injection of TXA may
37
38
39 325 be the optimal bleeding-control scheme.⁴⁷⁻⁴⁸ Previous studies have shown that knee
40
41 326 joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce
42
43
44 327 postoperative HBL, thereby relieving the swelling around the joint.⁴⁹ Given that
45
46
47 328 plasminogen activators play an important role in RA-involved inflammation, the
48
49 329 dissolution of fibrin will trigger an inflammatory response.⁵⁰ Therefore, we suspect
50
51
52 330 that multiple doses of TXA in the peroperative period may exert an auxiliary
53
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55 331 anti-inflammatory effect.

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57
58 332 This study will provide new evidence for managing perioperative HBL in TKA
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4 333 in Chinese RA patients.
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9 335 **Acknowledgment:**
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13 336 The authors thank all the patient advisers for participating in this study.
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14 **Table 1** Enhanced recovery after surgery blood management

15
16 Preoperative

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18 1 Treatment of hemorrhagic primary disease

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20 2 Nutritional guidance, balanced diet

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22 3 Iron application

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24 4 rHuEPO application

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27 Intraoperative

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29 5 Minimally invasive surgery

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31 6 Tourniquet optimization

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33 7 Controlled buck

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35 8 Autologous blood return

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37 9 Use of tranexamic acid

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40 Postoperative

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42 10 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)

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44 11 Nutritional support, iron supplementation, use of rHuEPO

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46 rHuEPO, recombinant human erythropoietin.

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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.

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

498 TXA,tranexamic acid.

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



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			

1 2 3 4 5 6	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
7 8		6b	Explanation for choice of comparators	
9 10	Objectives	7	Specific objectives or hypotheses	133-135
11 12 13 14 15 16	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.
17	Methods: Participants, interventions, and outcomes			
18 19 20 21 22 23 24	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.
25 26 27 28 29 30	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
31 32 33 34 35	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	223-227
36 37 38 39 40		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
41 42 43 44 45		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	
46 47 48		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	228-235
49 50 51 52 53 54 55 56 57 58 59 60	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			

1 2 3 4 5 6 7 8 9 10 11	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;
12 13 14 15 16 17		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
18 19 20 21 22 23 24 25	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
26 27 28 29 30 31	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
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
35 36 37 38 39 40		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)	
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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
53 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Surgery
Keywords:	Rheumatoid arthritis, tranexamic acid, total knee arthroplasty, perioperative blood management, Knee < ORTHOPAEDIC & TRAUMA

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

4 Bing-xin Kang*, Hui Xu*, Chen-xin Gao, Sheng Zhong, Jing Zhang, Jun Xie,
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58 44 **Author Contributions:**
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4 45 B-xK, HX and L-bX conceived the study while B-xK and HX drafted the study
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6 46 protocol, B-xK and HX contributed equally to this work and should be regarded as
7
8
9 47 co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX, S-tS, Y-hM,
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12 48 and W-tZ. All authors approved the final manuscript of this study protocol.

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22
23 53 **Conflicts of Interests**

24
25 54 The authors declared that there are no potential conflicts of interest with respect
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28 55 to the research, authorship, and/or publication of this study.

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33 57 **Abstract:**

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36 58 Introduction: This clinical trial is designed to evaluate the effect of multiple-dose
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38 59 tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with
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41 60 rheumatoid osteoarthritis (RA).

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44 61 Methods and analysis: A randomized, single-blinded, parallel-controlled study design
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46 62 will be designed. RA patients (age 50-75 years) undergoing unilateral primary
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49 63 end-stage total knee arthroplasty (TKA) will be randomly divided into Group A or
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51 64 Group B. Group A will be treated with one dose of TXA (1g; intravenous injection at
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54 65 the 3rdhour) and Group B with three doses (at the 3rd, 6th, and 12th hours; intravenous
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57 66 injection) after surgery. The primary outcomes will be evaluated with blood loss and
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60 67 haemoglobin level and the secondary outcomes with blood inflammatory factors,

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4 68 serum inflammatory factors, and coagulation parameters.
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6 69 Ethics and dissemination: This study has been approved by the ethics committee, and
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9 70 subsequent modifications of the protocol will be reported and approved by it. All of
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12 71 the participants or their authorised agents will give written informed consent before
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14 72 the study.
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17 73 Ethical number: 2019-K-13.
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20 74 Trial registration number: ChiCTR1900025013
21

22 75 Keywords: Rheumatoid arthritis, tranexamic acid, total knee arthroplasty,
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25 76 perioperative blood management, blood loss, clinical trial protocol.
26

27 28 29 30 78 **Article Summary**

31 32 79 *Strengths and limitations of this trial*

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35 80 (1) This is the first study in China to evaluate the efficacy and safety of
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38 81 perioperative multiple-dose regimen of TXA after TKA in RA patients.

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40 82 (2) The bias of this study reduced dramatically by extensive study design which
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43 83 includes proper randomization, allocation concealment and objective indicator.

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45 84 (3) Long-term follow-ups of some patients can only be conducted by phone.
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47
48 85 (4) The results can only be extrapolated to Chinese RA population.
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50 51 52 53 87 **Introduction**

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56 88 Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like
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58 89 anemia.¹ The overall prevalence of RA is 0.5-1% in Europe and North America,
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4 90 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.²⁻³ Total knee
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7 91 arthroplasty(TKA) is effective in treating flexion contracture and maintaining the
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9 92 stability of RA knee.⁴ About 0.005% of RA patients receive TKA, a rate that has
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12 93 gradually decreased over the past decades. Even though, surgery remains the first
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14 94 choice for articular deformity and pain, despite that disease-modifying antirheumatic
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17 95 drugs(DEMARs) and biologics agents can manage synovitis-related symptoms in
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19 96 RA patients.⁵ The haemorrhage is a major perioperative complications of TKA.⁶
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22 97 Excessive blood loss should be replenished with allogeneic blood transfusion, but it
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25 98 may cause immune complications, prolong hospitalization time and increase the
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28 99 infection rate.⁷⁻⁸ Haemoglobin has an obviously negative correlation with disease
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30 100 activity in RA.⁹ Therefore, we believe that perioperative blood management is need
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33 101 for patients with RA.

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35 102 Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as
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38 103 the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in
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41 104 the knee joint cavity and gets haemolyzed.¹⁰ As this blood is not involved in the blood
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44 105 circulation, HBL often leads to the joint swell, postoperative inflammation and
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47 106 pain.¹¹⁻¹²

48 107 Surgical tourniquet use, can reduce intraoperative bleeding,¹³ provide a clear
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51 108 view during the surgery, and facilitate the connection between the cement, bone and
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54 109 joint prostheses.¹⁴ However, after the release of the tourniquet, local tissue may be
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57 110 damaged by ischemia reperfusion injury, and fibrinolytic system activated.¹⁵⁻¹⁶ As a
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60 111 consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced,

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4 112 and postoperative HBL increased.¹⁵ Therefore, reducing the dissolution of fibrin can
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6 113 reduce postoperative HBL.¹⁷ Tranexamic acid (TXA) is a synthetic lysine derivative
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9 114 that can competitively inhibit the binding between plasminogen and fibrin, prevent the
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12 115 activation of plasminogen, and protect fibrin from degradation and dissolution by
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14 116 plasmin. TXA is initially used in obstetrics and gynaecology, then gradually
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17 117 replicated in surgeries to reduce bleeding and avoid blood transfusion rates.¹⁸⁻¹⁹ The
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19 118 CRASH-2 trial has demonstrated the effectiveness and safety of TXA in reducing
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22 119 blood loss.²⁰ A large amount of literature has reported that TXA can significantly
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25 120 reduce peri-TKA blood loss.²¹⁻²⁵ Currently, TXA is recommended for perioperative
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28 121 blood management of TKA.²⁶ But, its efficacy and safety in RA patients undergoing
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31 122 TKA has been rarely reported.²⁷ TXA can be administered through oral intake, single
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33 123 large-dose intravenous injection, intra-articular injection, joint cavity irrigation,
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35 124 postoperative drainage tube injection, and combination use.^{25,28-31} There is no
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38 125 consensus on the optimal dose and time of TXA administration during perioperative
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41 126 TKA.^{18,32-33} Studies have shown that fibrinolysis peaks at 6 hours and continues for
42
43 127 approximately 18 hours after TKA with tourniquets.³⁴ The half-life of TXA in plasma
44
45 128 is 2 hours, and its concentration peaks at 1 hour after injection.³⁵ Thus, we suspect
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48 129 that a single dose of TXA may not be sufficient to exert an anti-fibrinolytic. There are
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51 130 also studies suggesting that for patients with osteoarthritis, higher doses (within a
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54 131 limit) during the perioperative period can increase the efficacy of TXA.³⁶⁻³⁸ The
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56 132 purpose of this clinical trial is to verify the effectiveness and safety of multiple doses
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59 133 of TXA in reducing perioperative blood loss in RA patients treated with TKA, hoping
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4 134 to find a new mode of perioperative blood management for TKA.
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9 136 **Methods and analysis**

11 137 *Study context*

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15 138 This clinical trial will start on September 1, 2019 at the wards of Shanghai
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17 139 University of Traditional Chinese Medicine Guanghai Hospital (Shanghai,
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19 140 China).The annual surgical number of TKA for RA patients was about 300 in 2018.
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22 141 Eleven investigators include 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20
23
24 142 years of clinical experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM
25
26 143 and SZ), 2 data collectors and who are also statisticians (B-xK and HX) and a nurse
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28 144 (X-rX). Informed consent will be obtained. The perioperative ERAS blood
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30 145 management programme and the trial flow chart are shown in Table 1 and Figure 1.
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32
33 146 The schedule is shown in Table 2.
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38 147 *Sample size calculation*

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40 148 This trial uses a completely randomized design, and multiple sample sizes are
41
42 149 estimated by a previous clinical research review. The main outcome is measured with
43
44 150 the amount of HBL. The overall mean estimate is $\sigma = 320$, and the overall standard
45
46 151 deviation is $\mu = 79$, both estimated by the statistical formula
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51 152 $n = \frac{z^2 \left(\sum_{i=1}^k \sigma_i^2 / k \right) / \left[\sum_{i=1}^k (\mu_i - \mu)^2 / (k-1) \right]}$. Considering a dropout rate of 20%, 76 subjects are
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53 153 required to yield a power of 90% with a significance level of 0.05.
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56 154 *Randomization and allocation concealment*

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4 155 Patients are randomly assigned to two groups according to at 1:1 ratio; SPSS
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6 156 version25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence
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8
9 157 containing 76 random numbers, which are placed into an opaque envelope and put in
10
11
12 158 a computer by encryption. The group data is saved by the statistician. Only the nurse
13
14 159 is allowed to check the enrollment and give the corresponding treatment.

160 *Single-blinded design*

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

164 *Eligibility criteria*

165 The eligibility criteria are set in accordance with the "AMERICAN
166 RHEUMATISM ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS"
167 from the American Journal of Rheumatism (revised in 1978),³⁹ and the 2010
168 "ACR/EULAR classification criteria for rheumatoid arthritis"⁴⁰ (1)The patient is
169 diagnosed with RA in Stage III or IV according to the Kellgren-Lawrence⁴¹
170 classification; (2)The patient is 50 to 75 years old; (3)The patient will undergo the
171 unilateral primary TKA; (4)The patients will receive perioperative anti-fibrinolytic
172 TXA therapy; and (5)The patient will show normal blood-clotting function and no
173 preoperative anaemia.

174 *Exclusion criteria*

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

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4 177 tuberculous arthritis); (2)Bilateral knee arthroplasty (RA patients); (3)Severe
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6 178 cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina
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9 179 pectoris, and heart failure) or cerebrovascular disease (cerebral infarction and cerebral
10
11
12 180 haemorrhage);and (4)Prolonged use of oral anticoagulant drugs (such as aspirin,
13
14 181 warfarin, and clopidogrel).

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16
17 182 *Elimination criteria*

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19
20 183 Eliminated are those with: (1)Acquired color vision disorder; (2)Active
21
22 184 intravascular coagulation patients; and (3)a history of convulsions.

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25 185 *Termination criteria*

26
27 186 The study on one patient will be terminated if he/she shows the following
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29
30 187 events: (1)Shock; (2)Allergic symptoms, such as itching and a rash; (3)Digestive
31
32 188 disorders, such as nausea, vomiting, loss of appetite, and diarrhoea after medication;
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35 189 (4)Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions,
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38 190 visual impairment, and others; and (5)Adverse events, such as intracranial thrombosis
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40 191 and intracranial haemorrhage after medication.

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43 192 *Perioperative anti-rheumatic treatment*

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45 193 Methotrexate and hydroxychloroquine will be used during the perioperative
46
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48 194 period. Leflunomide will be discontinued at one week before surgery. Use of other
49
50 195 disease-modifying antirheumatic drugs (DMARDs) will be discontinued two days
51
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53 196 before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The
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55
56 197 use of newer biologic agents targeting tumor necrosis (TNF- α) will be discontinued
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58 198 for 4 to 5 half-lives before surgery and restarted after wound healing and infection
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4 199 elimination.⁴²⁻⁴³
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7 200 *Surgery and anesthesia*
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9 201 Surgery will be performed by two senior surgeons (L-bX and W-tZ). The
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11 202 operations will be conducted under general anaesthesia. A median incision (14-17 cm
12
13 203 long) is cut in the knee joint with a medial paramedian support band. Internal
14
15 204 positioning is used for femoral bone marrow and external positioning for tibial bone
16
17 205 marrow. All patients will use a tourniquet with a pressure of 230-250 mmHg. During
18
19 206 the operation, blood pressure will be reduced to 20% of the basal level through a
20
21 207 suction drainage tube, and limb surgery will be conducted with an elastic bandage.
22
23 208 During the operation, conventional anti-infective, combined analgesic,
24
25 209 anti-inflammatory, and anti-coagulation treatment and other symptomatic treatments
26
27 210 will be administered according to the "Chinese Hip and Total Knee Arthroplasty
28
29 211 Surgery Perioperative Anti-fibrinolytic Drug Sequential Anticoagulant Application
30
31 212 Programme Expert Consensus". Ten minutes before the incision, 1 g of TXA + 100
32
33 213 mL of intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be
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35 214 administered preoperatively in the sutured joint cavity.
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45 215 TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used
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47 216 according to the second edition of 2015 Chinese Pharmacopoeia and Drug
48
49 217 Supplement Application Approval (2013B02016), YBH07372010; the approval
50
51 218 number is National Drug Standard H43020565.
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56 219 *Intraoperative blood loss*
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58 220 The amount of intraoperative blood loss= the total volume of fluid in the
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4 221 negative pressure drain—the volume of normal saline.
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6 222 *Study interventions*
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9 223 Group A: 1 g of TXA + 100 mL of physiological saline will be injected
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11 224 intravenously at the 3rd hour after the operation. Group B: 1 g of TXA + 100 mL of
12
13 225 physiological saline is intravenously instilled at the 3rd, 6th, and 12th hours after the
14
15 226 operation.
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18 227 *Pain management and rehabilitation*
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21 228 A cocktail injection will be given during the operation, and 0.2 g of oral
22
23 229 celecoxib after surgery for analgesia. After anaesthesia the maximum angles of
24
25 230 flexion and extension of the ankle will be maintained for 6 seconds, and the foot is
26
27 231 relaxed for 5 seconds; the quadriceps contractions are equal between the two sides. At
28
29 232 the first postoperative day, the patients will exercise straight-leg-raise,
30
31 233 supine-knee-flexion and knee flexion and extension in sitting; the machine-assisted
32
33 234 exercises will begin on the third day after surgery, such as continuous passive motion.
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39 235 *Antibiotics*
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41 236 For perioperative prophylaxis, cefazolin sodium antibiotics are administered at
42
43 237 30 minutes before surgery, and 24-48 hours after surgery.
44
45

46 238 *Prevention of lower extremity venous thrombosis*
47
48

49 239 Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day
50
51 240 for 14 days) is injected for preventing deep vein thrombosis.
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54 241

55 242 *Outcomes*
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57 243 *Primary outcomes*
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4 244 *The blood loss, haemoglobin level*

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6 245 The blood loss is calculated according to the formula by Nadle⁴⁴ and Gross

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8
9 246 formula:⁴⁵ Patient's blood volume (PBV)= $K1 \times \text{height}^3(\text{m}^3) + K2 \times \text{weight}(\text{kg}) +$

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11
12 247 $K3$ (Male: $K1=0.3669, K2=0.03219, K3=0.6041$. Female: $K1=0.3561, K2=0.03308,$

13
14
15 248 $K3=0.1833$). Total blood loss (TBL)= $\text{PBV} \times (\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}})$. HBL= $\text{PBV} \times (\text{Hct}_{\text{pre}} -$

16
17 249 $\text{Hct}_{\text{post}}) / \text{Hct}_{\text{ave}}$.

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19
20 250 Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will calculate the

21
22 251 HBL based on the value of haematocrit and recorded the count of haemoglobin.

23
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25 252 *Secondary outcomes*

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27 253 *Inflammatory index, inflammatory factor and coagulation index*

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30 254 Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the

31
32 255 erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole

33
34
35 256 blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF- α in the plasma.

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37
38 257 Whole blood test indicators and plasma inflammatory factors will be assessed in the

39
40 258 participating hospital (Department of Clinical Laboratory of Guanghua Hospital of

41
42
43 259 Integrated Traditional Chinese Medicine and Western Medicine). The indicators and

44
45 260 factors will be tested by an inspector who is not involved in this clinical trial.

46
47
48 261 *Knee function and swelling*

49
50 262 Knee function will be measured using the American Keen Society Score (AKSS)

51
52
53 263 at one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained

54
55
56 264 researcher will educate all patients until they fully know how to assess their knee

57
58
59 265 function through the questionnaires. The rate of swelling is defined as the

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4 266 postoperative circumference of the upper tibia ÷ the preoperative circumference of the
5
6 267 upper tibia.

8
9 268 *Adverse events*

11 269 Adverse events include (1)Deep vein thrombosis⁴⁶ (acute onset, affected limb
12 swelling, sever pain, or significant tenderness at the femoral triangle or/and leg);
13
14 270 (2)Extensive swelling on the affected limb; (3)A dull red color and a rise in the skin
15
16 271 of the affected limb; (4)Generalized shallow venous tension on the affected limb;
17
18 272 (5)In the skin of the affected limb; (6)Pulmonary embolism diagnosed by Doppler
19
20 273 ultrasound and venography (clinical manifestations: cough, chest tightness,
21
22 274 palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased
23
24 275 respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism
25
26 276 diagnosed by CT.
27
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34
35 278 The wound healing process and complications⁴⁷ (wound bleeding, haematoma,
36
37 279 wound infection, and deep infection) will be observed and recorded in the patient's
38
39 280 case report forms (CRFs) during hospitalization and follow-ups. Wound exudation is
40
41 281 defined as the presence of exudation from the wound even 48 hours after surgery.
42
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45 282 *Adverse event treatment*

47 283 Adverse events during the follow-up will be recorded in the CRFs, and their
48
49 284 relevance to drug use will be evaluated. All the adverse events will be classified in
50
51 285 accordance with the five-level scoring systems (5.0) of the CTCAE.
52
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54 286 Serious adverse events are defined as those that may cause cancer, defects,
55
56 287 teratogenicity, death, and permanent damage to organ function, permanent or
57
58 288 significant disability, and prolonged hospital stay. In any event, the researcher should
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3 289 immediately take appropriate measures and report it to the hospital and ethics
4
5 290 committees within 24 hours.
6

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8 291 *Data management* >
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10 292 Data on the CRFs will be put in the computer by two independent trained
11
12 293 research assistants with a double-entry method. The hospital's independent
13
14 294 investigators will check the data periodically.
15

16
17 295 *Statistical analysis*
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19 296 The analyses are as follows: (1)Descriptive analysis on the characteristics of the
20
21 297 study participants; (2)Balance analysis on the baseline values in groups;
22
23 298 (3)Comparison of the balance between groups of primary outcomes; and
24
25 299 (4)Comparison of secondary outcomes and safety between groups.
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29 300 The total rate of adverse events of the two groups are tested by bidirectional
30
31 301 disordered R*C list chi-square test. The association between the incidence of adverse
32
33 302 events and the dose of TXA used is described.
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36

37 303 *Ethics and dissemination*
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39 304 Written inform consent will be obtained from all participants or their authorised
40
41 305 agents before the study. All TXA treatments will be free. Research data will be kept
42
43 306 strictly confidential and obtained from appropriate authors upon reasonable
44
45 307 request .Results of the trial will be published on the website of the China Clinical
46
47 308 Trials Registry and in peer-reviewed journals.
48
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51
52 309 *The Patient and Public Involvement*
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55 310 Patients and public will not be involved in the development of the research
56
57 311 question or in the design of the study. Patients will receive oral and written
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4 312 information about this trial, pertaining to the benefits, risks and discomforts that they
5
6 313 may get from the study. They will not be involved in the recruitment and conduct of
7
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9 314 the study. Besides, the burden of the intervention will be assessed by patients
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11 315 themselves. After signing an informed consent, they will be assessed for eligibility
12
13
14 316 and data will be collected. Dissemination of the general results (no personal data) will
15
16
17 317 be made on demand.

18 19 318 **Discussion**

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23 319 Controlling blood loss can facilitate the recovery from TKA surgery. Previous
24
25 320 clinical studies have shown that high dose of TXA can reduce blood loss after TKA in
26
27 321 patients with osteoarthritis.^{27,47-48} In this trial, we will exclude patients with a large
28
29 322 number of intravenous infusions to eliminate the effect of blood dilution on the results.
30
31 323 We will use a tourniquet to minimize the blood loss during the operation. Therefore,
32
33 324 what we will observed is the blood loss after the removal of tourniquet.¹⁰ It has been
34
35 325 reported that intravenous infusion combined with intra-articular injection of TXA may
36
37 326 be the optimal bleeding-control scheme.⁴⁹⁻⁵⁰ Previous studies have shown that knee
38
39 327 joint swelling after TKA is associated with HBL in the joint cavity. TXA can reduce
40
41 328 postoperative HBL, thereby relieving the swelling around the joint.⁵¹ Given that
42
43 329 plasminogen activators play an important role in RA-involved inflammation, the
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45 330 dissolution of fibrin will trigger an inflammatory response.⁵² Therefore, we suspect
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47 331 that multiple doses of TXA in the peroperative period may exert an auxiliary
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49 332 anti-inflammatory effect.
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4 333 This study will provide new evidence for managing perioperative HBL in TKA
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6 334 in Chinese RA patients.
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11 336 **Acknowledgment:**
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15 337 The authors thank all the patient advisers for participating in this study.
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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.

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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.

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

500 TXA, tranexamic acid.

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

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

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	SURGERY, Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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

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4 45 **ASBTRACT:**
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6 46 **Introduction** This clinical trial is designed to evaluate the effect of multiple-dose
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9 47 tranexamic acid (TXA) on perioperative hidden blood loss (HBL) in patients with
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12 48 rheumatoid osteoarthritis (RA).
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14 49 **Methods and analysis** A randomized, single-blinded, parallel-controlled study will
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16
17 50 be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage
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20 51 total knee arthroplasty (TKA) will be randomly divided into Group A or Group B.
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22 52 Group A will be treated with one dose of TXA (1g; intravenous injection at the 3rd
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25 53 hour) and Group B with three doses (at the 3rd, 6th, and 12th hours; intravenous
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28 54 injection) after surgery. The primary outcomes will be evaluated with blood loss and
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31 55 haemoglobin level and the secondary outcomes with blood inflammatory factors,
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33 56 serum inflammatory factors, and coagulation parameters.
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35 57 **Ethics and dissemination** This study has been approved by the ethics committee, and
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38 58 subsequent modifications of the protocol will be reported and approved by it. All of
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40
41 59 the participants or their authorised agents will give written informed consent before
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44 60 the study.

45 61 **Trial registration number** ChiCTR1900025013; Pre-results.
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48 62 **Article Summary**
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50 63 Strengths and limitations of this trial
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52
53 64 (1) This is the first study in China to evaluate the efficacy and safety of perioperative
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56 65 multiple-dose regimen of TXA after TKA in RA patients.
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4 66 (2) The bias of this study reduced dramatically by extensive study design which
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6 67 includes proper randomization, allocation concealment and objective indicator.
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9 68 (3) Long-term follow-ups of some patients can only be conducted by phone.
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12 69 (4) The results can only be extrapolated to Chinese RA population.
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21 72 **INTRODUCTION**

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23 73 Rheumatoid arthritis (RA) may be accompanied by hematological diseases, like
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25 74 anemia.¹ The overall prevalence of RA is 0.5-1% in Europe and North America,
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27 75 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.^{2 3} Total knee
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29 76 arthroplasty (TKA) is effective in treating flexion contracture and maintaining the
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31 77 stability of RA knee.⁴ About 0.005% of RA patients receive TKA, a rate that has
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33 78 gradually decreased over the past decades. Even though, surgery remains the first
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35 79 choice for articular deformity and pain, despite that disease-modifying antirheumatic
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37 80 drugs (DMARDs) and biologics agents can manage synovitis-related symptoms in
38
39 81 RA patients.⁵ The haemorrhage is a major perioperative complications of TKA.⁶
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41
42 82 Excessive blood loss should be replenished with allogeneic blood transfusion, but it
43
44 83 may cause immune complications, prolong hospitalization time and increase the
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46 84 infection rate.^{7 8} Haemoglobin has an obviously negative correlation with disease
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48 85 activity in RA.⁹ Therefore, we believe that perioperative blood management is need
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53 86 for patients with RA.

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57 87 Accounting for 50% of the total blood loss, hidden blood loss (HBL) happens as
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59 88 the blood lost infiltrates into the tissue intraoperatively and postoperatively, resides in

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4 89 the knee joint cavity and gets haemolyzed.¹⁰ As this blood is not involved in the blood
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7 90 circulation, HBL often leads to the joint swell, postoperative inflammation and pain.¹¹
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9 91 ¹²

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11 92 Surgical tourniquet use, can reduce intraoperative bleeding,¹³ provide a clear
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14 93 view during the surgery, and facilitate the connection between the cement, bone and
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17 94 joint prostheses.¹⁴ However, after the release of the tourniquet, local tissue may be
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20 95 damaged by ischemia reperfusion injury, and fibrinolytic system activated.^{15 16} As a
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23 96 consequence, peripheral blood circulation is accelerated, plasma fibrinolysis enhanced,
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26 97 and postoperative HBL increased.¹⁵ Therefore, reducing the dissolution of fibrin can
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29 98 reduce postoperative HBL.¹⁷

30 99 Tranexamic acid (TXA) is a synthetic lysine derivative that can competitively
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33 100 inhibit the binding between plasminogen and fibrin, prevent the activation of
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36 101 plasminogen, and protect fibrin from degradation and dissolution by plasmin. TXA is
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39 102 initially used in obstetrics and gynaecology, then gradually replicated in surgeries to
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42 103 reduce bleeding and avoid blood transfusion rates.^{18 19} The CRASH-2 trial has
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45 104 demonstrated the effectiveness and safety of TXA in reducing blood loss.²⁰ A large
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48 105 amount of literature has reported that TXA can significantly reduce peri-TKA blood
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51 106 loss.²¹⁻²⁵ Currently, TXA is recommended for perioperative blood management of
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54 107 TKA.²⁶ But, its efficacy and safety in RA patients undergoing TKA has been rarely
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56
57 108 reported.²⁷ TXA can be administered through oral intake, single large-dose
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60 109 intravenous injection, intra-articular injection, joint cavity irrigation, postoperative
110 110 drainage tube injection, and combination use.^{25 28-31} There is no consensus on the

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4 111 optimal dose and time of TXA administration during perioperative TKA.^{18 32 33}
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6 112 Studies have shown that fibrinolysis peaks at 6 hours and continues for approximately
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9 113 18 hours after TKA with tourniquets.³⁴ The half-life of TXA in plasma is 2 hours, and
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12 114 its concentration peaks at 1 hour after injection.³⁵ Thus, we suspect that a single dose
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14 115 of TXA may not be sufficient to exert an anti-fibrinolytic. There are also studies
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17 116 suggesting that for patients with osteoarthritis, higher doses (within a limit) during the
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19 117 perioperative period can increase the efficacy of TXA.³⁶⁻³⁸ The purpose of this clinical
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22 118 trial is to verify the effectiveness and safety of multiple doses of TXA in reducing
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24 119 perioperative blood loss in RA patients treated with TKA, hoping to find a new mode
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27 120 of perioperative blood management for TKA.
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35 123 **METHODS AND ANALYSIS**

36 37 124 **Study context**

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40 125 This clinical trial will start on September 1, 2019 at the wards of Shanghai University
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42 126 of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China). The annual
43
44 127 surgical number of TKA for RA patients was about 300 in 2018. Eleven investigators
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46
47 128 include 2 senior orthopaedic surgeons (L-bX, W-tZ) with 20 years of clinical
48
49 129 experience and 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM and SZ), 2 data
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51 130 collectors and who are also statisticians (B-xK and HX) and a nurse (X-rX). Informed
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54 131 consent will be obtained. The perioperative ERAS blood management programme and
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57 132 the trial flow chart are shown in Table 1 and Figure 1. The schedule is shown in Table
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9 135 **Sample size calculation**
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11 136 This trial uses a completely randomized design, and multiple sample sizes are
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14 137 estimated by a previous clinical research review.²⁵ The main outcome is measured
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16
17 138 with the amount of HBL. The the overall standard deviation is $\sigma = 250$, and allowable
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20 139 error estimate is $\delta = 200$, both estimated by the statistical formula

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23 140 $n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2} + Z_{\beta}) / \sigma}{\delta} \right]^2$. Considering a dropout rate of 10%, 104 subjects are required
24
25
26 141 to yield a power of 90% with a significance level of 0.05.
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31 143 **Randomization and allocation concealment**
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34 144 Patients will be randomly assigned to two groups according to at 1:1 ratio; SPSS
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36 145 version 25.0 (IBM Corporation, Armonk, NY) is used to generate a random sequence
37
38
39 146 containing 104 random numbers, which will be placed into an opaque envelope and
40
41
42 147 put in a computer by encryption. The group data is saved by the statistician. Only the
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44 148 nurse is allowed to check the enrollment and give the corresponding treatment.
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49 150 **Single-blinded design**
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52 151 Only the nurse will be allowed to know the patients' enrollment and give them
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54 152 corresponding treatment. The outcome evaluators will objectively record the patients'
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57 153 test results.
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4 155 **Eligibility criteria**
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6 156 The eligibility criteria are set in accordance with the “AMERICAN RHEUMATISM
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9 157 ASSOCIATION CRITERIA FOR RHEUMATOID ARTHRITIS” from the American
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12 158 Journal of Rheumatism (revised in 1978),³⁹ and the 2010 “ACR/EULAR classification
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14 159 criteria for rheumatoid arthritis”.⁴⁰ (1) The patient is diagnosed with RA in Stage III
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17 160 or IV according to the Kellgren-Lawrence⁴¹ classification; (2) The patient is 50 to 75
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20 161 years old; (3) The patient will undergo the unilateral primary TKA; (4) The patient
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22 162 will receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient will
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25 163 show normal blood-clotting function and no preoperative anaemia.
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30 165 **Exclusion criteria**
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32 166 (1) Other types of arthritis (such as primary arthritis, post-traumatic osteoarthritis,
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34 167 gouty osteoarthritis, haemophilic osteoarthritis, and tuberculous arthritis); (2) Bilateral
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37 168 knee arthroplasty (RA patients); (3) Severe cardiovascular disease (such as
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43 170 cerebrovascular disease (cerebral infarction and cerebral haemorrhage); and (4)
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45 171 Prolonged use of oral anticoagulant drugs (such as aspirin, warfarin, and clopidogrel).
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50 173 **Elimination criteria**
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53 174 (1) Acquired color vision disorder; (2) Active intravascular coagulation patients; and
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56 175 (3) a history of convulsions.
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4 177 **Termination criteria**

5
6 178 (1) Shock; (2) Allergic symptoms, such as itching and a rash; (3) Digestive disorders,
7
8
9 179 such as nausea, vomiting, loss of appetite, and diarrhoea after medication; (4)
10
11 180 Reactive dermatitis, dizziness, hypotension, drowsiness, headache; convulsions,
12
13
14 181 visual impairment, and others; and (5) Adverse events, such as intracranial thrombosis
15
16
17 182 and intracranial haemorrhage after medication.
18
19
20 183

21
22 184 **Perioperative anti-rheumatic treatment**

23
24 185 Methotrexate and hydroxychloroquine will be used during the perioperative period.
25
26
27 186 Leflunomide will be discontinued at one week before surgery. Use of other
28
29
30 187 disease-modifying antirheumatic drugs (DMARDs) will be discontinued two days
31
32 188 before surgery, and restarted at 1-2 days after gastrointestinal function recovery. The
33
34
35 189 use of newer biologic agents targeting tumor necrosis (TNF- α) will be discontinued
36
37
38 190 for 4 to 5 half-lives before surgery and restarted after wound healing and infection
39
40 191 elimination.^{42 43}

41
42
43 192
44
45 193 **Surgery and anesthesia**

46
47
48 194 Surgery will be performed by two senior surgeons (L-bX and W-tZ). The operations
49
50
51 195 will be conducted under general anaesthesia. A median incision (14-17 cm long) is cut
52
53 196 in the knee joint with a medial paramedian support band. Internal positioning is used
54
55
56 197 for femoral bone marrow and external positioning for tibial bone marrow. All patients
57
58 198 will use a tourniquet with a pressure of 230-250 mmHg. During the operation, blood
59
60

1
2
3
4 199 pressure will be reduced to 20% of the basal level through a suction drainage tube,
5
6
7 200 and limb surgery will be conducted with an elastic bandage. During the operation,
8
9
10 201 conventional anti-infective, combined analgesic, anti-inflammatory, and
11
12 202 anti-coagulation treatment and other symptomatic treatments will be administered
13
14 203 according to the "Chinese Hip and Total Knee Arthroplasty Surgery Perioperative
15
16
17 204 Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert
18
19
20 205 Consensus". Ten minutes before the incision, 1 g of TXA + 100 mL of
21
22 206 intravenous-saline and 1.5 g of TXA + 50 mL articular-injection saline will be
23
24
25 207 administered preoperatively in the sutured joint cavity.

26
27 208 TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used
28
29
30 209 according to the second edition of 2015 Chinese Pharmacopoeia and Drug
31
32
33 210 Supplement Application Approval (2013B02016), YBH07372010; the approval
34
35
36 211 number is National Drug Standard H43020565.
37
38
39

40 213 **Intraoperative blood loss**

41
42
43 214 The amount of intraoperative blood loss = the total volume of fluid in the negative
44
45
46 215 pressure drain - the volume of normal saline.
47

48 216

49 50 217 **Study interventions**

51
52
53 218 Group A: 1 g of TXA + 100 mL of physiological saline will be injected intravenously
54
55
56 219 at the 3rd hour after the operation. Group B: 1 g of TXA + 100 mL of physiological
57
58
59 220 saline is intravenously instilled at the 3rd, 6th, and 12th hours after the operation.
60

1
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3 221
45 222 **Pain management and rehabilitation**

6
7
8 223 A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib
9
10
11 224 after surgery for analgesia. After anaesthesia the maximum angles of flexion and
12
13
14 225 extension of the ankle will be maintained for 6 seconds, and the foot is relaxed for 5
15
16
17 226 seconds; the quadriceps contractions are equal between the two sides. At the first
18
19 227 postoperative day, the patients will exercise straight-leg-raise, supine-knee-flexion
20
21
22 228 and knee flexion and extension in sitting; the machine-assisted exercises will begin on
23
24 229 the third day after surgery, such as continuous passive motion.
25

26 230

27
28 231 **Antibiotics**

29
30 232 For perioperative prophylaxis, cefazolin sodium antibiotics are administered at 30
31
32
33 233 minutes before surgery, and 24-48 hours after surgery.
34

35 234

36
37 235 **Prevention of lower extremity venous thrombosis**

38
39
40 236 Six hours after the surgery, perioperative enoxaparin sodium (60mg, once a day for 14
41
42
43 237 days) is injected for preventing deep vein thrombosis.
44

45 238

46
47 239 **Outcomes**

48
49
50 240 Primary outcomes

51
52
53 241 *The blood lose, haemoglobin level*

54
55 242 The blood loss is calculated according to the formula by Nadle⁴⁴ and Gross formula:⁴⁵

56
57
58 243 Patient's blood volume (PBV) = K1 × height³ (m³) + K2 × weight (kg) + K3 (Male:
59
60

1
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3
4 244 $K1 = 0.3669, K2 = 0.03219, K3 = 0.6041$. Female: $K1 = 0.3561, K2 = 0.03308, K3 =$
5
6 245 0.1833). Total blood loss (TBL) = $PBV \times (Hct_{pre} - Hct_{post})$. HBL = $PBV \times (Hct_{pre} -$
7
8
9 246 $Hct_{post}) / Hct_{ave}$. Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will
10
11
12 247 calculate the HBL based on the value of haematocrit and recorded the count of
13
14 248 haemoglobin.

15
16
17 249
18
19 250 Secondary outcomes

20
21 251 *Inflammatory index, inflammatory factor and coagulation index*

22
23
24 252 Preoperatively, at the 1st, 3rd, 7th and 14th days after surgery, we will record the
25
26
27 253 erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the whole
28
29
30 254 blood and interleukin 6 (IL-6), interleukin 12 (IL-12), and TNF- α in the plasma.
31
32 255 Whole blood test indicators and plasma inflammatory factors will be assessed in the
33
34
35 256 participating hospital (Department of Clinical Laboratory of Guanghua Hospital of
36
37 257 Integrated Traditional Chinese Medicine and Western Medicine). The indicators and
38
39
40 258 factors will be tested by an inspector who is not involved in this clinical trial.

41
42
43 259
44
45 260 *Knee function and swelling*

46
47
48 261 Knee function will be measured using the American Keen Society Score (AKSS) at
49
50
51 262 one day before surgery and at the 3rd, 7th and 14th days after surgery. A trained
52
53
54 263 researcher will educate all patients until they fully know how to assess their knee
55
56
57 264 function through the questionnaires. The rate of swelling is defined as the
58
59
60 265 postoperative circumference of the upper tibia divide by the preoperative

1
2
3
4 266 circumference of the upper tibia.
5

6
7 267
8

9 268 *Adverse events*

10
11 269 Adverse events include (1) Deep vein thrombosis⁴⁶ (acute onset, affected limb
12
13
14 270 swelling, sever pain, or significant tenderness at the femoral triangle or/and leg); (2)
15
16
17 271 Extensive swelling on the affected limb; (3) A dull red color and a rise in the skin of
18
19
20 272 the affected limb; (4) Generalized shallow venous tension on the affected limb; (5) In
21
22
23 273 the skin of the affected limb; (6) Pulmonary embolism diagnosed by Doppler
24
25 274 ultrasound and venography (clinical manifestations: cough, chest tightness,
26
27 275 palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis, increased
28
29
30 276 respiratory rate, arteriovenous filling or pulsation, etc.) and pulmonary embolism
31
32
33 277 diagnosed by CT. The wound healing process and complications⁴⁷ (wound bleeding,
34
35 278 haematoma, wound infection, and deep infection) will be observed and recorded in
36
37
38 279 the patient's case report forms (CRFs) during hospitalization and follow-ups. Wound
39
40
41 280 exudation is defined as the presence of exudation from the wound even 48 hours after
42
43 281 surgery.
44

45
46 282
47

48 283 *Adverse event treatment*

49
50 284 Adverse events during the follow-up will be recorded in the CRFs, and their relevance
51
52 285 to drug use will be evaluated. All the adverse events will be classified in accordance
53
54 286 with the five-level scoring systems (5.0) of the CTCAE. Serious adverse events are
55
56
57 287 defined as those that may cause cancer, defects, teratogenicity, death, and permanent
58
59 288 damage to organ function, permanent or significant disability, and prolonged hospital
60

1
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3 289 stay. In any event, the researcher should immediately take appropriate measures and
4
5 290 report it to the hospital and ethics committees within 24 hours.
6
7

8 291

9 292 **Data management**

10 293 Data on the CRFs will be put in the computer by two independent trained research
11
12 294 assistants with a double-entry method. The hospital's independent investigators will
13
14 295 check the data periodically.
15
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18

19 296

20 297 **Statistical analysis**

21 298 (1) Descriptive analysis on the characteristics of the study participants; (2) Balance
22
23 299 analysis on the baseline values in groups; (3) Comparison of the balance between
24
25 300 groups of primary outcomes; and (4) Comparison of secondary outcomes and safety
26
27 301 between groups. The total rate of adverse events of the two groups are tested by
28
29 302 bidirectional disordered R*C list chi-square test. The association between the
30
31 303 incidence of adverse events and the dose of TXA used is described.
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38 304

39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 305 **Ethics and dissemination**

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

311

312 **The Patient and public involvement**

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4 313 Patients and public will not be involved in the development of the research question
5
6 314 or in the design of the study. Patients will receive oral and written information about
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8
9 315 this trial, pertaining to the benefits, risks and discomforts that they may get from the
10
11
12 316 study. Besides, the burden of the intervention will be assessed by patients themselves.
13
14 317 Dissemination of the general results (no personal data) will be made on demand.
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22 23 24 320 **DISCUSSION**

25
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28 321 Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical
29
30 322 studies have shown that high dose of TXA can reduce blood loss after TKA in
31
32 323 patients with osteoarthritis.^{25 47 48} Based on previous research,²⁵ we will set the
33
34 324 patient's age between 50-75 to improve the quality of study. In this trial, we will
35
36 325 exclude patients with a large number of intravenous infusions to eliminate the effect
37
38 326 of blood dilution on the results. We will use a tourniquet to minimize the blood loss
39
40
41 327 during the operation. Therefore, what we will observed is the blood loss after the
42
43 328 removal of tourniquet.¹⁰ It has been reported that intravenous infusion combined with
44
45 329 intra-articular injection of TXA may be the optimal bleeding-control scheme.^{49 50}
46
47
48 330 Previous studies have shown that knee joint swelling after TKA is associated with
49
50 331 HBL in the joint cavity. TXA can reduce postoperative HBL, thereby relieving the
51
52 332 swelling around the joint.⁵¹ Given that plasminogen activators play an important role
53
54 333 in RA-involved inflammation, the dissolution of fibrin will trigger an inflammatory
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4 334 response.⁵² Therefore, we suspect that multiple doses of TXA in the perioperative
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6
7 335 period may exert an auxiliary anti-inflammatory effect.
8

9 336 This study will provide new evidence for managing perioperative HBL in TKA
10
11 337 in Chinese RA patients.
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18
19 340 **Author Contributions** B-xK, HX and L-bX conceived the study while B-xK and HX
20
21
22 341 drafted the study protocol, B-xK and HX contributed equally to this work and should
23
24
25 342 be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX,
26
27
28 343 S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study
29
30 344 protocol.
31

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33
34 346 planning Commission of Shanghai (Grant NO. ZY (2018-2020)-FWTX-6023).
35

36 347 **Conflicts of Interests** The authors declared that there are no potential conflicts of
37
38
39 348 interest with respect to the research, authorship, and/or publication of this study.
40

41 349 **Patient consent for publication** Obtained.
42
43

44 350 **Ethics approval** This study has been approved by the ethics committee Shanghai
45
46
47 351 Guanghua Hospital of Integrated Traditional Chinese Medicine and Western
48
49
50 352 Medicine (approval NO. 2019-K-13), and any modification of the protocol will be
51
52
53 353 reported and approved by it.
54

55 354 **Provenance and peer review** Not commissioned; externally peer reviewed.
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57 355
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60 356

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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

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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.

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14 **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		•	•	•	•

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

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

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497 tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th
498 day after surgery; D14, the 14th day after surgery.
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For peer review only

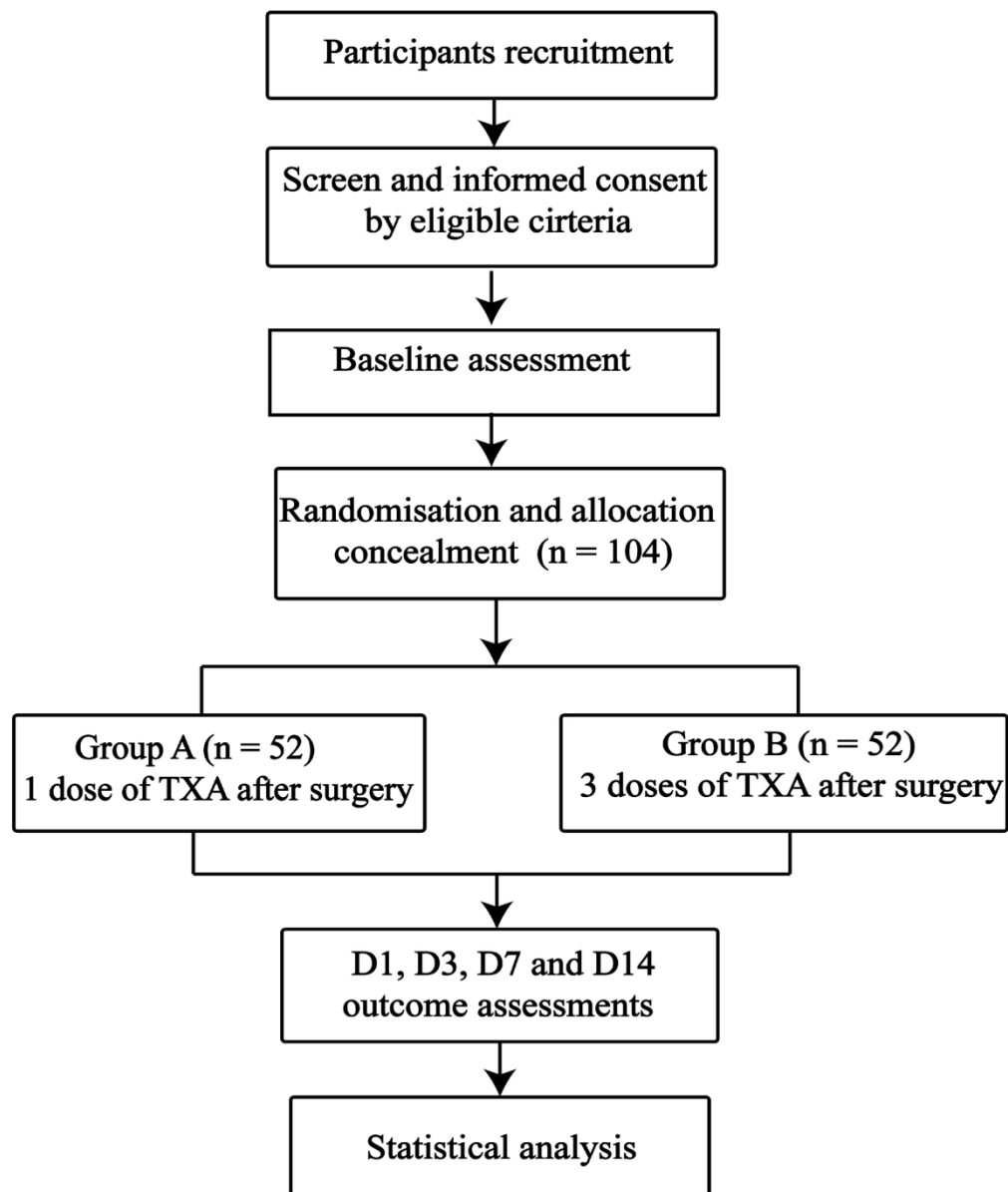


Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA, tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

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

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

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	orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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4 1 **Multiple-dose tranexamic acid for perioperative blood loss in total knee**
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6 2 **arthroplasty in patients with rheumatoid arthritis : A single-blinded,**
7
8 3 **randomized, parallel-controlled study protocol**

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58 45 **ABSTRACT**

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4 46 **Introduction** This clinical trial is designed to evaluate the effect of multiple-dose
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6 47 tranexamic acid (TXA) on perioperative blood loss in patients with rheumatoid
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9 48 arthritis (RA).

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11 49 **Methods and analysis** A randomized, single-blinded, parallel-controlled study will
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14 50 be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage
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17 51 total knee arthroplasty will be randomly divided into Group A or Group B. Group A
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20 52 will be treated with one dose of TXA (1 g; intravenous injection 3 hours post-surgery)
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23 53 and Group B with three doses (1 g; intravenous injection at 3, 6, and 12 hours
24
25 54 post-surgery) after surgery. The primary outcomes will be evaluated with blood loss,
26
27 55 maximum haemoglobin drop, and transfusion rate. The secondary outcomes will be
28
29
30 56 evaluated with knee function and complications.

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32 57 **Ethics and dissemination** This study has been approved by the ethics committee, and
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35 58 subsequent modifications of the protocol will be reported and approved by it. All of
36
37
38 59 the participants or their authorised agents will give written informed consent before
39
40
41 60 the study.

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43 61 **Trial registration number** ChiCTR1900025013; Pre-results.

44 45 62 **Article Summary**

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48 63 Strengths and limitations of this trial

49
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51 64 (1) This is the first study in China to evaluate the efficacy and safety of a
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54 65 perioperative multiple-dose regimen of tranexamic acid during total knee arthroplasty
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56 66 in rheumatoid arthritis patients.

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4 67 (2) The bias of this study was reduced dramatically by the extensive study design,
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6 68 which included proper randomization, allocation concealment, and objective
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9 69 indications.
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12 70 (3) The short follow-up time, may be insufficient in fully assessing the risk of
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14 71 complications in a multiple-dose regimen of tranexamic acid during total knee
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17 72 arthroplasty in rheumatoid arthritis patients.
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75 INTRODUCTION

26
27 76 Rheumatoid arthritis (RA) may be accompanied by haematological diseases such as
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30 77 anaemia.^[1] The overall prevalence of RA is 0.5-1% in Europe and North America,
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32
33 78 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.^[2,3] Total knee
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35 79 arthroplasty (TKA) is effective in treating flexion contractures and maintaining the
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38 80 stability of knees effected by RA.^[4] About 0.005% of RA patients receive TKA, a rate
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41 81 that has gradually decreased over the past decades. However, surgery remains the first
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44 82 choice for articular deformity and pain, despite the fact that disease-modifying
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47 83 antirheumatic drugs and biologics agents can manage synovitis-related symptoms in
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50 84 RA patients.^[5] Haemorrhage is a major perioperative complication of TKA.^[6]
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52
53 85 Excessive blood loss should be treated with an allogeneic blood transfusion, but this
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56 86 has adverse effects such as immune complications, prolong hospitalization time, and
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59 87 increased infection rate.^[7,8] Haemoglobin has a negative correlation with disease
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88 88 activity in RA.^[9] Therefore, we believe that perioperative blood loss management is

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4 89 needed for patients with RA.
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6 90 Accounting for approximately 50% of the total blood loss, hidden blood loss (HBL)
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9 91 is the blood lost as infiltrates into the tissue intraoperatively and postoperatively. This
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12 92 blood resides in the knee joint cavity before being haemolyzed.^[10] HBL often leads to
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15 93 the joint swelling, postoperative inflammation, and pain.^[11,12]
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17 94 Use of a surgical tourniquet can reduce intraoperative bleeding,^[13] provide a clear
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20 95 view during the surgery, and facilitate the connection between the cement, bone and
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23 96 joint prostheses.^[14] However, after the release of the tourniquet, local tissue may be
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26 97 damaged by ischemic reperfusion injury, and the fibrinolytic system may be
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29 98 activated.^[15,16] As a consequence, peripheral blood circulation can be accelerated,
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32 99 plasma fibrinolysis enhanced, and postoperative HBL increased.^[15] Therefore,
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35 100 reducing the dissolution of fibrin can reduce postoperative HBL.^[17]
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37 101 Tranexamic acid (TXA) is a synthetic lysine derivative that competitively inhibits
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40 102 the binding between plasminogen and fibrin, prevents the activation of plasminogen,
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43 103 and protects fibrin from degradation and dissolution by plasmin. TXA was initially
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46 104 used in obstetric and gynaecologic surgery, and its use was then gradually replicated
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49 105 in other surgeries to reduce bleeding and blood transfusion rates.^[18,19] The CRASH-2
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52 106 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.^[20]
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55 107 A large amount of literature has reported that TXA can significantly reduce peri-TKA
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58 108 blood loss.^[21-25] Currently, TXA is recommended for perioperative management of
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61 109 blood loss during TKA.^[26] However, its efficacy and safety in RA patients undergoing
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64 110 TKA has rarely been reported.^[27] TXA can be administered through oral intake, a
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4 111 single large-dose intravenous injection, an intra-articular injection, joint cavity
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6 112 irrigation, postoperative drainage tube injection, or through a combination of these
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9 113 methods.^[25,28-30] There is no consensus on the optimal dosage and timing of
10
11 114 perioperative TXA administration for TKA.^[18,31,32] Studies have shown that
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13 115 fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKAs
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15 116 that were performed with tourniquets.^[33] The half-life of TXA in the plasma is 2
16
17 117 hours, and its concentration peaks at 1 hour after injection.^[34] Thus, we suspect that a
18
19 118 single dose of TXA may not be sufficient to exert an anti-fibrinolytic effect. There are
20
21 119 also studies suggesting that, for patients with osteoarthritis, higher doses (within the
22
23 120 normal range) during the perioperative period can increase the efficacy of TXA.^[35,36]
24
25 121 The purpose of this clinical trial is to verify the effectiveness and safety of multiple
26
27 122 doses of TXA in reducing perioperative blood loss in RA patients treated with TKA,
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29 123 in order to determine a new strategy for management of perioperative blood loss
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31 124 during TKA.
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42 127 **METHODS AND ANALYSIS**

43 128 **Study context**

44 129 This clinical trial was initiated on 1 September 2019 in the wards of Shanghai
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46 130 University of Traditional Chinese Medicine Guanghua Hospital (Shanghai, China).
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48 131 The annual number of TKA cases performed in RA patients was about 300 in 2018.
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50 132 Eleven investigators will be involved in this study including 2 senior orthopaedic
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52 133 surgeons (L-bX, W-tZ) with 20 years of clinical experience, 6 orthopaedic physicians

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4 134 (C-xG, JZ, JX, S-sT, Y-hM, and SZ), 2 data collectors who are also statisticians
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7 135 (B-xK and HX), and a nurse (X-rX). Informed consent will be obtained from all
8
9
10 136 patients. The perioperative ERAS blood management programme and the trial flow
11
12 137 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.

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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.

139

140 Sample size calculation

141 This study uses a completely randomized trial design. Multiple sample sizes will
 142 evaluated by a review of previously conducted clinical research.^[25] The primary
 143 outcome will be measured with the amount of HBL, dependent on TXA therapy. The
 144 overall standard deviation is $\sigma = 250$, and the allowable error estimate is $\delta = 200$.

145 These values were estimated using the statistical formula
$$n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{\delta^2} \right]$$
.

146 Predicting an estimated dropout rate of 10%, 104 subjects will be required to yield a

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4 147 power of 90% with a significance level of 0.05.
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8 149 **Randomization and allocation concealment**
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11 150 Patients will be randomly assigned to two groups (1:1 ratio). This will be done by
12
13 151 assigning each patient a number from 1 to 104. SPSS version 25.0 (IBM Corporation,
14
15
16 152 Armonk, NY) will be used to generate a random sequence containing the numbers 1
17
18 153 to 104, dividing these numbers in two groups. These group lists will be placed in an
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20
21 154 opaque envelope and put into a computer by encryption. The group data will be saved
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24 155 by the statistician. Only the nurse will be allowed to check the enrolment and give the
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27 156 corresponding treatment.
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34 158 **Single-blinded design**
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38 159 Only the nurse will be allowed to know the patients' enrolment and give them the
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41 160 corresponding treatment. The outcome evaluators will objectively record the patients'
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43 161 test results.
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48 163 **Eligibility criteria**
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50
51 164 The eligibility criteria have been set in accordance with the 'American Rheumatism
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53 165 Association criteria for rheumatoid arthritis'^[37] and the 2010 'ACR/EULAR
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55
56 166 classification criteria for rheumatoid arthritis'.^[38] The eligibility criteria are as follows:
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59 167 (1) The patient must have been diagnosed with RA in Stage III or IV according to the
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4 168 Kellgren-Lawrence classification;^[39] (2) The patient must be 50 to 75 years old; (3)
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7 169 The patient must be willing to undergo the unilateral primary TKA; (4) The patient
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9 170 must receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient must
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12 171 show normal blood-clotting function and must not have preoperative anaemia.
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16 173 **Exclusion criteria**

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19 174 The exclusion criteria are as follows: (1) Other types of arthritis (such as primary
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21
22 175 arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis,
23
24 176 and tuberculous arthritis); (2) Bilateral knee arthroplasty (RA patients); (3) Severe
25
26
27 177 cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina
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30 178 pectoris, and cardiac failure) or cerebrovascular disease (such as cerebral infarction
31
32
33 179 and cerebral haemorrhage); and (4) Prolonged use of oral anticoagulant drugs (such as
34
35 180 aspirin, warfarin, and clopidogrel).
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37
38

39 182 **Elimination criteria**

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41
42 183 The elimination criteria are as follows: (1) Acquired colour vision disorder; (2) Active
43
44 184 intravascular coagulation patients; and (3) A history of seizures.
45
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49 186 **Termination criteria**

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51
52 187 The termination criteria are as follows: (1) Shock; (2) Allergic symptoms such as
53
54 188 itching and a rash; (3) Digestive disorders such as nausea, vomiting, loss of appetite,
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57 189 and diarrhoea after medication; (4) Symptoms such as reactive dermatitis, dizziness,
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60 190 hypotension, drowsiness, headache; convulsions, and visual impairment; and (5)

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4 191 Adverse events such as intracranial thrombosis and intracranial haemorrhage after
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6 192 medication.

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10 11 194 **Perioperative anti-rheumatic treatment**

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14 195 Methotrexate and hydroxychloroquine will be used during the perioperative period.

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16 196 Leflunomide will be discontinued one week before surgery. Use of other
17
18 197 disease-modifying antirheumatic drugs will be discontinued two days before surgery,
19
20 198 and restarted 1-2 days after gastrointestinal function recovery. The use of newer
21
22 199 biologic agents such as tumour necrosis factor alpha will be discontinued 4 to 5
23
24 200 half-lives before surgery and restarted after wound healing and infection
25
26 201 elimination.^[40,41]

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29 202

30 31 32 33 203 **Surgery and anesthesia**

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35
36 204 Surgery will be performed by two senior surgeons (L-bX and W-tZ). During each
37
38 205 surgery, a standard midline incision will be followed by a medial parapatellar capsular
39
40 206 incision to expose the knee joint. A tourniquet will be used for all patients at a
41
42 207 pressure of 200-250 mmHg. The operations will be conducted under general
43
44 208 anaesthesia and blood pressure will be controlled within a range of 80 to 100 mmHg /
45
46 209 60 to 70 mmHg by anaesthetists throughout the surgical procedure. During the
47
48 210 operation, conventional anti-infective, combined analgesic, anti-inflammatory,
49
50 211 anti-coagulation treatment, and other symptomatic treatments will be administered
51
52 212 according to the 'Chinese Hip and Total Knee Arthroplasty Surgery Perioperative
53
54 213 Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert

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4 214 Consensus'.^[26] Ten minutes prior to skin incision, 1 g of TXA + 100 mL of
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6 215 intravenous-saline will be administered, and then 1.5 g of TXA + 50 mL
7
8 216 articular-injection saline will be administered post-operatively into the sutured joint
9
10 217 cavity. Group A and B will then receive additional TXA therapy according to the
11
12 218 treatment regime devised for each group.
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17 219 TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according
18
19 220 to the second edition of the 2015 Chinese Pharmacopoeia and Drug Supplement
20
21 221 Application Approval (2013B02016), YBH07372010; the National Drug Standard
22
23 222 approval number is H43020565.
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28 29 224 **Study interventions**

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31 225 Group A: 1 g of TXA + 100 mL of physiological saline will be administered
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33 226 intravenously 3 hours after the operation. Group B: 1 g of TXA + 100 mL of
34
35 227 physiological saline will be administered intravenously 3, 6, and 12 hours after the
36
37 228 operation.
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42 43 230 **Pain management and rehabilitation**

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46 231 A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib
47
48 232 will be given after surgery for analgesia. After the anaesthesia, the maximum angles
49
50 233 of flexion and extension of the ankle will be maintained for 6 seconds, and the foot
51
52 234 will then be allowed to relax for 5 seconds. This exercise will be performed on both
53
54 235 limbs in order to ensure the quadriceps contractions are equal. On the first
55
56 236 postoperative day, the patients will be encouraged to exercise using straight-leg-raises,
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4 237 supine-knee-flexion, and knee flexion and extension in sitting. Machine-assisted
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6 238 exercises, such as continuous passive motion, will begin on the third day after
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9 239 surgery.

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11 241 **Antibiotics**

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16 242 For perioperative infection prophylaxis, cefazolin (40 mg) will be administered 30
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18 243 minutes before surgery and 24-48 hours after surgery.^[42]

19 244

20 245 **Prevention of lower extremity venous thrombosis**

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26 246 Six hours after the surgery, enoxaparin sodium injections (60 mg) will be initiated and
27
28 247 continued daily for 14 days to prevent formation of a deep vein thrombosis.^[26]

29 248

30 249 **Outcomes**

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36 250 Complete blood count, hepatic function, renal function, and coagulation function will
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38 251 be tested before surgery routinely. Complete blood count, inflammatory index,
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41 252 inflammatory factor and coagulation index will be tested at the 1st, 3rd, 7th and 14th
42
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44 253 days after surgery. All the blood test will be assessed in our hospital (Department of
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46 254 Clinical Laboratory of Guanghai Hospital of Integrated Traditional Chinese Medicine
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49 255 and Western Medicine) by an inspector who is not involved in this clinical trial.

50 256

51 257 **Primary outcomes**

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56 258 *The blood lose, haemoglobin level, and transfusion rate*

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4 259 The blood loss is calculated according to the formulae by Nadle^[43] and Gross:^[44]
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6 260 Patient's blood volume (PBV) = $K1 \times \text{height}^3 (\text{m}^3) + K2 \times \text{weight} (\text{kg}) + K3$. Male:
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9 261 $K1 = 0.3669$, $K2 = 0.03219$, $K3 = 0.6041$; Female: $K1 = 0.3561$, $K2 = 0.03308$, $K3 =$
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11 262 0.1833 . Total blood loss (TBL) = $\text{PBV} \times (\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}) / \text{Hct}_{\text{ave}}$. Hct_{pre} = the initial
12
13 263 pre-operative Hct level; Hct_{post} = the lowest Hct post-operative; Hct_{ave} = the average
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15 264 of the Hct_{pre} and Hct_{post} . The amount of intraoperative blood loss = the total volume of
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17 265 fluid in the negative pressure drain - the volume of normal saline. HBL volume =
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19 266 TBL volume - intra-operative blood loss volume.

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24 267 The maximum haemoglobin decline will be defined as the difference between the
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26 268 pre-operative Hb level and the minimal Hb level drawn post-operatively during the
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28 269 hospitalization and prior to any blood transfusion. The transfusion rate for patients
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30 270 requiring a transfusion will be determined post-operatively during the inpatient
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32 271 hospital stay.
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40 273 Secondary outcomes

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42 274 *Knee function and swelling*

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44 275 Knee function will be measured using the American Knee Society Score (AKSS) one
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46 276 day before surgery and on the 3rd, 7th and 14th days after surgery. A trained researcher
47
48 277 will educate all patients until they fully understand how to assess their knee function
49
50 278 using the questionnaires. The degree of swelling is defined as the postoperative
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52 279 circumference of the upper tibia divided by the preoperative circumference of the
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54 280 upper tibia.
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6 282 *Adverse events*

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9 283 Potential adverse events include deep vein thrombosis (clinical manifestations: acute
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11 284 onset, affected limb swelling, sever pain, or significant tenderness at the femoral
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13 285 triangle or/and leg) and pulmonary embolism (clinical manifestations: cough, chest
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15 286 tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis,
16
17 287 increased respiratory rate, arteriovenous filling, or pulsation, etc.). Deep vein
18
19 288 thrombosis and pulmonary embolism will be diagnosed by Doppler ultrasound and
20
21 289 computer tomography, respectively. The wound healing process and complications
22
23 290 (wound bleeding, haematoma, wound infection, and deep infection) will be observed
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25 291 and recorded in the patient's case report forms (CRFs) during hospitalization and
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27 292 follow-ups.
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37 294 *Adverse event treatment*

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39 295 Adverse events during the follow-up period will be recorded in the CRFs, and their
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41 296 relevance to drug use will be evaluated. All the adverse events will be classified in
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43 297 accordance with the five-level scoring systems (5.0) of the CTCAE. Serious adverse
44
45 298 events are defined as those that may cause cancer, teratogenicity, death, permanent
46
47 299 damage to organ function, permanent or significant disability, and prolonged hospital
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49 300 stay. In the case of adverse events occurring, the researcher should immediately take
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51 301 appropriate measures and report these events to the hospital and ethics committees
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53 302 within 24 hours.
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60 304 **Data management**

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3 305 Data on the CRFs will be put into the computer by two independent trained research
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5 306 assistants with a double-entry method. The hospital's independent investigators will
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7 307 check the data periodically.
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11 309 **Statistical analysis**

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14 310 (1) Descriptive analysis on the characteristics of the study participants; (2) Balance
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16 311 analysis on the baseline values in groups; (3) Comparison of the balance of primary
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18 312 outcomes between groups; and (4) Comparison of secondary outcomes and safety
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20 313 between groups. The total rate of adverse events in the two groups will be tested by
21
22 314 the bidirectional disordered R*C list chi-square test. The association between the
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24 315 incidence of adverse events and the dose of TXA use will be described.
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31 317 **Ethics and dissemination**

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34 318 Written inform consent will be obtained from all participants or their authorised
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36 319 agents before the study. All TXA treatments will be free. Research data will be kept
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38 320 strictly confidential and obtained from appropriate authors upon reasonable request.
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40 321 Results of the trial will be published on the website of the China Clinical Trials
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42 322 Registry and in peer-reviewed journals.
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49 324 **The Patient and public involvement**

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52 325 Patients and public will not be involved in the development of the research question
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54 326 or in the design of the study. Patients will receive oral and written information about
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56 327 this trial, pertaining to the benefits, risks and discomforts that they may get from the
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58 328 study. Besides, the burden of the intervention will be assessed by patients themselves.
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4 329 Dissemination of the general results (no personal data) will be made on demand.
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14 332 **DISCUSSION**
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18 333 Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical
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20 334 studies have shown that high doses of TXA can reduce blood loss after TKA in
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23 335 patients with osteoarthritis.^[25,45,46] It has been reported that an intravenous infusion of
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26 336 TXA, combined with intra-articular injection may be the optimal bleeding-control
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28 337 scheme.^[47,48] Previous studies have shown that knee joint swelling after TKA is
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31 338 associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby
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34 339 relieving the swelling around the joint.^[11] Given that plasminogen activators play an
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36 340 important role in RA-involved inflammation, the dissolution of fibrin will trigger an
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39 341 inflammatory response.^[49] Therefore, we suspect that multiple doses of TXA in the
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41 342 perioperative period may exert an auxiliary anti-inflammatory effect.
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44 343 Enhanced recovery after surgery is strongly advocated, and the management of
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46 344 perioperative blood loss is an essential component. The RA patients aged 50-80 years
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49 345 undergoing TKA have a lower risk of requiring a revision, and are likely to obtain
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52 346 higher knee function and present with fewer complications.^[50,51] In order to reduce
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54 347 bias caused by a wide age range, patients aged 50-75 will be selected. This study will
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57 348 provide new evidence for managing perioperative blood loss in TKA in Chinese RA
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59 349 patients if the results indicate that the administration of the additional three doses of
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4 350 TXA therapy after surgery is beneficial over a single dose.
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10 353 **Author Contributions** B-xK, HX and L-bX conceived the study while B-xK and HX
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12
13 354 drafted the study protocol, B-xK and HX contributed equally to this work and should
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15
16 355 be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX,
17
18 356 S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study
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20
21 357 protocol.

22
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24
25
26 359 planning Commission of Shanghai (Grant NO. ZY (2018-2020)-FWTX-6023).

27
28 360 **Conflicts of Interests** The authors declared that there are no potential conflicts of
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30
31 361 interest with respect to the research, authorship, and/or publication of this study.

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34 362 **Patient consent for publication** Written informed consent will be obtained.

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36 363 **Ethics approval** This study has been approved by the ethics committee Shanghai
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39 364 Guanghua Hospital of Integrated Traditional Chinese Medicine and Western
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42 365 Medicine (approval NO. 2019-K-13), and any modification of the protocol will be
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44
45 366 reported and approved by it.

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47 367 **Provenance and peer review** Not commissioned; externally peer reviewed.

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54 370 **REFERENCES**

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59 521 Figure 1: The study flow diagram, including participants recruitment, eligibility,
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4 522 screening, randomisation, allocation concealment and outcome assessments. TXA,
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6 523 tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th
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For peer review only

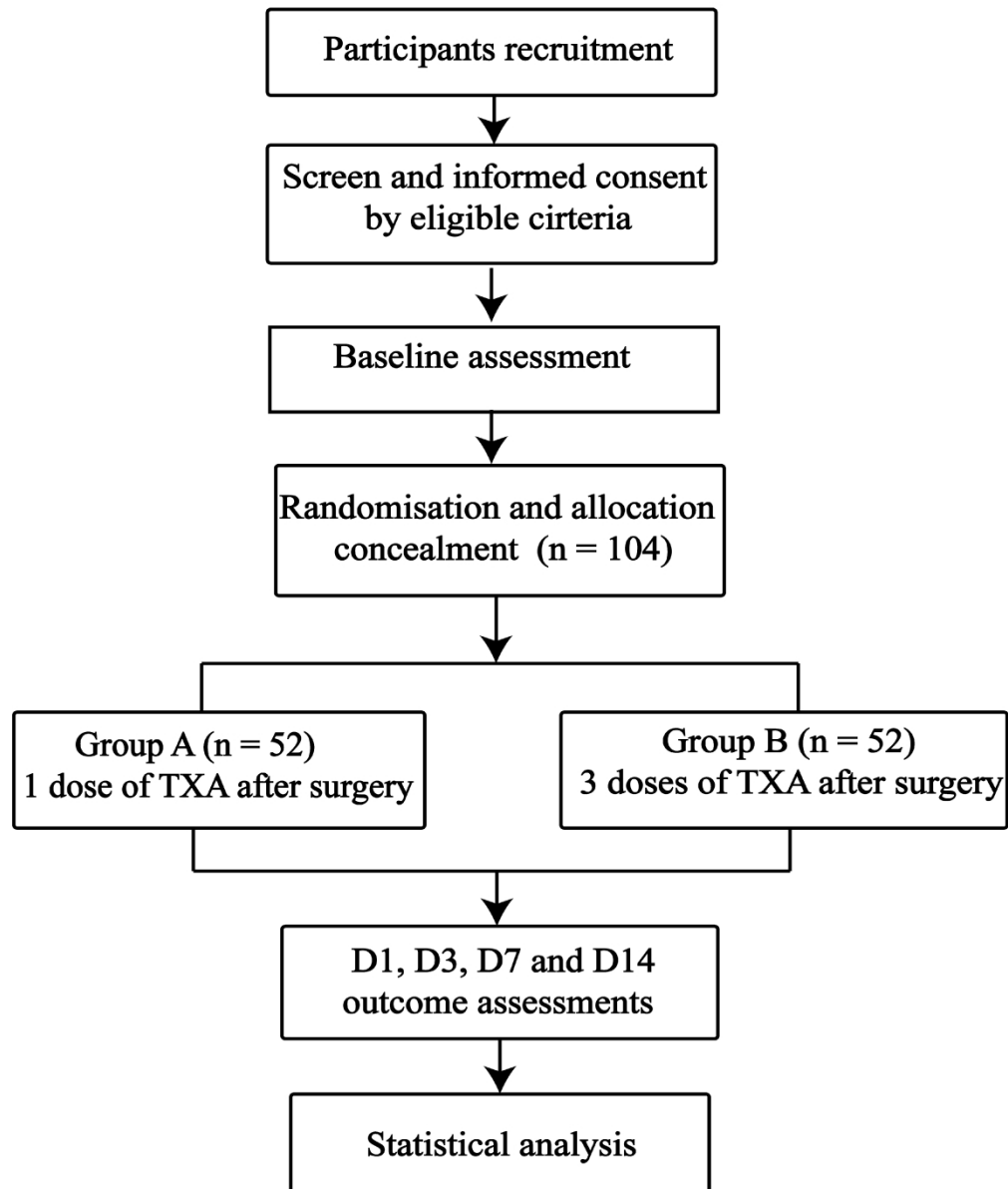


Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA, tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

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 in China

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

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	orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

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4 1 **Multiple-dose tranexamic acid for perioperative blood loss in total knee**
5
6 2 **arthroplasty in patients with rheumatoid arthritis : A single-blinded,**
7
8 3 **randomized, parallel-controlled study protocol in China**

11 4 Bing-xin Kang*, Hui Xu*, Chen-xin Gao, Sheng Zhong, Jing Zhang, Jun Xie,
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54 55 56 57 58 59 60 **ABSTRACT**

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4 46 **Introduction** This clinical trial is designed to evaluate the effect of multiple-dose
5
6 47 tranexamic acid (TXA) on perioperative blood loss in patients with rheumatoid
7
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9 48 arthritis (RA).

10
11 49 **Methods and analysis** A randomized, single-blinded, parallel-controlled study will
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13
14 50 be designed. RA patients (age 50-75 years) undergoing unilateral primary end-stage
15
16
17 51 total knee arthroplasty will be randomly divided into Group A or Group B. Group A
18
19
20 52 will be treated with one dose of TXA (1 g; intravenous injection 3 hours post-surgery)
21
22
23 53 and Group B with three doses (1 g; intravenous injection at 3, 6, and 12 hours
24
25 54 post-surgery) after surgery. The primary outcomes will be evaluated with blood loss,
26
27 55 maximum haemoglobin drop, and transfusion rate. The secondary outcomes will be
28
29
30 56 evaluated with knee function and complications.

31
32 57 **Ethics and dissemination** The Shanghai Guanghua Hospital of Integrated Traditional
33
34
35 58 Chinese Medicine and Western Medicine Ethics Committee approved in this study in
36
37
38 59 July 2019. Informed consent will be obtained from all participants. Results of the trial
39
40
41 60 will be published in the Dryad and repository in a peer-reviewed journal. Additionally,
42
43
44 61 deidentified data collected and analysed for this study will be available for review
45
46
47 62 from the corresponding author on reasonable request.

48 63 **Trial registration number** ChiCTR1900025013; Pre-results.

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56 66 **Article Summary**

57
58 67 Strengths and limitations of this trial
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4 68 (1) This is the first study in China to evaluate the efficacy and safety of a
5
6 69 perioperative multiple-dose regimen of tranexamic acid during total knee arthroplasty
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9 70 in rheumatoid arthritis patients.

10
11 71 (2) The bias of this study was reduced dramatically by the extensive study design,
12
13
14 72 which included proper randomization, allocation concealment, and objective
15
16
17 73 indications.

18
19 74 (3) If multiple-dose TXA after surgery can reduce postoperative blood loss in
20
21
22 75 rheumatoid arthritis patients without adverse events, this medication regimen may
23
24
25 76 reduce the occurrence of postoperative anaemia in rheumatoid arthritis patients.

26
27 77 (4) The short follow-up time may be insufficient in fully assessing the risk of
28
29
30 78 complications in a multiple-dose regimen of tranexamic acid during total knee
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33 79 arthroplasty in rheumatoid arthritis patients.

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39 40 82 **INTRODUCTION**

41
42
43 83 Rheumatoid arthritis (RA) may be accompanied by haematological diseases such as
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45 84 anaemia.^[1] The overall prevalence of RA is 0.5-1% in Europe and North America,
46
47
48 85 0.31% in France, 0.32-0.38% in China, and 0.02-0.047% in Japan.^[2,3] Total knee
49
50
51 86 arthroplasty (TKA) is effective in treating flexion contractures and maintaining the
52
53
54 87 stability of knees effected by RA.^[4] About 0.005% of RA patients receive TKA, a rate
55
56
57 88 that has gradually decreased over the past decades. However, surgery remains the first
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60 89 choice for articular deformity and pain, despite the fact that disease-modifying

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4 90 antirheumatic drugs and biologics agents can manage synovitis-related symptoms in
5
6 91 RA patients.^[5] Haemorrhage is a major perioperative complication of TKA.^[6]
7
8
9 92 Excessive blood loss should be treated with an allogeneic blood transfusion, but this
10
11 93 has adverse effects such as immune complications, prolong hospitalization time, and
12
13
14 94 increased infection rate.^[7,8] Haemoglobin has a negative correlation with disease
15
16
17 95 activity in RA.^[9] Therefore, we believe that perioperative blood loss management is
18
19
20 96 needed for patients with RA.

21
22 97 Accounting for approximately 50% of the total blood loss, hidden blood loss (HBL)
23
24 98 is the blood lost as infiltrates into the tissue intraoperatively and postoperatively. This
25
26
27 99 blood resides in the knee joint cavity before being haemolyzed.^[10] HBL often leads to
28
29
30 100 the joint swelling, postoperative inflammation, and pain.^[11,12]

31
32 101 Use of a surgical tourniquet can reduce intraoperative bleeding,^[13] provide a clear
33
34
35 102 view during the surgery, and facilitate the connection between the cement, bone and
36
37
38 103 joint prostheses.^[14] However, after the release of the tourniquet, local tissue may be
39
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41 104 damaged by ischemic reperfusion injury, and the fibrinolytic system may be
42
43
44 105 activated.^[15,16] As a consequence, peripheral blood circulation can be accelerated,
45
46
47 106 plasma fibrinolysis enhanced, and postoperative HBL increased.^[15] Therefore,
48
49
50 107 reducing the dissolution of fibrin can reduce postoperative HBL.^[17]

51 108 Tranexamic acid (TXA) is a synthetic lysine derivative that competitively inhibits
52
53 109 the binding between plasminogen and fibrin, prevents the activation of plasminogen,
54
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56 110 and protects fibrin from degradation and dissolution by plasmin. TXA was initially
57
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59 111 used in obstetric and gynaecologic surgery, and its use was then gradually replicated
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4 112 in other surgeries to reduce bleeding and blood transfusion rates.^[18,19] The CRASH-2
5
6 113 trial has demonstrated the effectiveness and safety of TXA in reducing blood loss.^[20]
7
8
9 114 A large amount of literature has reported that TXA can significantly reduce peri-TKA
10
11 115 blood loss.^[21-25] Currently, TXA is recommended for perioperative management of
12
13 116 blood loss during TKA.^[26] However, its efficacy and safety in RA patients undergoing
14
15 117 TKA has rarely been reported.^[27] TXA can be administered through oral intake, a
16
17 118 single large-dose intravenous injection, an intra-articular injection, joint cavity
18
19 119 irrigation, postoperative drainage tube injection, or through a combination of these
20
21 120 methods.^[25,28-30] There is no consensus on the optimal dosage and timing of
22
23 121 perioperative TXA administration for TKA.^[18,31,32] Studies have shown that
24
25 122 fibrinolysis peaks at 6 hours and continues for approximately 18 hours after TKAs
26
27 123 that were performed with tourniquets.^[33] The half-life of TXA in the plasma is 2
28
29 124 hours, and its concentration peaks at 1 hour after injection.^[34] Thus, we suspect that a
30
31 125 single dose of TXA may not be sufficient to exert an anti-fibrinolytic effect. There are
32
33 126 also studies suggesting that, for patients with osteoarthritis, higher doses (within the
34
35 127 normal range) during the perioperative period can increase the efficacy of TXA.^[35,36]
36
37 128 The purpose of this clinical trial is to verify the effectiveness and safety of multiple
38
39 129 doses of TXA in reducing perioperative blood loss in RA patients treated with TKA,
40
41 130 in order to determine a new strategy for management of perioperative blood loss
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43 131 during TKA.
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134 **METHODS AND ANALYSIS**

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4 **135 Study context**

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6 136 This clinical trial was initiated on 1 September 2019 in the wards of Guanghua
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9 137 Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Shanghai
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11 138 University of Traditional Chinese Medicine (Shanghai, China). The annual number of
12
13
14 139 TKA cases performed in RA patients was about 300 in 2018. Eleven investigators will
15
16
17 140 be involved in this study including 2 senior orthopaedic surgeons (L-bX, W-tZ) with
18
19
20 141 20 years of clinical experience, 6 orthopaedic physicians (C-xG, JZ, JX, S-sT, Y-hM,
21
22 142 and SZ), 2 data collectors who are also statisticians (B-xK and HX), and a nurse
23
24
25 143 (X-rX). Informed consent will be obtained from all patients. The perioperative ERAS
26
27
28 144 blood management programme and the trial flow chart are shown in Table 1 and
29
30 145 Figure 1. The schedule is shown in Table 2.

31
32 **Table 1** Enhanced recovery after surgery blood management

33
34 Preoperative

35
36 1 Treatment of haemorrhagic primary disease

37
38 2 Nutritional guidance, balanced diet

39
40 3 Iron application

41
42 4 Rhu-Epo application

43
44 Intraoperative

45
46 5 Minimally invasive surgery

47
48 6 Tourniquet optimization

49
50 7 Controlled buck

51
52 8 Autologous blood return

53
54 9 Use of tranexamic acid

55
56 Postoperative

57
58 10 Reduce bleeding (pressure dressing of wounds, prevent stress ulcers)

59
60

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

Rhu-Epo, recombinant human erythropoietin.

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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.

147

148 **Sample size calculation**

149 This study uses a completely randomized trial design. Multiple sample sizes will
150 evaluated by a review of previously conducted clinical research.^[25] The primary
151 outcome will be measured with the amount of HBL, dependent on TXA therapy. The
152 overall standard deviation is $\sigma = 250$, and the allowable error estimate is $\delta = 200$.

153 These values were estimated using the statistical formula $n_1 = n_2 = 2 \times \left[\frac{(Z_{\alpha/2} + Z_{\beta})/\sigma}{\delta} \right]^2$.

154 Predicting an estimated dropout rate of 10%, 104 subjects will be required to yield a
155 power of 90% with a significance level of 0.05.

157 **Randomization and allocation concealment**

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

166 **Single-blinded design**

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

1
2
3
4 169 test results.
5
6

7 170
8

9 171 **Eligibility criteria**

10
11 172 The eligibility criteria have been set in accordance with the ‘American Rheumatism

12
13
14 173 Association criteria for rheumatoid arthritis’^[37] and the 2010 ‘ACR/EULAR

15
16
17 174 classification criteria for rheumatoid arthritis’.^[38] The eligibility criteria are as follows:

18
19
20 175 (1) The patient must have been diagnosed with RA in Stage III or IV according to the

21
22 176 Kellgren-Lawrence classification;^[39] (2) The patient must be 50 to 75 years old; (3)

23
24 177 The patient must be willing to undergo the unilateral primary TKA; (4) The patient

25
26
27 178 must receive perioperative anti-fibrinolytic TXA therapy; and (5) The patient must

28
29
30 179 show normal blood-clotting function and must not have preoperative anaemia.
31

32 180
33

34 181 **Exclusion criteria**

35
36
37 182 The exclusion criteria are as follows: (1) Other types of arthritis (such as primary

38
39
40 183 arthritis, post-traumatic osteoarthritis, gouty osteoarthritis, haemophilic osteoarthritis,

41
42 184 and tuberculous arthritis); (2) Bilateral knee arthroplasty (RA patients); (3) Severe

43
44
45 185 cardiovascular disease (such as myocardial infarction, atrial fibrillation, angina

46
47
48 186 pectoris, and cardiac failure) or cerebrovascular disease (such as cerebral infarction

49
50
51 187 and cerebral haemorrhage); and (4) Prolonged use of oral anticoagulant drugs (such as

52
53 188 aspirin, warfarin, and clopidogrel).
54

55 189

56
57 190 **Elimination criteria**

58
59
60 191 The elimination criteria are as follows: (1) Acquired colour vision disorder; (2) Active

1
2
3
4 192 intravascular coagulation patients; and (3) A history of seizures.
5
6

7 193
8

9 194 **Termination criteria**

10
11 195 The termination criteria are as follows: (1) Shock; (2) Allergic symptoms such as
12
13
14 196 itching and a rash; (3) Digestive disorders such as nausea, vomiting, loss of appetite,
15
16
17 197 and diarrhoea after medication; (4) Symptoms such as reactive dermatitis, dizziness,
18
19
20 198 hypotension, drowsiness, headache; convulsions, and visual impairment; and (5)
21
22 199 Adverse events such as intracranial thrombosis and intracranial haemorrhage after
23
24
25 200 medication.
26

27 201
28

29 202 **Perioperative anti-rheumatic treatment**

30
31
32 203 Methotrexate and hydroxychloroquine will be used during the perioperative period.
33
34 204 Leflunomide will be discontinued one week before surgery. Use of other
35
36
37 205 disease-modifying antirheumatic drugs will be discontinued two days before surgery,
38
39
40 206 and restarted 1-2 days after gastrointestinal function recovery. The use of newer
41
42
43 207 biologic agents such as tumour necrosis factor alpha will be discontinued 4 to 5
44
45 208 half-lives before surgery and restarted after wound healing and infection
46
47 209 elimination.^[40,41]
48

49
50 210
51

52 211 **Surgery and anaesthesia**

53
54 212 Surgery will be performed by two senior surgeons (L-bX and W-tZ). During each
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56
57 213 surgery, a standard midline incision will be followed by a medial parapatellar capsular
58
59
60 214 incision to expose the knee joint. A tourniquet will be used for all patients at a

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4 215 pressure of 200-250 mmHg. The operations will be conducted under general
5
6 216 anaesthesia and blood pressure will be controlled within a range of 80 to 100 mmHg /
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8
9 217 60 to 70 mmHg by anaesthetists throughout the surgical procedure. During the
10
11 218 operation, conventional anti-infective, combined analgesic, anti-inflammatory,
12
13 219 anti-coagulation treatment, and other symptomatic treatments will be administered
14
15 220 according to the 'Chinese Hip and Total Knee Arthroplasty Surgery Perioperative
16
17 221 Anti-fibrinolytic Drug Sequential Anticoagulant Application Programme Expert
18
19 222 Consensus'.^[26] Ten minutes prior to skin incision, 1 g of TXA + 100 mL of
20
21 223 intravenous-saline will be administered, and then 1.5 g of TXA + 50 mL
22
23 224 articular-injection saline will be administered post-operatively into the sutured joint
24
25 225 cavity. Group A and B will then receive additional TXA therapy according to the
26
27 226 treatment regime devised for each group.
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35 227 TXA is produced by Hunan Dongting Pharmaceutical Co., Ltd., and used according
36
37 228 to the second edition of the 2015 Chinese Pharmacopoeia and Drug Supplement
38
39 229 Application Approval (2013B02016), YBH07372010; the National Drug Standard
40
41 230 approval number is H43020565.
42
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49 232 **Study interventions**

50 233 Group A: 1 g of TXA + 100 mL of physiological saline will be administered
51
52 234 intravenously 3 hours after the operation. Group B: 1 g of TXA + 100 mL of
53
54 235 physiological saline will be administered intravenously 3, 6, and 12 hours after the
55
56 236 operation.
57
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60 237

1
2
3 **238 Pain management and rehabilitation**
4
5

6 239 A cocktail injection will be given during the operation, and 0.2 g of oral celecoxib
7
8 240 will be given after surgery for analgesia. After the anaesthesia, the maximum angles
9
10 241 of flexion and extension of the ankle will be maintained for 6 seconds, and the foot
11
12 242 will then be allowed to relax for 5 seconds. This exercise will be performed on both
13
14 243 limbs in order to ensure the quadriceps contractions are equal. On the first
15
16 244 postoperative day, the patients will be encouraged to exercise using straight-leg-raises,
17
18 245 supine-knee-flexion, and knee flexion and extension in sitting. Machine-assisted
19
20 246 exercises, such as continuous passive motion, will begin on the third day after
21
22 247 surgery.
23
24
25
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30
31 **249 Antibiotics**
32
33

34 250 For perioperative infection prophylaxis, cefazolin (40 mg) will be administered 30
35
36 251 minutes before surgery and 24-48 hours after surgery.^[42]
37
38
39

40 252

41 **253 Prevention of lower extremity venous thrombosis**
42
43

44 254 Six hours after the surgery, enoxaparin sodium injections (60 mg) will be initiated and
45
46 255 continued daily for 14 days to prevent formation of a deep vein thrombosis.^[26]
47
48

49 256

50
51 **257 Outcome measures**
52
53

54 258 Complete blood count, hepatic function, renal function, and coagulation function will
55
56 259 be routinely tested before surgery. Complete blood count, inflammatory index,
57
58 260 inflammatory factor and coagulation index will be tested on the 1st, 3rd, 7th and 14th
59
60

1
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3
4 261 days after surgery. All the blood tests will be assessed in our hospital (Department of
5
6 262 Clinical Laboratory of Guanghai Hospital of Integrated Traditional Chinese Medicine
7
8
9 263 and Western Medicine, Shanghai University of Traditional Chinese Medicine) by an
10
11
12 264 inspector who is not involved in this clinical trial.
13
14
15

16 266 **Primary outcome measures**

17 18 19 267 *Blood loss, haemoglobin level, and transfusion rate*

20
21
22 268 Blood loss is calculated according to the formulae by Nadle^[43] and Gross:^[44] Patient's
23
24 269 blood volume (PBV) = $K1 \times \text{height}^3 \text{ (m}^3\text{)} + K2 \times \text{weight (kg)} + K3$. Male: $K1 =$
25
26
27 270 0.3669 , $K2 = 0.03219$, $K3 = 0.6041$; Female: $K1 = 0.3561$, $K2 = 0.03308$, $K3 =$
28
29 271 0.1833 . Total blood loss (TBL) = $\text{PBV} \times (\text{Hct}_{\text{pre}} - \text{Hct}_{\text{post}}) / \text{Hct}_{\text{ave}}$. Hct_{pre} = the initial
30
31
32 272 pre-operative Hct level; Hct_{post} = the lowest Hct post-operative; Hct_{ave} = the average
33
34 273 of the Hct_{pre} and Hct_{post} . The amount of intraoperative blood loss = the total volume of
35
36
37 274 fluid in the negative pressure drain – the volume of normal saline. HBL volume =
38
39
40 275 TBL volume – intra-operative blood loss volume.

41
42 276 The maximum haemoglobin decline will be defined as the difference between the
43
44
45 277 pre-operative Hb level and the minimal Hb level drawn post-operatively during the
46
47
48 278 hospitalization and prior to any blood transfusion. The transfusion rate for patients
49
50
51 279 requiring a transfusion will be determined post-operatively during the inpatient
52
53
54 280 hospital stay.

55
56 281

57 58 282 **Secondary outcome measures**

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3
4 283 *Knee function and swelling*
5

6 284 Knee function will be measured using the American Knee Society Score (AKSS) one
7
8
9 285 day before surgery and on the 3rd, 7th and 14th days after surgery. A trained researcher
10
11
12 286 will educate all patients until they fully understand how to assess their knee function
13
14 287 using the questionnaires. The degree of swelling is defined as the postoperative
15
16
17 288 circumference of the upper tibia divided by the preoperative circumference of the
18
19 289 upper tibia.
20

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22 290

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24
25 291 *Adverse event measures*
26

27 292 Potential adverse events include deep vein thrombosis (clinical manifestations: acute
28
29
30 293 onset, affected limb swelling, severe pain, or significant tenderness at the femoral
31
32 294 triangle or/and leg) and pulmonary embolism (clinical manifestations: cough, chest
33
34
35 295 tightness, palpitations, haemoptysis, shortness of breath, dizziness, shock, cyanosis,
36
37
38 296 increased respiratory rate, arteriovenous filling, or pulsation, etc.). Deep vein
39
40 297 thrombosis and pulmonary embolism will be diagnosed by Doppler ultrasound and
41
42
43 298 computed tomography, respectively. The wound healing process and complications
44
45 299 (wound bleeding, haematoma, wound infection, and deep infection) will be observed
46
47
48 300 and recorded in the patient's case report forms (CRFs) during hospitalization and
49
50
51 301 follow-ups.
52

53 302

54
55 303 *Adverse event treatment*
56

57 304 Adverse events during the follow-up period will be recorded in the CRFs, and their
58
59 305 relevance to drug use will be evaluated. All the adverse events will be classified in
60

1
2
3 306 accordance with the five-level scoring systems (5.0) of the CTCAE. Serious adverse
4
5 307 events are defined as those that may cause cancer, teratogenicity, death, permanent
6
7 308 damage to organ function, permanent or significant disability, and prolonged hospital
8
9
10 309 stay. In the case of adverse events occurring, the researcher should immediately take
11
12 310 appropriate measures and report these events to the hospital and ethics committees
13
14
15 311 within 24 hours.
16

312

313 **Data management**

314 Data on the CRFs will be put into the computer by two independent trained research
315 assistants with a double-entry method. The hospital's independent investigators will
316 check the data periodically.
317

318

318 **Statistical analysis**

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

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

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4 331 may experience during the study. Further, the burden of the intervention will be
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6 332 assessed by patients themselves. Dissemination of the general results (no personal
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9 333 data) will be made available on reasonable request.
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17 336 **ETHICS AND DISSEMINATION**

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19 337 Ethics approval has been granted by the Shanghai Guanghua Hospital of Integrated
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22 338 Traditional Chinese Medicine and Western Medicine Ethics Committee. Written
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25 339 inform consent will be obtained from all participants or their authorised agents before
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27 340 initiation of the study. All TXA treatments will be free. Personal data of participants
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30 341 will be kept strictly confidential and obtained from appropriate authors upon
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33 342 reasonable request. Results of the trial will be published on the Dryad website and in a
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35 343 peer-reviewed journal.
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47 346 **DISCUSSION**

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50 347 Controlling blood loss can facilitate the recovery from TKA surgery. Previous clinical
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53 348 studies have shown that high doses of TXA can reduce blood loss after TKA in
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55 349 patients with osteoarthritis.^[25,45,46] It has been reported that an intravenous infusion of
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58 350 TXA, combined with intra-articular injection may be the optimal bleeding-control
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4 351 scheme.^[47,48] Previous studies have shown that knee joint swelling after TKA is
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6 352 associated with HBL in the joint cavity. TXA can reduce postoperative HBL, thereby
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9 353 relieving the swelling around the joint.^[11] Given that plasminogen activators play an
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11 354 important role in RA-involved inflammation, the dissolution of fibrin will trigger an
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14 355 inflammatory response.^[49] Therefore, we suspect that multiple doses of TXA in the
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17 356 perioperative period may exert an auxiliary anti-inflammatory effect.

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19 357 Enhanced recovery after surgery is strongly advocated, and the management of
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22 358 perioperative blood loss is an essential component. The RA patients aged 50-80 years
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25 359 undergoing TKA have a lower risk of requiring a revision, and are likely to obtain
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28 360 higher knee function and present with fewer complications.^[50,51] In order to reduce
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31 361 bias caused by a wide age range, patients aged 50-75 will be selected. This study will
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34 362 provide new evidence for managing perioperative blood loss in TKA in Chinese RA
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37 363 patients if the results indicate that the administration of the additional three doses of
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40 364 TXA therapy after surgery is beneficial over a single dose.

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45 367 **Author Contributions** B-xK, HX and L-bX conceived the study while B-xK and HX
46
47
48 368 drafted the study protocol, B-xK and HX contributed equally to this work and should
49
50
51 369 be regarded as co-first authors. The study protocol was designed by C-xG, SZ, JZ, JX,
52
53
54 370 S-tS, Y-hM, and W-tZ. All authors approved the final manuscript of this study
55
56
57 371 protocol.

58
59 372 **Funding** This work will be supported by the Foundation of Health and Family
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373 planning Commission of Shanghai (Grant NO. ZY (2018-2020)-FWTX-6023).

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

376 **Patient consent for publication** Written informed consent will be obtained.

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

381 **Provenance and peer review** Not commissioned; externally peer reviewed.

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28 535 Figure 1: The study flow diagram, including participants recruitment, eligibility,
29 536 screening, randomisation, allocation concealment and outcome assessments. TXA,
30 537 tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th
31 538 day after surgery; D14, the 14th day after surgery.

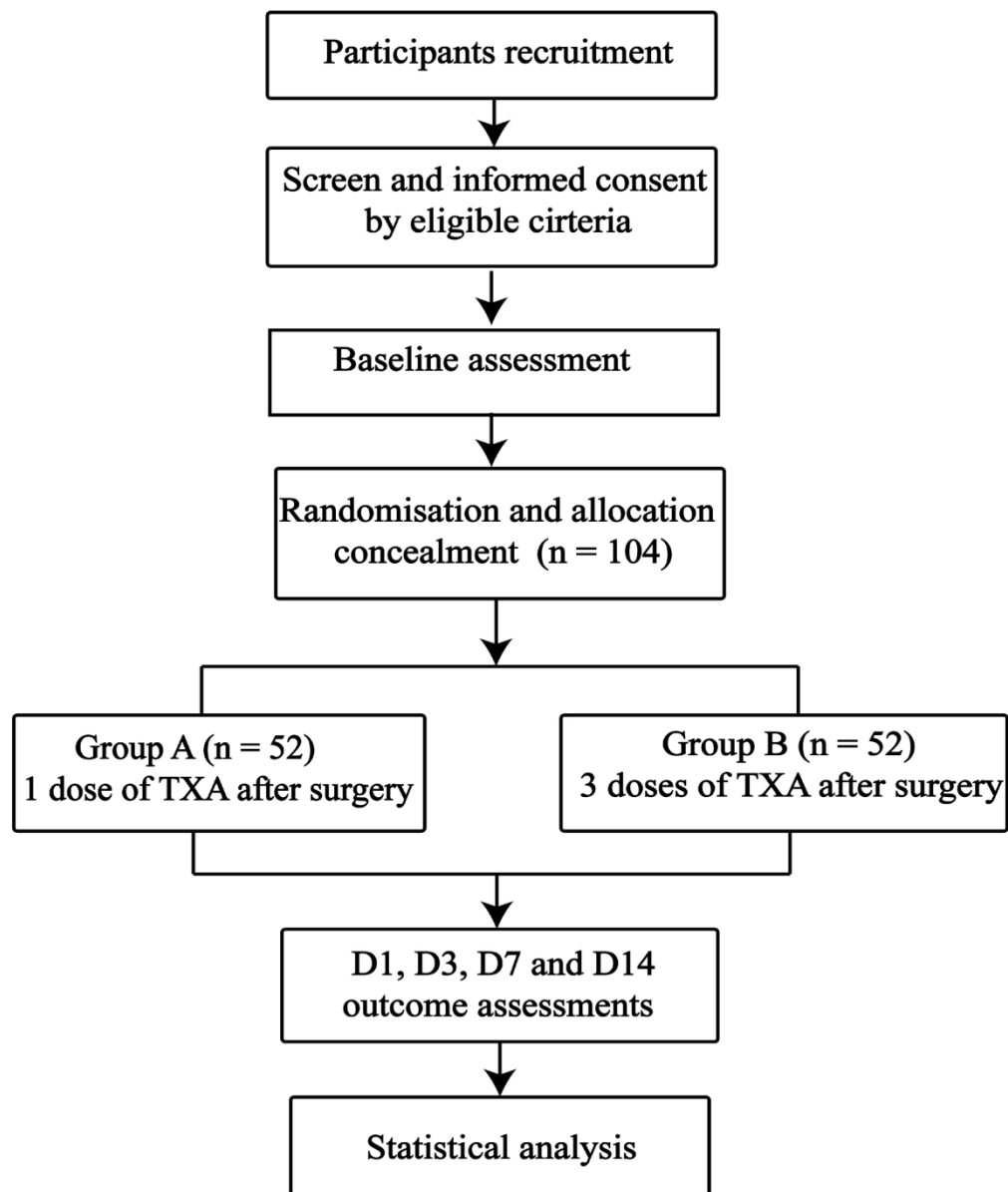


Figure 1: The study flow diagram, including participants recruitment, eligibility, screening, randomisation, allocation concealment and outcome assessments. TXA, tranexamic acid; D1, the 1st day after surgery; D3, the 3rd day after surgery; D7, the 7th day after surgery; D14, the 14th day after surgery.

163x195mm (300 x 300 DPI)



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			

1 2 3 4 5 6	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.
7 8		6b	Explanation for choice of comparators	Line 116-131.
9 10	Objectives	7	Specific objectives or hypotheses	Line 360-363.
11 12 13 14 15 16	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.
17	Methods: Participants, interventions, and outcomes			
18 19 20 21 22 23 24	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.
25 26 27 28 29 30	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.
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	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	
49 50 51 52 53 54 55 56 57 58 59 60	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			

1 2 3 4 5 6 7 8 9 10 11	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.
12 13 14 15 16 17		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	
18 19 20 21 22 23 24 25	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.
26 27 28 29 30 31	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.
32 33 34		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
35 36 37 38 39 40		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)	
41 42	Methods: Monitoring			
43 44 45 46 47 48 49 50 51 52	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 54 55 56 57 58 59 60		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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.