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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-077393
Article Type:	Protocol
Date Submitted by the Author:	03-Jul-2023
Complete List of Authors:	Wei, Zhanqi; Peking Union Medical College Hospital, Yu, Muyang; Peking Union Medical College Hospital, Department of Orthopedics Xu, Yiming; Peking Union Medical College Hospital, Department of Orthopedics Weng, Xisheng; Peking Union Medical College Hospital, Department of Orthopedic Surgery Feng, Bin; Peking Union Medical College Hospital, Department of Orthopedics
Keywords:	ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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Manuscripts

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5 1 **Impact of intraosseous regional administration of tranexamic**
6 **acid in total knee arthroplasty on perioperative blood loss: a**
7 **protocol for a randomized controlled trial**
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14 Zhanqi Wei^{1,2}, Muiyang Yu¹, Yiming Xu¹, Xisheng Weng¹, Bin Feng¹
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18 ¹Department of Orthopedics, Peking Union Medical College Hospital, Chinese
19 Academy of Medical Sciences and Peking Union Medical College, Beijing 100730,
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26 ²School of Medicine, Tsinghua University, Beijing 100084, China.

28 Correspondence to Bin Feng; pumcfeng@163.com

32 **Abstract**

36 **Introduction:** Total knee arthroplasty (TKA) is a common surgical intervention to treat
37 joint diseases. However, TKA is associated with significant blood loss. Tranexamic
38 acid (TXA) has been used to reduce perioperative bleeding and postoperative blood
39 transfusion. This study aims to explore the effectiveness and safety of intraosseous
40 regional administration (IORA) of TXA in TKA and compare differences in
41 perioperative blood loss between IORA of TXA, intravenous infusion of TXA, and
42 combined IORA and intravenous infusion of TXA.
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54 **Methods and analysis:** This randomized controlled trial will enroll 105 patients with
55 osteoarthritis who meet the inclusion criteria for unilateral TKA. Patients were
56 randomly divided into three groups using the random number table method. Group A
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4 21 received 1.0 g TXA via IORA, group B received 1.0 g TXA via intravenous infusion
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6 22 15 minutes prior to tourniquet release, and group C received both IORA of 1.0 g TXA
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9 23 and intravenous infusion of 1.0 g TXA. The primary outcome measure is perioperative
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11 24 total blood loss. Secondary outcomes include bleeding events, VTE events,
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14 25 inflammation reactions, other complications, and knee function assessments.

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17 26 **Ethics and dissemination:** This study has been approved by the Ethics Committee of
18
19 27 Peking Union Medical College Hospital and registered in the Chinese Clinical Trial
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21 28 Registry. Informed consent will be obtained from all patients before enrollment. The
22
23 29 trial will be conducted in accordance with the principles of the Declaration of Helsinki
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25 30 and the International Conference on Harmonization Good Clinical Practice guidelines.
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27 31 The results of this study will be disseminated through peer-reviewed publications,
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29 32 conference presentations, and social media platforms. The findings will provide
30
31 33 valuable insights into the use of IORA of TXA in TKA, and may lead to the
32
33 34 development of new strategies for perioperative blood management in joint
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35 35 replacement surgery.

36
37 36 **Trial registration number:** The Ethics Committee of Peking Union Medical College
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39 37 Hospital (approval number: K2371); Chinese Clinical Trial Registry
40
41 38 (ChiCTR2200066293).

39 **Strengths and limitations of this study**

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41 40 1. The study design is a randomized controlled trial, providing a comprehensive
42
43 41 exploration of the effectiveness and safety of IORA of TXA in TKA.

- 42 2. The study uses a uniform cocktail injection formula for postoperative analgesia
43 during the procedure and a uniform postoperative joint rehabilitation program and
44 blood management strategies, which may minimize potential confounding factors.
- 45 3. The study collects a wide range of medical data, including bleeding events, VTE
46 events, inflammation reactions, other complications, and knee function assessments,
47 which may provide a comprehensive evaluation of the efficacy and safety of IORA
48 of TXA in TKA.
- 49 4. The study includes a detailed eligibility criteria and exclusion criteria, which may
50 ensure the reliability and validity of the study results.
- 51 5. The sample size is relatively small, which may limit the generalizability of the study.

52 **Introduction**

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

62 The use of a tourniquet during TKA can significantly reduce intraoperative blood loss,

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4 63 with an average TBL of 1474 ml and hidden blood loss of 735 ml, which accounts for
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6 64 50% of TBL. However, releasing the tourniquet may lead to an imbalance of
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9 65 fibrinolysis-coagulation, causing an excessive activation of the fibrinolysis system. In
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11 66 addition, tourniquet use can cause lower limb ischemia, microcirculation disorders, and
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14 67 distal ischemia-reperfusion injury, leading to further exacerbate the fibrinolytic
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17 68 response (2).

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21 69 Tranexamic acid (TXA) is a lysine derivative that can effectively block the interaction
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23 70 between lysine residues and the heavy chain of plasmin, preventing plasmin from
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26 71 binding to fibrin monomers and inhibiting the lysis of fibrin clots. This mechanism
27
28 72 provides the basis for the use of TXA, often used to reduce perioperative bleeding and
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31 73 postoperative blood transfusion.

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35 74 In 1987, Benoni et al. (3) first applied TXA to postoperative bleeding control in TKA.
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37 75 In 2011, Seo (4) conducted a randomized controlled trial on patients undergoing TKA,
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40 76 and found that local use of TXA could significantly reduce the degree of soft tissue
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43 77 swelling compared with the placebo group by measuring the circumference of the
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46 78 patella, patellar tendon, and knee joint area.

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49 79 The methods for using TXA include intravenous infusion, local application, and oral
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51
52 80 administration. Intravenous infusion of TXA can achieve maximum blood drug
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55 81 concentration in 5-15 minutes, rapidly diffusing into synovial tissue and synovial fluid,
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58 82 achieving a concentration similar to the maximum plasma concentration, and with a
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60 83 half-life in the synovial fluid of up to 3 hours. Alshryda et al. (5) analyzed a randomized

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4 84 controlled trial of intravenous infusion of TXA during TKA and found that the use of
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6 85 TXA could reduce the average TBL by 591 ml, shorten the average length of hospital
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9 86 stay by 0.76 days, and the transfusion rate was only 25% of patients not using TXA.
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11 87 The therapeutic effect is related to the dose of the drug, and an overdose can cause
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14 88 systemic complications, while an insufficient dose can lead to ineffective local
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17 89 concentration of TXA in the joints. Additionally, for patients using tourniquets during
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20 90 TKA, the therapeutic effect of intravenous TXA is related to the timing of
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22 91 administration during procedure; typically, TXA should be administered intravenously
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25 92 15 minutes before the tourniquet is released, but mistakes may happen in practice,
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27 93 which may impact the effectiveness of intravenous TXA infusion.
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31 94 Since TXA can quickly penetrate into tissues in the joint cavity and reach the maximum
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34 95 drug activity in the target organs, local application can limit the systemic accumulation
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37 96 of TXA and broaden the indications for TXA. Seo et al. (4) reported that local
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39 97 application of TXA could reduce blood loss by about 400 ml and reduce the
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42 98 postoperative decrease in hemoglobin (Hb) by about 1.3 g/dl. Ishida et al. (6) found that
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44 99 local application of TXA during TKA not only reduced TBL but also reduced the
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47 100 degree of swelling on the operated limb. Wind et al. compared the effects of intravenous
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50 101 infusion and local application of TXA on intraoperative blood loss in TKA. They found
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52 102 that none of the patients in the local application group required blood transfusion, while
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55 103 the transfusion rate in the intravenous infusion group was 0.3%. A randomized
56
57 104 controlled study directly compared the efficacy of intravenous and intra-articular TXA,
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60 105 concluding that local application of TXA was more advantageous in reducing blood

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4 106 loss and had relatively fewer systemic complications, but the intravenous infusion
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6 107 group was more effective in reducing the decline in Hb (4). Hamlin et al. (7) compared
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9 108 the efficacy of 1.0 g TXA administered via intravenous infusion before procedure and
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12 109 3 g TXA diluted in 100ml of saline and locally injected into the joint cavity through a
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15 110 drainage tube. The local application group had significantly lower Hb decline (2.2 g vs
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17 111 2.8 g) and transfusion rate (0% vs 2.4%) compared to the intravenous infusion group,
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20 112 but there was no difference in hospital stay or incidence of venous thromboembolism
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22 113 (VTE) between the two groups.

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26 114 According to the published studies, intravenous administration of tranexamic acid
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28 115 (TXA) at a dosage of 10-20 mg/kg and local application at a dosage of 1-3 g have high
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31 116 efficacy in reducing blood loss. However, there is still uncertainty about the optimal
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34 117 dosage of TXA. Currently favored options include a single dose of 10 mg/kg, 15 mg/kg,
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37 118 or 20 mg/kg or a standardized dose of 1.0 g. In a randomized controlled trial conducted
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40 119 by Levine et al. (8), the difference in TBL between the standardized dose group (1.0 g)
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43 120 and personalized dose group (20 mg/kg) was investigated. The results showed that the
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46 121 TBL for the standardized dose group and the personalized dose group was
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49 122 (293.75±77.96) mL and (356.5±77.61) mL, respectively, with no significant statistical
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52 123 difference between the two groups.

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54 124 Intraosseous infusion (IO), a drug delivery approach, uses the rich vascular network of
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57 125 the medullary canal in long bones to deliver drugs and fluids into the bloodstream. The
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60 126 medullary canal is composed of a network of venous sinuses and spaces which

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4 127 communicate with the circulatory system through the central canal, nutrient veins, and
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6 128 emissary veins. Therefore, drugs and fluids administered into the medullary canal can
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9 129 enter the circulatory system quickly and effectively. The medullary canal is surrounded
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11
12 130 by a bony structure, which provides anatomical basis for the delivery of drugs and fluids
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14 131 into the bone marrow and is unaffected by blood volume changes and has a high degree
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17 132 of permeability. IO can achieve similar pharmacokinetic and pharmacodynamic effects
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20 133 as intravascular administration and has the advantage of not increasing systemic
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23 134 complications, which has historically been used in the treatment of hematologic
24
25 135 malignancies. It can also be utilized in patients who are not suitable for intravascular
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28 136 drug administration. Recently, orthopedic surgeons have focused on the use of IO,
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31 137 primarily in periprosthetic joint infection. Young et al. (9) demonstrated in animal
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33 138 experiments that using intraosseous regional administration (IORA) to deliver
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36 139 equipotent doses of cefazolin or low doses of vancomycin can achieve better
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39 140 antibacterial effects and reduce the amount of bacterial colony formation (7.0 vs. 283,
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42 141 $P=0.0183$) compared to an intravenous infusion of equipotent doses of cefazolin or high
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45 142 doses of vancomycin. Young et al. (10) administered 500mg vancomycin via IORA or
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48 143 1000mg vancomycin intravenously to patients undergoing revision TKA. They found
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51 144 that the vancomycin concentration in the IORA group was 5.3 times that of the
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54 145 intravenous infusion group. Symonds et al. (11) suggested that administering antibiotics
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57 146 via IORA during TKA might reduce the incidence of periprosthetic joint infections.
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60 147 These studies suggest the feasibility of using IORA to deliver TXA in TKA.
148 However, there is currently a lack of study on IORA of TXA. As the femur medullary

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4 149 canal needs to be opened during conventional TKA, a natural pathway for IORA can
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6 150 be created and a sufficient amount of TXA can be delivered. Furthermore, hidden blood
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9 151 loss is mainly sourced from blood extravasation in the tissue spaces and blood
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11 152 accumulation in the joint cavity, as well as the loss of Hb due to its hemolytic activity.
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14 153 Intraoperative and postoperative bleeding from the medullary canals is also a significant
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16 154 source of hidden blood loss due to the need for invasive procedures that disrupt the
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18 155 medullary canals during TKA. Han et al. (12) reported a meta-analysis showing that
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20 156 the utilization of navigation technology during surgical procedures could significantly
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22 157 increase postoperative Hb levels, and reduce wound drainage (P=0.03) and TBL
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24 158 (P=0.002) by avoiding damage to the medullary canals. Thus, IORA of TXA combined
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26 159 with medullary canal blocking can theoretically increase the local concentration of
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28 160 TXA and reduce intraoperative blood loss. Also, as the infusion site is located at the far
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30 161 end of the tourniquet, there may be reduced restriction of tourniquet timing when
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32 162 administering TXA compared to intravenous infusion.
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42 163 We hypothesize that IORA of TXA combined with medullary canal blocking can
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44 164 reduce medullary canal bleeding and ensure local concentration of TXA, leading to
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46 165 reduce TBL of TKA. In comparison to traditional intravenous infusion, IORA of TXA
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48 166 has comparable safety and does not increase systemic complications. This study aims
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50 167 to provide a comprehensive exploration of the effectiveness and safety of IORA of TXA
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52 168 in TKA and to compare differences in perioperative blood loss between IORA of TXA,
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54 169 intravenous infusion of TXA, and combined IORA and intravenous infusion of TXA.
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59 170 Given the potential benefits of IORA of TXA, it is essential to investigate its feasibility

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4 171 and efficacy, and the resulting data will shed light on alternative use of TXA during
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6 172 TKA. If the hypothesis is confirmed, this technique might eventually become an
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9 173 effective choice for reducing perioperative blood loss, promoting postoperative
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12 174 recovery, and improving the overall efficacy of TKA.
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15 175 **Methods and analysis**

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19 176 This study is a randomized controlled trial that enrolled 105 patients with osteoarthritis
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22 177 who met the inclusion criteria for unilateral TKA from the Joint Surgery Center of
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25 178 Peking Union Medical College Hospital. Patients were randomly divided into three
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28 179 groups using the random number table method 30 minutes prior to the procedure. Group
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31 180 A received 1.0 g TXA via IORA from intraoperative femoral canal, group B received
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34 181 1.0 g TXA via intravenous infusion 15 minutes prior to tourniquet release, and group
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37 182 C received both intraoperative femoral canal infusion of 1.0 g TXA and intravenous
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40 183 infusion of 1.0 g TXA 15 minutes prior to tourniquet release. A detailed schema of the
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43 184 trial is presented in **Figure 1**.

44 185 **Eligibility criteria**

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48 186 Inclusion criteria were as follows: (1) with knee osteoarthritis; (2) receive primary
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51 187 unilateral TKA; (3) age between 20 and 80 years old; (4) voluntary signature of
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54 188 informed consent form.

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57 189 Exclusion criteria were as follows: (1) allergy to TXA, (2) high-risk factors for
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60 190 thrombosis, including a history of VTE, myocardial infarction, or stroke, concomitant

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4 191 malignant tumors, hypercoagulable state and prior thrombotic events; (3) concomitant
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6 192 severe organ diseases such as heart, brain, lung, kidney, or hematological disorders; (4)
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9 193 preoperative Hb level below 11 g/L; (5) underwent open orthopedic surgery within
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11 194 three weeks before the current procedure; (6) use of aspirin or other antiplatelet agents
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14 195 within one week before procedure; and (7) diseases requiring anticoagulant therapy or
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17 196 history of regular anticoagulant therapy.

197 **Treatment Protocol**

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

207 For IORA group, the effusion from the femoral medullary canal is aspirated with
208 suction, the opening femoral canal is sealed as previously described, 1.0 g (10 ml) of
209 TXA is injected into the distal femur from the opening of femoral canal with a 14 gauge
210 needle and 20 ml syringe. For IV group, 1.0 g TXA is administrated via intravenous
211 infusion 15 minutes prior to tourniquet release. After final implantation and the

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4 212 component is completely fixed, the tourniquet is released and careful hemostasis is
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6 213 performed before wound closure for all the patients. No drainage is placed in this study.
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9 214 All the patients accepted extra 1.0 g TXA intravenous treatment at 3 hours after the
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11 215 surgery.

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15 216 A uniform cocktail injection formula (ropivacaine 40mg, epinephrine 0.25 mg,
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17 217 flurbiprofen 50 mg, betamethasone 2 mg and 0.9% normal saline 30 ml) is used for
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19 218 periarticular injection for analgesia. Postoperative treatment follows *Expert consensus*
20
21 219 *in enhanced recovery after total knee arthroplasty in China*, which includes anti-
22
23 220 infection, analgesia, and anticoagulation therapy (13). Ten mg rivaroxaban is used for
24
25 221 VTE prevention within 24 hours after procedure and continue for 14 days. All patients
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27 222 receive physical thromboprophylaxis with lower limb gradient compression pump
28
29 223 during hospitalization. A uniform postoperative joint rehabilitation program and blood
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31 224 management strategies are adopted during the perioperative period. 10,000 IU of
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33 225 erythropoietin (EPO) is injected and 100 mg of iron agent is intravenously infused for
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35 226 red blood cell mobilization for postoperative 3 days.

36 37 38 39 40 41 42 43 44 45 227 **Data collection**

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49 228 The patients are followed until postoperative 3 months. The following medical data of
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51 229 patients will be collected during the investigation: sex; age; weight; comorbidities
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53 230 including primary hypertension, coronary atherosclerotic heart disease, hyperlipidemia,
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55 231 diabetes, and other cardiovascular and cerebrovascular diseases; laboratory test results
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57 232 including blood routine test, liver and kidney function test, coagulation function test
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4 233 (including D-dimer), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR);
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6 234 bilateral lower extremity venous ultrasound; leg circumference; complications
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9 235 including lower limb symptomatic VTE, cardiovascular and cerebrovascular events,
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11 236 bruising, TXA-related allergic reactions, allogeneic blood transfusion, etc.

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15 237 **Assessment of outcomes**

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19 238 *Primary outcome:*

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23 239 The primary outcome measure in this study is perioperative TBL, calculated by changes
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25 240 between the preoperative and postoperative hematocrit (HCT). The calculation method
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27 241 is as follows:

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31 242 (1) Measurements of HCT are taken preoperatively, and on POD 3.

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35 243 (2) Information on intraoperative and postoperative blood transfusion type and volume
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37 244 is recorded. Patients require blood transfusions in the following scenarios: (1) Hb <
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39 245 75 g/L; (2) Hb < 90 g/L in combination with circulatory disorders caused by low
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41 246 Hb, such as unstable circulation and ischemic heart disease. The TBL is calculated
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44 247 using the following formula:

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$$\text{TBL} = \text{PBV} \times (\text{HCT}_{\text{pre-op}} - \text{HCT}_{\text{post-op}}) \times 2 / (\text{HCT}_{\text{pre-op}} - \text{HCT}_{\text{post-op}}) + V_t$$

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51 249
$$\text{PBV} = k_1 \times \text{height}^3 \text{ (m}^3\text{)} + k_2 \times \text{weight (kg)} + k_3$$

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55 250 PBV: patient blood volume

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4 251 Vt: volume of allogeneic or autologous blood transfusion
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8 252 Male: $k_1 = 0.3669$, $k_2 = 0.03219$, $k_3 = 0.6041$
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11 253 Female: $k_1 = 0.3561$, $k_2 = 0.03308$, $k_3 = 0.1833$
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15 254 *Secondary outcomes:*
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19 255 1. Bleeding events:
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23 256 (1) The onset, location, extent, duration and evolution of postoperative bleeding
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25 257 events are recorded, including gastrointestinal bleeding, melena, and cutaneous
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27 258 mucosal bleeding (including ecchymosis and petechia).
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32 259 2. VTE events:
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36 260 (1) Measurements of coagulation function and CRP levels are taken preoperatively,
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38 261 on POD 1, 3.
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42 262 (2) Lower limb deep vein ultrasound is performed preoperatively. Postoperative
43
44 263 deep vein ultrasound is performed from on POD 14 to POD 28.
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49 264 (3) Postoperative symptomatic VTE is recorded including lower limb swelling and
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51 265 pain caused by deep vein thrombosis, as well as symptomatic pulmonary
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53 266 embolism.
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4 267 3. Inflammation reactions: Measurements of ESR, CRP, and IL-6 levels are taken
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6 268 preoperatively, on POD 1, 3, and 14.
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10 269 4. Other complications:
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14 270 (1) The relevant information of postoperative discomfort symptoms is recorded,
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16 271 including gastrointestinal symptoms, central nervous system symptoms, allergic
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18 272 reactions, fever, etc.
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23 273 (2) Preoperative and postoperative measurements of the circumference of both legs at
24
25 274 10cm above the patella and 10cm below the tibial tuberosity are taken, and the
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27 275 healing progress of the incision is recorded.
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32 276 (3) Cardiovascular and cerebrovascular complications during medication management
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34 277 are recorded, such as cerebral infarction, cerebral hemorrhage, myocardial
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36 278 infarction, heart failure, arrhythmia, shock, etc.
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41 279 5. Knee function assessments: Measurements of duration of straight leg raise exercise,
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43 280 knee range of motion (ROM), and Knee Society Score (KSS) are taken
44
45 281 preoperatively, and on POD 14 and 3 months follow-up.
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50 282 **Data evaluation and sample size**

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54 283 The sample size was calculated using the TBL of unilateral TKA in previous studies,
55
56 284 and a difference in postoperative Hb of 10g/L or more was considered significant. With
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58 285 $\alpha=0.05$, $\beta=0.2$, and a follow-up loss rate of 10%, 35 cases are required per group.
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4 286 Statistical analysis is performed using SPSS 16.0 software. For qualitative data, the χ^2
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6 287 test for independent $R \times C$ contingency table data should be used. For quantitative data,
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9 288 expressed as mean \pm standard deviation in this study, the t -test for paired design data or
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11 289 two independent samples should be used. A test level of $\alpha=0.05$ is adopted, and $P <$
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14 290 0.05 is considered to be statistically significant.

17 18 291 **Safety evaluation and risk minimization measures**

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22 292 Exclusion criteria for this study include patients with a hypercoagulable state. We
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24 293 actively encourage and monitor lower extremity functional exercise and early
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27 294 ambulation for patients after procedure. Routine postoperative use of rivaroxaban,
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30 295 compression stockings, and continuous passive motion (CPM), are employed to prevent
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32 296 VTE. For potential cardiovascular events, postoperative monitoring of vital signs such
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35 297 as electrocardiogram and blood oxygen levels is regularly conducted. We closely
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38 298 monitor patient complaints and proactively prevent and manage any potential risks.
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40 299 Internal medicine specialists are involved as necessary for diagnosis and treatment.
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43 300 Potential risk factors for this study include TXA-related hypersensitivity reactions and
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46 301 thromboembolic risks.

47 48 49 302 **Clinical specimen management and data preservation**

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53 303 We retain all information related to this study, including records of drug dosages and
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56 304 timings administered to study participants, all signed informed consent forms, and all
57
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59 305 data collected throughout the study process. The retention period is five years.
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4 **306 Patient and public involvement**
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8 307 The development of the research question and outcome measures is not influenced by
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10 308 patients' priorities, experiences and preferences. Participants and the public do not
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13 309 involve in the design, recruitment or conduct of the study.
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17 **310 Ethics and dissemination**
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21 311 This study has been authorised by the Ethics Committee of Peking Union Medical
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23 312 College Hospital (approval number: K2371) and Chinese Clinical Trial Registry (trial
24
25 313 registration number: ChiCTR2200066293), and is being conducted in accordance with
26
27 314 the Helsinki Declaration. Prior to participating, all participants provide signed informed
28
29 315 consent. Participation in the study do not interfere with hospital care, and they have the
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31 316 right to withdraw consent at any time without experiencing any negative consequences.
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34 317 Authorship is granted to investigators who have contributed to the project's design,
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36 318 conduct, statistical analysis, interpretation, and reporting. The findings of this study will
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39 319 be published in a peer-reviewed academic journal.
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45 **320 Ethics statements**
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49 **321 Patient consent for publication**
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53 322 Not required.
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57 **323 Author contributions**
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4 324 This study was designed by Bin Feng and Xisheng Weng. This manuscript was written
5
6 325 by Zhanqi Wei, Muyang Yu, Yiming Xu and Bin Feng. All authors approved the final
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9 326 version.
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11 12 13 327 **Competing interest statement**

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16
17 328 The authors declare that the research was conducted in the absence of any commercial
18
19 329 or financial relationships that could be construed as a potential conflict of interest.
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22

23 330 **Funding statement**

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27 331 This work was supported by Chinese Academy of Medical Sciences (CAMS)
28
29 332 Innovation Fund for Medical Sciences (CIFMS; No. 2022-I2M-C&T-B-031), the
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32 333 National High Level Hospital Clinical Research Funding (No. 2022-PUMCH-A-124).
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36 334 **References**

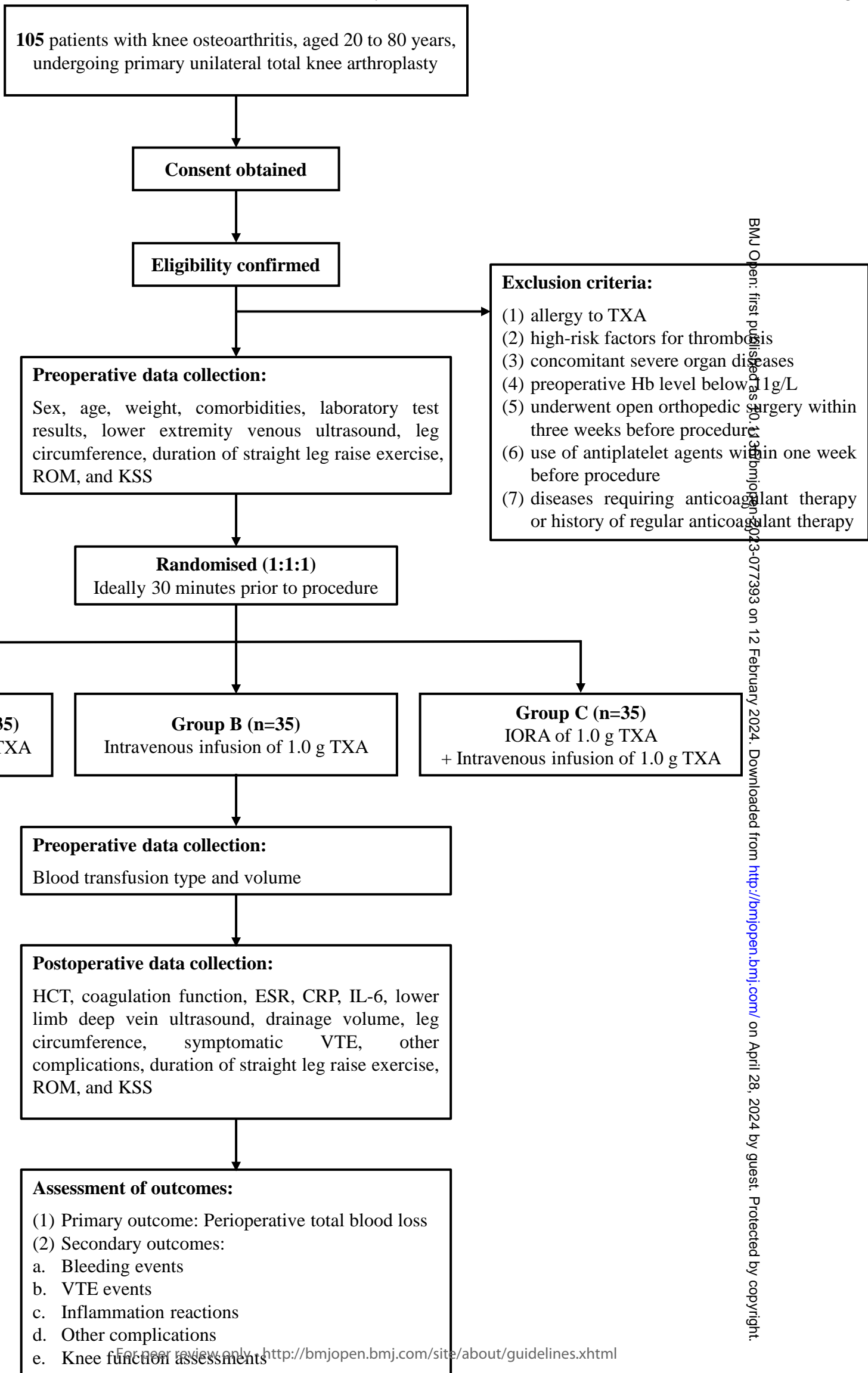
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37 377 **Figure legends**
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40 378 **Figure 1. Trial schema.** TXA, tranexamic acid; Hb, hemoglobin; ROM, range of
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42 379 motion; KSS, Knee Society Score; IORA, intraosseous regional administration; HCT,
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44 380 hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VTE,
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46 381 venous thromboembolism.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-077393.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Dec-2023
Complete List of Authors:	Wei, Zhanqi; Peking Union Medical College Hospital, Yu, Muyang; Peking Union Medical College Hospital, Department of Orthopedics Xu, Yiming; Peking Union Medical College Hospital, Department of Orthopedics Weng, Xisheng; Peking Union Medical College Hospital, Department of Orthopedic Surgery Feng, Bin; Peking Union Medical College Hospital, Department of Orthopedics
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	ORTHOPAEDIC & TRAUMA SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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Manuscripts

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5 1 **Impact of intraosseous regional administration of tranexamic**
6 **acid in total knee arthroplasty on perioperative blood loss: a**
7 **protocol for a randomized controlled trial**
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14 Zhanqi Wei^{1,2}, MUYANG Yu¹, Yiming Xu¹, Xisheng Weng¹, Bin Feng¹
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18 ¹Department of Orthopedics, Peking Union Medical College Hospital, Chinese
19 Academy of Medical Sciences and Peking Union Medical College, Beijing 100730,
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26 ²School of Medicine, Tsinghua University, Beijing 100084, China.

28 Correspondence to Bin Feng: pumcfeng@163.com

32 **Abstract**

36 **Introduction:** Total knee arthroplasty (TKA) is a common surgical intervention to treat
37 joint diseases. However, TKA is associated with significant blood loss. Tranexamic
38 acid (TXA) has been used to reduce perioperative bleeding and postoperative blood
39 transfusion. This study aims to explore the effectiveness and safety of intraosseous
40 regional administration (IORA) of TXA in TKA and compare differences in
41 perioperative blood loss between IORA of TXA, intravenous infusion of TXA, and
42 combined IORA and intravenous infusion of TXA.
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54 **Methods and analysis:** This randomized controlled trial will enroll 105 patients with
55 osteoarthritis who meet the inclusion criteria for unilateral TKA. Patients were
56 randomly divided into three groups using the random number table method. Group A
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4 21 received 1.0 g TXA via IORA, group B received 1.0 g TXA via intravenous infusion
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6 22 15 minutes prior to tourniquet release, and group C received both IORA of 1.0 g TXA
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9 23 and intravenous infusion of 1.0 g TXA. The primary outcome measure is perioperative
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11 24 total blood loss. Secondary outcomes include bleeding events, VTE events,
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14 25 inflammation reactions, other complications, and knee function assessments.

16
17 26 **Ethics and dissemination:** This study has been approved by the Ethics Committee of
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19 27 Peking Union Medical College Hospital and registered in the Chinese Clinical Trial
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21 28 Registry. Informed consent will be obtained from all patients before enrollment. The
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23 29 trial will be conducted in accordance with the principles of the Declaration of Helsinki
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25 30 and the International Conference on Harmonization Good Clinical Practice guidelines.
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27 31 The results of this study will be disseminated through peer-reviewed publications,
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29 32 conference presentations, and social media platforms. The findings will provide
30
31 33 valuable insights into the use of IORA of TXA in TKA, and may lead to the
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33 34 development of new strategies for perioperative blood management in joint
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35 35 replacement surgery.

36
37 36 **Trial registration number:** The Ethics Committee of Peking Union Medical College
38
39 37 Hospital (approval number: K2371); Chinese Clinical Trial Registry (trial registration
40
41 38 number: ChiCTR2200066293).

39 **Strengths and limitations of this study**

- 40
41 40 1. The study design is a randomized controlled trial, providing a comprehensive
42
43 41 exploration of the effectiveness and safety of IORA of TXA in TKA.

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4 42 2. The study uses a uniform cocktail injection formula for postoperative analgesia
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6 43 during the procedure and a uniform postoperative joint rehabilitation program and
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9 44 blood management strategies, which may minimize potential confounding factors.
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11
12 45 3. The study collects a wide range of medical data, including bleeding events, VTE
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14 46 events, inflammation reactions, other complications, and knee function assessments,
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16
17 47 which may provide a comprehensive evaluation of the efficacy and safety of IORA
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19 48 of TXA in TKA.
20
21
22 49 4. The study includes a detailed eligibility criteria and exclusion criteria, which may
23
24 50 ensure the reliability and validity of the study results.
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26
27 51 5. The sample size is relatively small, which may limit the generalizability of the study.
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30 52 The estimation formula for TBL has certain limitations that may affect the accuracy
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32 53 of the results.
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54 **Introduction**

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

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4 63 The use of a tourniquet during TKA can significantly reduce intraoperative blood loss,
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6 64 with an average TBL of 1474 ml and hidden blood loss of 735 ml, which accounts for
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9 65 50% of TBL. However, releasing the tourniquet may lead to an imbalance of
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11 66 fibrinolysis-coagulation, causing an excessive activation of the fibrinolysis system. In
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14 67 addition, tourniquet use can cause lower limb ischemia, microcirculation disorders, and
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17 68 distal ischemia-reperfusion injury, leading to further exacerbate the fibrinolytic
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20 69 response (2).
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22

23 70 Tranexamic acid (TXA) is a lysine derivative that can effectively block the interaction
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26 71 between lysine residues and the heavy chain of plasmin, preventing plasmin from
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29 72 binding to fibrin monomers and inhibiting the lysis of fibrin clots. This mechanism
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32 73 provides the basis for the use of TXA, often used to reduce perioperative bleeding and
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34 74 postoperative blood transfusion.
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37 75 In 1987, Benoni et al. (3) first applied TXA to postoperative bleeding control in TKA.
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40 76 The methods for using TXA include intravenous infusion, local application, and oral
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43 77 administration. Intravenous infusion of TXA can achieve maximum blood drug
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46 78 concentration in 5-15 minutes, rapidly diffusing into synovial tissue and synovial fluid,
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49 79 achieving a concentration similar to the maximum plasma concentration, and with a
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52 80 half-life in the synovial fluid of up to 3 hours. Alshryda et al. (4) analyzed a randomized
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55 81 controlled trial of intravenous infusion of TXA during TKA and found that the use of
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58 82 TXA could reduce the average TBL by 591 ml, and shorten the average length of
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60 83 hospital stay by 0.76 days. The therapeutic effect is related to the dose of the drug, and

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4 84 an overdose can cause systemic complications, while an insufficient dose can lead to
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6 85 ineffective local concentration of TXA in the joints. Additionally, for patients using
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9 86 tourniquets during TKA, the therapeutic effect of intravenous TXA is related to the
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11 87 timing of administration during procedure; typically, TXA should be administered
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14 88 intravenously 15 minutes before the tourniquet is released, but mistakes may happen in
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17 89 practice, which may impact the effectiveness of intravenous TXA infusion.

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21 90 Since TXA can quickly penetrate into tissues in the joint cavity and reach the maximum
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23 91 drug activity in the target organs, local application can limit the systemic accumulation
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26 92 of TXA and broaden the indications for TXA. Seo et al. (5) conducted a randomized
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28 93 controlled trial on patients undergoing TKA, and reported that local application of TXA
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31 94 could reduce blood loss by about 400 ml, reduce the postoperative decrease in
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33
34 95 hemoglobin (Hb) by about 1.3 g/dl, and have relatively fewer systemic complications.
35
36 96 Ishida et al. (6) found that local application of TXA during TKA not only reduced TBL
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39 97 but also reduced the degree of swelling on the operated limb. Wind et al. (7) compared
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41
42 98 the effects of intravenous infusion and local application of TXA on intraoperative blood
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45 99 loss in TKA. They found that none of the patients in the local application group required
46
47 100 blood transfusion, while the transfusion rate in the intravenous infusion group was 0.3%.
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49 101 Hamlin et al. (8) compared the efficacy of 1.0 g TXA administered via intravenous
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52 102 infusion before procedure and 3 g TXA diluted in 100ml of saline and locally injected
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55 103 into the joint cavity through a drainage tube. The local application group had
56
57 104 significantly lower Hb decline (2.2 g vs 2.8 g) and transfusion rate (0% vs 2.4%)
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60 105 compared to the intravenous infusion group, but there was no difference in hospital stay

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4 106 or incidence of venous thromboembolism (VTE) between the two groups.
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8 107 However, there is still uncertainty about the optimal dosage of TXA. Currently favored
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10 108 options include a single dose of 10 mg/kg, 15 mg/kg, or 20 mg/kg or a standardized
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13 109 dose of 1.0 g. In a randomized controlled trial conducted by Levine et al. (9), the
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16 110 difference in TBL between the standardized dose group (1.0 g) and personalized dose
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18 111 group (20 mg/kg) was investigated. The results showed that the TBL for the
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21 112 standardized dose group and the personalized dose group was (293.75 ± 77.96) mL and
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23 113 (356.5 ± 77.61) mL, respectively, with no significant statistical difference between the
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26 114 two groups.
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30 115 Intraosseous infusion (IO), a drug delivery approach, uses the rich vascular network of
31
32 116 the medullary canal in long bones to deliver drugs and fluids into the bloodstream. The
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35 117 medullary canal is composed of a network of venous sinuses and spaces which
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38 118 communicate with the circulatory system through the central canal, nutrient veins, and
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41 119 emissary veins. Therefore, drugs and fluids administered into the medullary canal can
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44 120 enter the circulatory system quickly and effectively. The medullary canal is surrounded
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47 121 by a bony structure, which provides anatomical basis for the delivery of drugs and fluids
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50 122 into the bone marrow and is unaffected by blood volume changes and has a high degree
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53 123 of permeability. IO can achieve similar pharmacokinetic and pharmacodynamic effects
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56 124 as intravascular administration and has the advantage of not increasing systemic
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59 125 complications, which has historically been used in the treatment of hematologic
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126 malignancies. It can also be utilized in patients who are not suitable for intravascular

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4 127 drug administration. Recently, orthopedic surgeons have focused on the use of IO,
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6 128 primarily in periprosthetic joint infection. Young et al. (10) demonstrated in animal
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9 129 experiments that using intraosseous regional administration (IORA) to deliver
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11
12 130 equipotent doses of cefazolin or low doses of vancomycin can achieve better
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14 131 antibacterial effects and reduce the amount of bacterial colony formation compared to
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17 132 an intravenous infusion of equipotent doses of cefazolin or high doses of vancomycin.
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19 133 Young et al. (11) administered 500mg vancomycin via IORA or 1000mg vancomycin
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22 134 intravenously to patients undergoing revision TKA. They found that the vancomycin
23
24 135 concentration in the IORA group was 5.3 times that of the intravenous infusion group.
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27 136 Symonds et al. (12) suggested that administering antibiotics via IORA during TKA
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30 137 might reduce the incidence of periprosthetic joint infections. These studies suggest the
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33 138 feasibility of using IORA to deliver TXA in TKA.
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36 139 However, there is currently a lack of study on IORA of TXA. As the femur medullary
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39 140 canal needs to be opened during conventional TKA, a natural pathway for IORA can
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42 141 be created and a sufficient amount of TXA can be delivered. Furthermore, hidden blood
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45 142 loss is mainly sourced from blood extravasation in the tissue spaces and blood
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48 143 accumulation in the joint cavity, as well as the loss of Hb due to its hemolytic activity.
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51 144 Intraoperative and postoperative bleeding from the medullary canals is also a significant
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54 145 source of hidden blood loss due to the need for invasive procedures that disrupt the
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57 146 medullary canals during TKA. Han et al. (13) reported a meta-analysis showing that
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60 147 the utilization of navigation technology during surgical procedures could significantly
148 increase postoperative Hb levels, and reduce TBL by avoiding damage to the medullary

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4 149 canals. Thus, IORA of TXA combined with medullary canal blocking can theoretically
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6 150 increase the local concentration of TXA and reduce intraoperative blood loss. Also, as
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9 151 the infusion site is located at the far end of the tourniquet, there may be reduced
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12 152 restriction of tourniquet timing when administering TXA compared to intravenous
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15 153 infusion.

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18 154 Given the potential benefits of IORA of TXA, it is essential to investigate its feasibility
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21 155 and efficacy, and the resulting data will shed light on alternative use of TXA during
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24 156 TKA. This study aims to provide a comprehensive exploration of the effectiveness and
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27 157 safety of IORA of TXA in TKA and to compare differences in perioperative blood loss
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30 158 between IORA of TXA, intravenous infusion of TXA, and combined IORA and
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33 159 intravenous infusion of TXA. We hypothesize that IORA of TXA combined with
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36 160 medullary canal blocking can reduce medullary canal bleeding and ensure local
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39 161 concentration of TXA, leading to reduce TBL of TKA. In comparison to traditional
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41
42 162 intravenous infusion, IORA of TXA has comparable safety and does not increase
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45 163 systemic complications. If the hypothesis is confirmed, this technique might eventually
46
47
48 164 become an effective choice for reducing perioperative blood loss, promoting
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51 165 postoperative recovery, and improving the overall efficacy of TKA.

166 **Methods and analysis**

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53
54 167 This study is a randomized controlled trial that enrolled 105 patients with osteoarthritis
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57 168 who met the inclusion criteria for unilateral TKA from the Joint Surgery Center of
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60 169 Peking Union Medical College Hospital. Patients were randomly divided into three

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4 170 groups using the random number table method 30 minutes prior to the procedure.
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6 171 Specially, the number table was generated using a random number generator, consisting
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9 172 of a sequence of 46 numbers (1, 2, or 3) representing the 46 beds in our center. The
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11 173 patients' bed numbers were matched with the numbers in the random number table,
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14 174 where 1, 2, and 3 corresponded to Groups A, B, and C, respectively. Group A received
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17 175 1.0 g TXA via IORA from intraoperative femoral canal, group B received 1.0 g TXA
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19 176 via intravenous infusion 15 minutes prior to tourniquet release, and group C received
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22 177 both intraoperative femoral canal infusion of 1.0 g TXA and intravenous infusion of
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24 178 1.0 g TXA 15 minutes prior to tourniquet release. A detailed schema of the trial is
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27 179 presented in **Figure 1**.

180 **Eligibility criteria**

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

184 Exclusion criteria were as follows: (1) allergy to TXA, (2) high-risk factors for
185 thrombosis, including a history of VTE, myocardial infarction, or stroke, concomitant
186 malignant tumors, hypercoagulable state and prior thrombotic events; (3) concomitant
187 severe organ diseases such as heart, brain, lung, kidney, or hematological disorders; (4)
188 preoperative Hb level below 11 g/L; (5) underwent open orthopedic surgery within
189 three weeks before the current procedure; (6) use of aspirin or other antiplatelet agents

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4 190 within one week before procedure; and (7) diseases requiring anticoagulant therapy or
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6 191 history of regular anticoagulant therapy.
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10 192 **Treatment Protocol**

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14 193 All the TKA procedure is performed under tourniquet. The proximal tibia cut is
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16 194 performed with an extramedullary guide. The distal femoral cut is performed with an
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18 195 intramedullary guide and femoral canal is opened. The anterior, posterior, anterior
19
20 196 chamfer and posterior chamfer are prepared with conventional cutting jig. Posterior
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22 197 stabilized (PS) prosthesis is used for all the patients and the intercondylar box is prepared
23
24 198 with cutting jig. The femur component with open box design is used for femur side
25
26 199 (Weigao, Shandong, China). All the components are fixed with cement. Before final
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28 200 implantation, the opening of femoral canal is filled with gelatin sponge and completely
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30 201 sealed with compaction autogenous bone from the anterior chamfer cut.
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39 202 For IORA group, the effusion from the femoral medullary canal is aspirated with
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41 203 suction, the opening femoral canal is sealed as previously described, 1.0 g (10 ml) of
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43 204 TXA is injected into the distal femur from the opening of femoral canal with a 14 gauge
44
45 205 needle and 20 ml syringe. For IV group, 1.0 g TXA is administrated via intravenous
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47 206 infusion 15 minutes prior to tourniquet release. After final implantation and the
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49 207 component is completely fixed, the tourniquet is released and careful hemostasis is
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51 208 performed before wound closure for all the patients. No drainage is placed in this study.
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57 209 All the patients accepted extra 1.0 g TXA intravenous treatment at 3 hours after the
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59 210 surgery.
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4 211 A uniform cocktail injection formula (ropivacaine 40mg, epinephrine 0.25 mg,
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6 212 flurbiprofen 50 mg, betamethasone 2 mg and 0.9% normal saline 30 ml) is used for
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9 213 periarticular injection for analgesia. Postoperative treatment follows *Expert consensus*
10
11 214 *in enhanced recovery after total knee arthroplasty in China*, which includes anti-
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14 215 infection, analgesia, and anticoagulation therapy (14). Ten mg rivaroxaban is used for
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17 216 VTE prevention within 24 hours after procedure and continue for 14 days. All patients
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20 217 receive physical thromboprophylaxis with lower limb gradient compression pump
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22 218 during hospitalization. A uniform postoperative joint rehabilitation program and blood
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25 219 management strategies are adopted during the perioperative period. 10,000 IU of
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27 220 erythropoietin (EPO) is injected and 100 mg of iron agent is intravenously infused for
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30 221 red blood cell mobilization for postoperative 3 days.

32 33 34 222 **Data collection**

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37 223 The patients are followed until postoperative 3 months. The following medical data of
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40 224 patients will be collected during the investigation: sex; age; weight; comorbidities
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42
43 225 including primary hypertension, coronary atherosclerotic heart disease, hyperlipidemia,
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46 226 diabetes, and other cardiovascular and cerebrovascular diseases; laboratory test results
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48
49 227 including blood routine test, liver and kidney function test, coagulation function test
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51 228 (including D-dimer), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR);
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54 229 bilateral lower extremity venous ultrasound; leg circumference; complications
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57 230 including lower limb symptomatic VTE, cardiovascular and cerebrovascular events,
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59 231 bruising, TXA-related allergic reactions, allogeneic blood transfusion, etc.

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4 232 **Assessment of outcomes**

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8 233 *Primary outcome:*

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11 234 The primary outcome measure in this study is perioperative TBL, calculated by changes
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14 235 between the preoperative and postoperative hematocrit (HCT). The calculation method
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17 236 is as follows:

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21 237 (1) Measurements of HCT are taken preoperatively, and on POD 3.

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24 238 (2) Information on intraoperative and postoperative blood transfusion type and volume
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26
27 239 is recorded. Patients require blood transfusions in the following scenarios: (1) Hb <
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30 240 75 g/L; (2) Hb < 90 g/L in combination with circulatory disorders caused by low
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33 241 Hb, such as unstable circulation and ischemic heart disease. The TBL is calculated
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35 242 using the following formula:

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39 243
$$\text{TBL} = \text{PBV} \times (\text{HCT}_{\text{pre-op}} - \text{HCT}_{\text{post-op}}) \times 2 / (\text{HCT}_{\text{pre-op}} - \text{HCT}_{\text{post-op}}) + \text{Vt}$$

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43 244
$$\text{PBV} = k_1 \times \text{height}^3 (\text{m}^3) + k_2 \times \text{weight} (\text{kg}) + k_3$$

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47 245 PBV: patient blood volume

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51 246 Vt: volume of allogeneic or autologous blood transfusion

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55 247 Male: $k_1 = 0.3669$, $k_2 = 0.03219$, $k_3 = 0.6041$

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59 248 Female: $k_1 = 0.3561$, $k_2 = 0.03308$, $k_3 = 0.1833$

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4 249 *Secondary outcomes:*
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8 250 1. Bleeding events:
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11 251 (1) The onset, location, extent, duration and evolution of postoperative bleeding
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13 252 events are recorded, including gastrointestinal bleeding, melena, and cutaneous
14
15 253 mucosal bleeding (including ecchymosis and petechia).
16
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21 254 2. VTE events:
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25 255 (1) Measurements of coagulation function and CRP levels are taken preoperatively,
26
27 256 on POD 1, 3.
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31 257 (2) Lower limb deep vein ultrasound is performed preoperatively. Postoperative
32
33 258 deep vein ultrasound is performed from on POD 14 to POD 28.
34
35

36
37 259 (3) Postoperative symptomatic VTE is recorded including lower limb swelling and
38
39 260 pain caused by deep vein thrombosis, as well as symptomatic pulmonary
40
41 261 embolism.
42
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47 262 3. Inflammation reactions: Measurements of ESR, CRP, and IL-6 levels are taken
48
49 263 preoperatively, on POD 1, 3, and 14.
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53 264 4. Other complications:
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4 265 (1) The relevant information of postoperative discomfort symptoms is recorded,
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6 266 including gastrointestinal symptoms, central nervous system symptoms, allergic
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9 267 reactions, fever, etc.

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13 268 (2) Preoperative and postoperative measurements of the circumference of both legs at
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15 269 10cm above the patella and 10cm below the tibial tuberosity are taken, and the
16
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18 270 healing progress of the incision is recorded.

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22 271 (3) Cardiovascular and cerebrovascular complications during medication management
23
24 272 are recorded, such as cerebral infarction, cerebral hemorrhage, myocardial
25
26
27 273 infarction, heart failure, arrhythmia, shock, etc.

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31 274 5. Knee function assessments: Measurements of duration of straight leg raise exercise,
32
33 275 knee range of motion (ROM), and Knee Society Score (KSS) are taken
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36 276 preoperatively, and on POD 14 and 3-month follow-up.

37 38 39 40 277 **Data evaluation and sample size**

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44 278 The sample size was calculated using the TBL of unilateral TKA in previous studies,
45
46 279 and a difference in postoperative Hb of 10g/L or more was considered significant. With
47
48
49 280 $\alpha=0.05$, $\beta=0.2$, and a follow-up loss rate of 10%, 35 cases are required per group.

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51
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53 281 Statistical analysis is performed using SPSS 16.0 software. For qualitative data, the χ^2
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55 282 test for independent $R \times C$ contingency table data should be used. For quantitative data,
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57
58 283 expressed as mean \pm standard deviation in this study, the t -test for paired design data or
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60

284 two independent samples should be used. A test level of $\alpha=0.05$ is adopted, and $P <$
285 0.05 is considered to be statistically significant.

286 **Safety evaluation and risk minimization measures**

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

297 **Clinical specimen management and data preservation**

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

301 **Patient and public involvement**

302 The development of the research question and outcome measures is not influenced by

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4 303 patients' priorities, experiences and preferences. Participants and the public do not
5
6 304 involve in the design, recruitment or conduct of the study.
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10 305 **Ethics and dissemination**

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14 306 This study has been authorised by the Ethics Committee of Peking Union Medical
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16 307 College Hospital (approval number: K2371) and Chinese Clinical Trial Registry (trial
17
18 308 registration number: ChiCTR2200066293), and is being conducted in accordance with
19
20 309 the Helsinki Declaration. Prior to participating, all participants provide signed informed
21
22 310 consent. Participation in the study do not interfere with hospital care, and they have the
23
24 311 right to withdraw consent at any time without experiencing any negative consequences.
25
26 312 Authorship is granted to investigators who have contributed to the project's design,
27
28 313 conduct, statistical analysis, interpretation, and reporting. The findings of this study will
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30 314 be published in a peer-reviewed academic journal.
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39 315 **Ethics statements**

40 41 42 43 316 **Patient consent for publication**

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46 47 317 Not required.
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50 51 318 **Author contributions**

52
53 54 319 This study was designed by Bin Feng and Xisheng Weng. This manuscript was written
55
56 57 320 by Zhanqi Wei, Muiyang Yu, Yiming Xu and Bin Feng. All authors approved the final
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59 321 version.
60

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4 322 **Competing interest statement**
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7

8 323 The authors declare that the research was conducted in the absence of any commercial
9
10 324 or financial relationships that could be construed as a potential conflict of interest.
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14 325 **Funding statement**
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18 326 This work was supported by the Beijing Natural Science Foundation (L232006),
19
20 327 Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences
21
22 328 (CIFMS; No. 2022-I2M-C&T-B-031), the National High Level Hospital Clinical
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24 329 Research Funding (No. 2022-PUMCH-A-124).
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30 330 **References**
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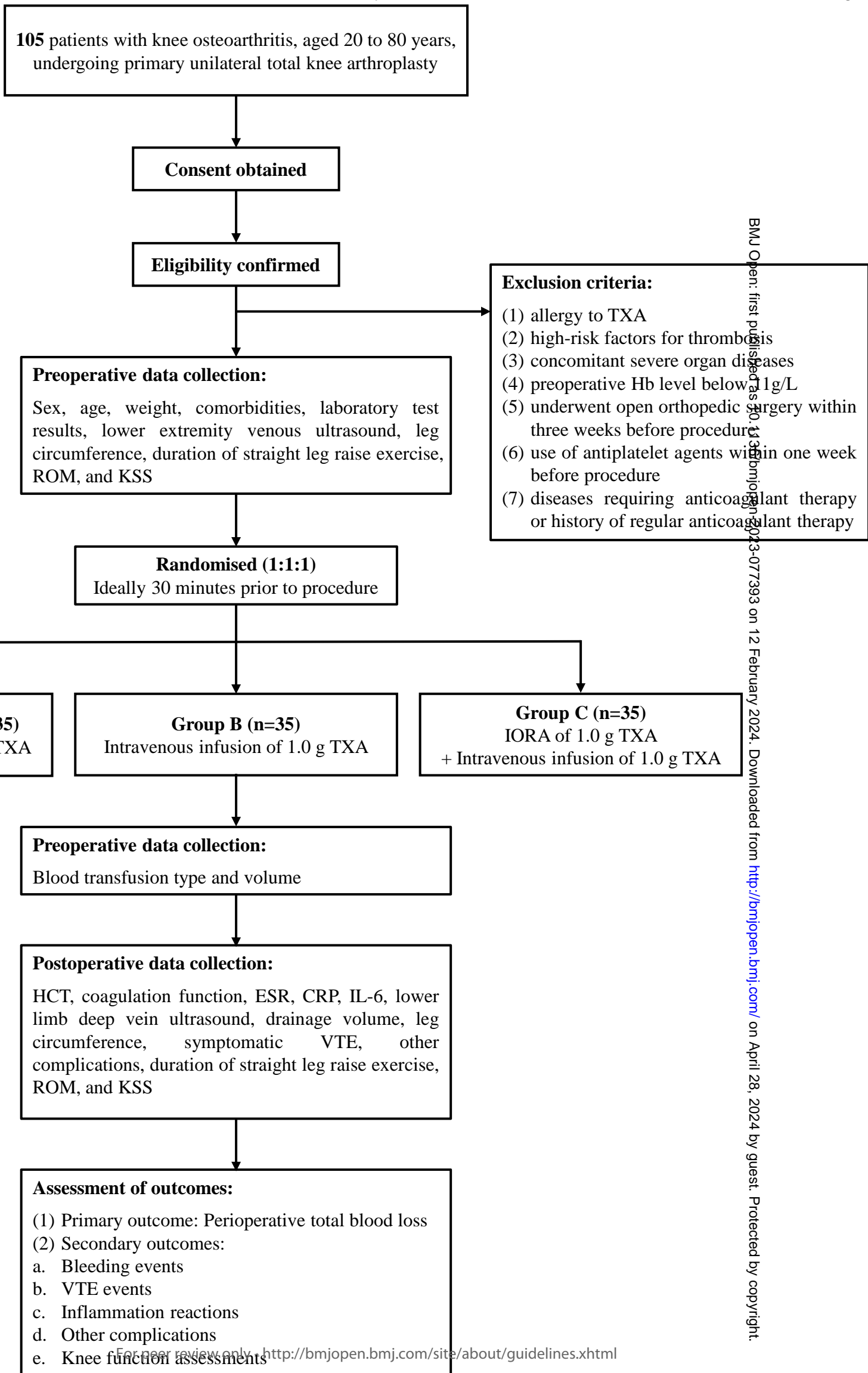
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29 373 **Figure legends**

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32 374 **Figure 1. Trial schema.** TXA, tranexamic acid; Hb, hemoglobin; ROM, range of
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34 375 motion; KSS, Knee Society Score; IORA, intraosseous regional administration; HCT,
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36 376 hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VTE,
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39 377 venous thromboembolism.
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