Multiple intravenous tranexamic acid doses in total knee arthroplasty in patients with rheumatoid arthritis: a randomized controlled study

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Research article

Abstract

Background: To identify the efficacy and safety of multiple doses of intravenous tranexamic acid (IV-TXA) on perioperative blood loss in patients with rheumatoid arthritis (RA) who have undergone primary unilateral total knee arthroplasty (TKA).

Methods: For this single-center, single-blind randomized controlled clinical trial, 10 male and 87 female participants aged 50–75 years, with RA who underwent unilateral primary TKA were recruited. The patients received one dose of 1g IV-TXA was 10 min before skin incision, followed by articular injection 1.5 g TXA after cavity suture during the surgery. The patients were randomly assigned (1:1) into two groups and received an additional single dose of IV-TXA (1 g) for 3 h (group A) or three doses of IV-TXA (1 g) for 3, 6, and 12 h (group B) postoperatively. Primary outcomes were total blood loss (TBL), hidden blood loss (HBL), and maximum hemoglobin (Hb) decrease. Secondary outcomes were transfusion rate and D-dimer levels. All parameters were measured postoperatively during inpatient hospital stay.

Results: Between September 2019 and May 2020, 104 participants were randomized, but 7 were lost to follow-up. The mean TBL, HBL, and maximum Hb decrease in group B (506.1 ± 227.0 mL, 471.6 ± 224.0 mL, and 17.5 ± 7.7 g/L, respectively) were significantly lower than those in group A (608.8 ± 244.8 mL, P = 0.035; 574.0 ± 242.3 mL, P = 0.033; and 23.42 ± 9.2 g/L, P = 0.001, respectively). No episode of transfusion occurred. D-dimer level was lower in group B than in group A on postoperative day 1 ($P <$ 0.001), and the incidence of thromboembolic events was similar between the two groups ($P >$ 0.05).

Conclusion: In patients with RA, three doses of postoperative IV-TXA further enabled HBL and Hb decrease without increasing the incidence of adverse events in a short period of time after TKA.

Trial registration: The trial was registered in Chinese Clinical Trial Registry (ChiCTR1900025013).

Background

Rheumatoid arthritis (RA) is an autoimmune disease with erosive arthritis as the main clinical manifestation. The basic pathological manifestations are synovitis, pannus formation, and articular cartilage, and gradual bone destruction, eventually leading to joint deformity and dysfunction[1]. The main onset age for RA is 40–60 years old[2]. Use of anti-rheumatic drugs and biological agents delayed the progress of bone destruction in patients with RA; in fact, the number of RA patients receiving total knee arthroplasty (TKA) has gradually decreased over the past few decades. However, in advanced-stage RA patients with severe knee joint destruction, TKA is effective for improving knee function and quality of life[3,4]. However, TKA can lead to blood loss; the mean blood loss during the perioperative period of TKA can reach 1470mL[5].Moreover, RA patients have a higher incidence of anemia[6]. Low of hemoglobin (Hb) levels before surgery also increases the risk of blood transfusion after surgery[7]. Considering that blood transfusion increases the risk of postoperative infections and prolongs hospital stay[8], it is vital important to reduce TKA perioperative blood loss and accelerate postoperative recovery. In a previous study, perioperative use of multi-mode blood management successfully reduced perioperative blood loss

[9,10]. Moreover, in 2010, a combination of multiple strategies of blood management was shown to reduce total blood transfusion rate after TKA to less than 4%[11].

Postoperative bleeding is mainly caused by fibrinolysis due to surgical trauma. Although tourniquet application can reduce intraoperative bleeding, fibrinolysis and postoperative bleeding will increase following postoperative release of tourniquet[12]. The anti-fibrinolytic drug tranexamic acid (TXA), by preventing the combination between plasminogen and fibrin, protects fibrin from degradation by plasmin to achieve hemostasis[13]. Clinical studies have confirmed that TXA can reduce the incidence of anemia incidence after TKA and reduce transfusion rate without elevating the incidence of venous thrombosis[14−[15][16]17]. A meta-analysis by Poeran J showed that 2g TXA has the best effectiveness and safety profile[18]. However, there is still no consensus on the optimal dosage and timing of TXA administration[19].

Patients with RA may suffer from mild to moderate anemia; thus, they have higher risk of infection at the surgical site than that in patients with OA[20]. Therefore, we hypothesized that high drug doses will be beneficial for RA patients undergoing TKA. In our orthopedic department, enhanced recovery after surgery (ERAS) is strongly advocated, for which blood management is an essential. Thus, in this randomized controlled trial, the pharmacokinetics of TXA were determined to evaluate the efficacy and safety of multi-dose intravenous TXA (IV-TXA) in alleviating postoperative blood loss in patients with RA who underwent primary unilateral TKA.

Methods

Study design

This was a single-center, single-blind, randomized controlled trial. The study was conducted at the Department of Orthopedics in Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine and registered in the Chinese Clinical Trial Registry (ChiCTR1900025013). The study was approved by the institutional review board (Ethics Committee of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine). All experimental procedures were conducted according to the Standards of Reporting Trials (CONSORT) recommendations for randomized controlled trials[21], and all participants provided written informed consent prior to enrolment.

Sample size calculation

The sample size was calculated based on the amount of hidden blood loss (HBL) during TXA therapy. The overall standard deviation was σ = 250, and the allowed error estimate was δ = 200. These values were estimated using the statistical formula

$$n_1 = n_2 = 2 \times \left[\frac{(z_{\alpha/2} + z_\beta)/_\sigma}{\delta} \right]^2.$$

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

Patients

From September 2019 to May 2020, we consecutively screened patients aged 50–75 years old who underwent primary unilateral TKA for RA. Doppler ultrasound examination without deep vein thrombosis (DVT). The exclusion criteria included a diagnosis of other types of arthritis than RA, renal dysfunction, or severe cardiovascular or cerebrovascular diseases, and patients with prolonged use of oral anticoagulant drugs. The elimination criteria included acquired color vision disorder, active intravascular coagulation patients, and a history of seizures.

Randomization and drug administration

All eligible patients were randomized into two groups using computer-generated randomization by a statistician who was not involved in the trial. The group data were saved by the statistician. Allocation was concealed in consecutively numbered, sealed, opaque envelopes. IV-TXA (1 g) was administered 10 min prior to skin incision by an anesthesiologist, and articular-injection TXA (1.5 g) was administered via articular injection by a surgeon after cavity suture during the surgery. The patients were allocated into two groups: group A, one dose of IV-TXA (1 g) at postoperatively 3 h; group B, three doses of IV-TXA (1 g) at postoperatively 3, 6, and 12 h. The doses were administration by a nurse after surgery. The surgeon, anesthesiologist, and statistician were blinded to the trial. Only the nurses knew of the patients' enrolment.

Perioperative anti-rheumatic treatment

Methotrexate and hydroxychloroquine were to be used during the perioperative period. Leflunomide was to discontinued at 1 week before surgery. The use of other disease-modifying anti-rheumatic drugs was to be discontinued at 2 days before surgery and restarted at 1–2 days after gastrointestinal function recovery. The use of newer biologic agents, such as tumor necrosis factor alpha, was to be discontinued at four to five half-lives before surgery and restarted after wound healing and infection elimination[22,23].

Surgical procedure and postoperative management

For perioperative prophylaxis, cefazolin sodium antibiotics were administered at 30 min before surgery, and 24–48 h after surgery. General anesthesia was administered an anesthetist. Blood pressure was controlled to within 80–100 mmHg / 60–70 mmHg throughout the procedure. Tourniquet was inflated to 100 mmHg above the systolic pressure before incision and deflated after incision closure. The surgery was performed by a single surgeon using the same technique. All patients received a surgeon-selected, cemented, posterior-stabilized prosthetic design with patellar resurfacing. Drains and blood salvage after surgery were not performed for these patients. Postoperatively, the elastic bandage was compressed, and operated limb was bandaged for 24 h. The patients were discharged on the post-operative day (POD) 14

when they met discharge criteria, which included independent mobility and no wound leakage, swelling, and pain, or infection, independent mobility.

During hospitalization, all patients received physical prophylaxis and chemoprophylaxis for venous thromboembolism. The patients were asked to performed equal-length contractions of the femoral quadriceps, and ankle pump movements, lower-extremity strength training, and motion exercises on the day after surgery. At 6 h after surgery, perioperative oral rivaroxaban (10 mg, once a day for 14 days) was prescribed to prevent thrombosis[24]. Blood transfusions was given to patients with postoperative Hb level of less than 70 g/L or any organ dysfunction related to anemia regardless of Hb level[25].

Outcome measures

Perioperative hematocrit (Hct) and Hb levels, coagulation index, and renal function were measured preoperatively, and on POD 1, 3, 7, and 14.

The Nadler formula[26] was used to estimate patient blood volume (PBV), and the Gross[27] formula was used to calculate blood loss based on PBV and Hct drop.

Intraoperative blood loss (IBL) was estimated based on the amount of liquid in the negative pressure drainage bottle + the amount of liquid in the gauze − the amount of saline. A piece of gauze was soaked in approximately 20 mL of the liquid.

$PBV = K1 \times height^3 (m^3) + K2 \times weight (kg) + K3$. For males: K1 = 0.3669, K2 = 0.03219, K3 = 0.6041. For females: K1 = 0.3561, K2 = 0.03308, K3 = 0.1833. Total red blood cell loss (TBL) = $PBV \times (Hct_{pre} - Hct_{post})/ Hct_{ave}$, where Hct_{pre} = initial pre-operative Hct level, Hct_{post} = lowest Hct postoperative, Hct_{ave} = average of Hct_{pre} and Hct_{post}. HBL is defined as TBL minus IBL plus transfusion. Thus, HBL = TBL − IBL + transfusion.

Patients were monitored for adverse events (DVT, PE, wound complications, infection, acute renal failure). Transfusion rate and adverse events were assessed postoperatively during inpatient hospital stay.

Statistical analysis

Analyses were performed using SPSS Version 25.0 (IBM Corp., Armonk, New York). Data of continuous variables were evaluated for normal distribution using the Shapiro-Wilk test, and presented as means ± standard deviations (SDs). Differences between groups were compared using two independent sample *t*-tests. Pearson's chi-square test was used to analyze categorical variables. A *P*-value of less than 0.05 indicated statistical significance.

Results

Patient characteristics

Between September 2019 to May 2020, a total of 104 participants were assessed for eligibility. They were randomized homogeneously into two groups (52 in groups A and 52 in groups B) to receive the study medication. The duration of follow-up was 2 weeks. A total of 7 patients were lost during the follow-up period owing to the following reasons: 3 patients were discharged within 10 days, 1 had infection, and 3 refused to received blood products (**Figure 1**). Patient demographic characteristics as well as per- and intraoperative variables were compared between the two groups (**Table 1**).

Table 1 Preoperative and intraoperative characteristics of the patients

Variable Mean ± SD	Group A (n = 48)	Group B (n = 49)	P-value
Patient characteristics			
Age (y)	66.4 ± 5.9	66.5 ± 5.5	0.921*
Gender (male/female),	4/44	6/43	0.529△
Body mass index (kg m^{-2})	21.8 ± 3.4	22.4 ± 3.1	0.397*
Patient blood volume (mL)	3487.7 ± 512.9	3525.3 ± 520.5	0.721*
Preoperative laboratory values			
Hematocrit (%)	36.1 ± 3.2	36.9 ± 3.7	0.215*
Hemoglobin (g/L)	117.5 ±13.9	119.2 ± 14.8	0.565*
Platelets (× 10^9/L)	232.6 ± 60.6	226.3 ± 60.2	0.605*
D-dimer (mg/L)	1.1 ± 0.6	1.0 ± 0.5	0.623*
Activated partial thromboplastin time (s)	26.3 ± 4.0	25.9 ± 3.6	0.685*
Fibrinogen (g/L)	3.6 ± 0.9	3.7 ± 1.1	0.608*
Prothrombin time (s)	11.5 ± 0.8	11.3 ± 0.6	0.191*
International normalized ratio	1.0 ± 0.1	1.0 ± 0.1	0.294*
Erythrocyte sedimentation rate (mm/h)	38.0±18.8	37.1 ± 19.8	0.819*
C-reactive protein (mg/L)	11.2±7.3	11.4 ± 6.4	0.902*
Intraoperative blood loss (mL)	34.8 ± 6.8	34.5 ± 7.1	0.842*

*, Two independent sample t tests. △, Pearson's chi-

Blood loss, maximum Hb drop, and transfusion rate

The mean TBL, HBL, and Hct and Hb decreases were lower in group B than in group A. D-dimer levels were lower in group B than in group A on POD1. None of the patients received a blood transfusion during the follow-up period (**Table 2**).

Table 2 Primary and secondary outcomes of regarding laboratory values after surgery

Variable Mean ± SD	Group A (n = 48)	Group B (n = 49)	P-value[*]
Primary outcomes			
Total red blood loss (mL)	608.5 ± 239.9	506.1 ± 227.0	0.038
Hidden red blood loss (mL)	571.0 ± 237.3	471.6 ± 224.0	0.036
Maximum hemoglobin drop	23.7 ± 9.4	17.5 ± 7.7	< 0.001
Secondary outcomes			
Transfusion (%)	0	0	-
Postop. laboratory values			
Hematocrit (%)			
POD1	32.8 ± 2.8	34.1 ± 3.5	0.040
POD3	30.4 ± 2.6	32.5 ± 3.4	0.001
POD7	31.8 ± 3.1	33.5 ± 3.5	0.014
POD14	33.8 ± 2.8	34.4 ± 3.0	0.346
Hemoglobin (g/L)			
POD1	105.0 ± 9.3	108.7 ± 12.4	0.108
POD3	94.2 ± 9.3	102.2 ± 11.8	< 0.001
POD7	101.5 ± 10.6	106.8 ± 12.3	0.024
POD14	109.2 ± 8.8	110.4 ± 10.2	0.542
D-Dimer (mg/L)			
POD1	5.5 ± 2.9	1.0 ± 0.5	< 0.001
POD3	3.8 ± 1.8	3.8 ± 2.1	0.998
POD7	3.6 ± 1.4	3.1 ± 1.4	0.085
POD14	2.9 ± 1.2	2.7 ± 1.2	0.326

[*], Two independent sample t tests. POD1, post-operative day 1; POD3, post-operative day 3; POD7, post-operative day 7; POD14, post-operative day 14.

Complications and adverse events

All incisions were healed by the first intention, and no patient developed DVT, PE, acute renal failure, or other adverse events. There were no statistically significant differences in calf vein thrombosis and superficial infection between the two groups (P > 0.05; **Table 3**).

Table 3 *Complications*

Variable	Group A (n = 48)	Group B (n = 49)	P-value
Deep vein thrombosis	0	0	
Pulmonary embolism	0	0	
Calf muscular vein thrombosis	3	4	0.717△
Superficial infection	1	0	0.312△
Deep prosthetic infection	0	0	
Shock	0	0	
Cardiac infarction	0	0	
Wound complications	0	0	
Acute renal failure	0	0	

△, Pearson's chi-square test.

Discussion

Our results revealed the effectiveness of three regimens of TXA therapy in reducing postoperative HBL in RA patients. The stress-induced damage of peripheral blood vessels caused by stress caused by operation and the use of tourniquet during operation promote the occurrence of postoperative fibrinolysis and increase the amount of HBL, which is the blood lost into the tissue intraoperatively and postoperatively, accounting for approximately 50% of the TBL[28]. With reduction of the tourniquet, the fibrinolysis around the wound reached a peak within 6 h and was maintained for 18 h[29]. The half-life of TXA in plasma is 2–3 h[13], and its antifibrinolytic effect is maintained for approximately 8 h[30]; after intravenous administration, its 24 h recovery from urine is approximately about 90%[13]. Based on in vivo and in vitro data, the effective therapeutic plasma concentration of tranexamic acid in inhibiting fibrinolysis was determined to be 5–10mg/L or 10–15mg/L [30,31].

Considering the pharmacological characteristics of TXA, we believe that a single dose of IV-TXA (1g) after surgery may not achieve the maximum antifibrinolytic effect. Although it has been reported that TXA does not reduce the rate of blood transfusion rate after joint replacement in patients with RA[32], we investigated three doses postoperative IV-TXA (1 g). Our results showed that the blood concentration and the antifibrinolytic effect of TXA were maintained during the whole process of fibrinolysis. HBL as well as Hct and Hb decrease during hospitalization were lower with multiple doses than that with a single dose. Hct and Hb levels in both groups decreased to the lowest level on POD3, indicating that HBL persisted within 3 days after surgery.

Multiple strategies have been developed to reduce blood loss in perioperative period, including preoperative anemia assessment, minimally invasive surgery, shortening of operation time, use of antifibrinolytic drugs, and postoperative nutritional supplement. Owing to these approaches, the number of patients requiring blood transfusion after operation has been decreasing.

Many studies have shown that repeated administration of postoperative TXA (mainly in OA patients) is not associated with an increased risk of venous thromboembolic events[15,33,34]. Tzatzairis et al.[35] showed that during TKA without the use of tourniquet, three doses of perioperative IV-TXA(15mg/kg) reduced blood loss, Hb decrease, and transfusion rate, and led to faster rehabilitation. Sun et al. [36] showed that administration of a total dose of 30mg/kg TXA preoperatively combined with administration of TXA twice postoperatively was more effective in reducing postoperative blood loss. Lei et al. [17]conducted a randomized controlled trial involving 159 patients, and claimed that a five dose regimen could further reduce the blood loss, minimize inflammation, enhance mobility, and shorten the length of hospital stay, without increasing the risk of DVT and PE. Maniar and his colleagues[7] conducted a prospective randomized controlled trial in 240 patients, claiming that a three-dose regimen was more successful than a single-dose regimen, and a two-dose administration could be the least effective regimen in reducing TBL.

To the best of our acknowledge, this study was the first randomized controlled study to investigate the efficacy of multi-dose TXA after TKA in reducing postoperative HBL in patients with RA. Although our results differed from those of Good et al.[37], we believe that postoperative TXA administration of at least three times and adequate drug dose can effectively reduce HBL after surgery.

Unlike OA patients, RA patients highly express inflammatory factors, such as IL-1, IL-6, and TNF- α, which leads to the up-regulation of procoagulant factors and down-regulation of anticoagulation factors[38]. Thus, repeated postoperative administration of IV-TXA may increase the incidence of DVT and PE. We evaluated the occurrence of DVT and PE on the basis of the clinical symptoms of patients, D-dimer level, Doppler ultrasound data, and pulmonary computed tomography data. The results showed that the average level of D-dimer in group A was significantly higher than that in group B within 1 day after surgery, indicating that three doses of postoperative IV-TXA could minimize fibrinolysis and inhibit fibrinolysis more effective, thereby reducing HBL after surgery.

D-dimer level responds to changes in blood coagulation and fibrinolysis in the body. An increase in D-dimer level is an indicator of hypercoagulability and hyperfibrinolysis in the body, and it is a preferred index for determining the occurrence of DVT [39]. D-dimer levels can increase under trauma, inflammation, and surgery[40]. Conventionally, D-dimer level of higher than 0.5mg/L is the cut-off value for the diagnosis of venous thrombosis; however, D-dimer level naturally increases with age, and in patients above 50 years old, the D-dimer cut-off value is defined as the patient's age times 10μg/L[41]. The occurrence of venous thrombosis can be safety ruled out in patients with no symptoms of venous thrombosis, as their D-dimer level is lower than normal[42]. Thus, determination of D-dimer level is recommend for patients with a low or moderate clinical probability of DVT[43].

According to the Chinese expert guidelines for the prevention of venous thrombosis after TKA, anticoagulants should be used for at least 10–14 days, and postoperative lower limb functional rehabilitation training should be performed to prevent the occurrence of venous thrombosis[44]. Studies

have shown that under the contemporary prophylactic regimens, the incidence of DVT and PE after TKA is very low[45], and the top-ranking intervention for preventing DVT is rivaroxaban[46].

Tourniquet can decrease intraoperative bleeding and facilitate bone-prosthesis adhesion, but can also increase HBL after operation[47]. Some studies have also shown that tourniquet increases the degree of pain for a short time after surgery, but does not increase the recovery time of knee function after TKA[48]. We used tourniquet during operation and administered multi-dose TXA antifibrinolytic therapy after operation. Our results showed that our perioperative blood management program can achieve a balance between bleeding and hemostasis as well as anticoagulation and anti-fibrinolysis effects.

There were, however, some limitations to be present study. Firstly, there was an uneven male to female ratio owing to the higher number of female patients than male patients. Second, owing to postoperative blood loss and ethical considerations, we did not establish a placebo group to evaluate the effectiveness of TXA. Third, the examination period of postoperative outcomes was not strictly 24 and 72 h after operation; thus, we are planning to design another study to obtain more accurate results. Fourth, functional recovery of the knee after surgery was not evaluated in this study. Finally, although the half-life of TXA is short, the short follow-up time may not be adequate to fully assess the risk of DVT and other complications after multiple doses of IV-TXA in patients with RA; extension of the follow-up period will be considered in future studies.

Conclusion

This prospective, randomized controlled trial based on multi-strategic blood management revealed that three doses of IV-TXA administered postoperatively could further reduce HBL and Hb decrease, but cause no adverse events within a short period of time after TKA in patients with RA.

Abbreviations

IV-TXA: intravenous tranexamic acid; RA: rheumatoid arthritis; TKA: total knee arthroplasty; TXA: tranexamic acid; TBL: total red blood cell loss; HBL: hidden red blood loss; Hb: hemoglobin; Hct: hematocrit; DVT: deep vein thrombosis; PE: pulmonary embolism; POD: Post-operative day; ERAS: enhanced recovery after surgery.

Declarations

Ethics approval and consent to participate

This study had been approved by the ethics committee Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. Written informed consent to participate was obtained from all of the individual participants included in the study.

Patient consent for publication

Not required.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None declared.

Authors' contributions

BXK and LBX conceived the study; BXK drafted the study; HX, CXG, JZ, JX, STS, YHM, and WTZ recruited the participants. XRX collected clinical data. CZ was responsible for statistical analyses and tables. BXK and LBX have primary responsibility for the final content. All authors contributed to writing and revising the paper and agreed to submission.

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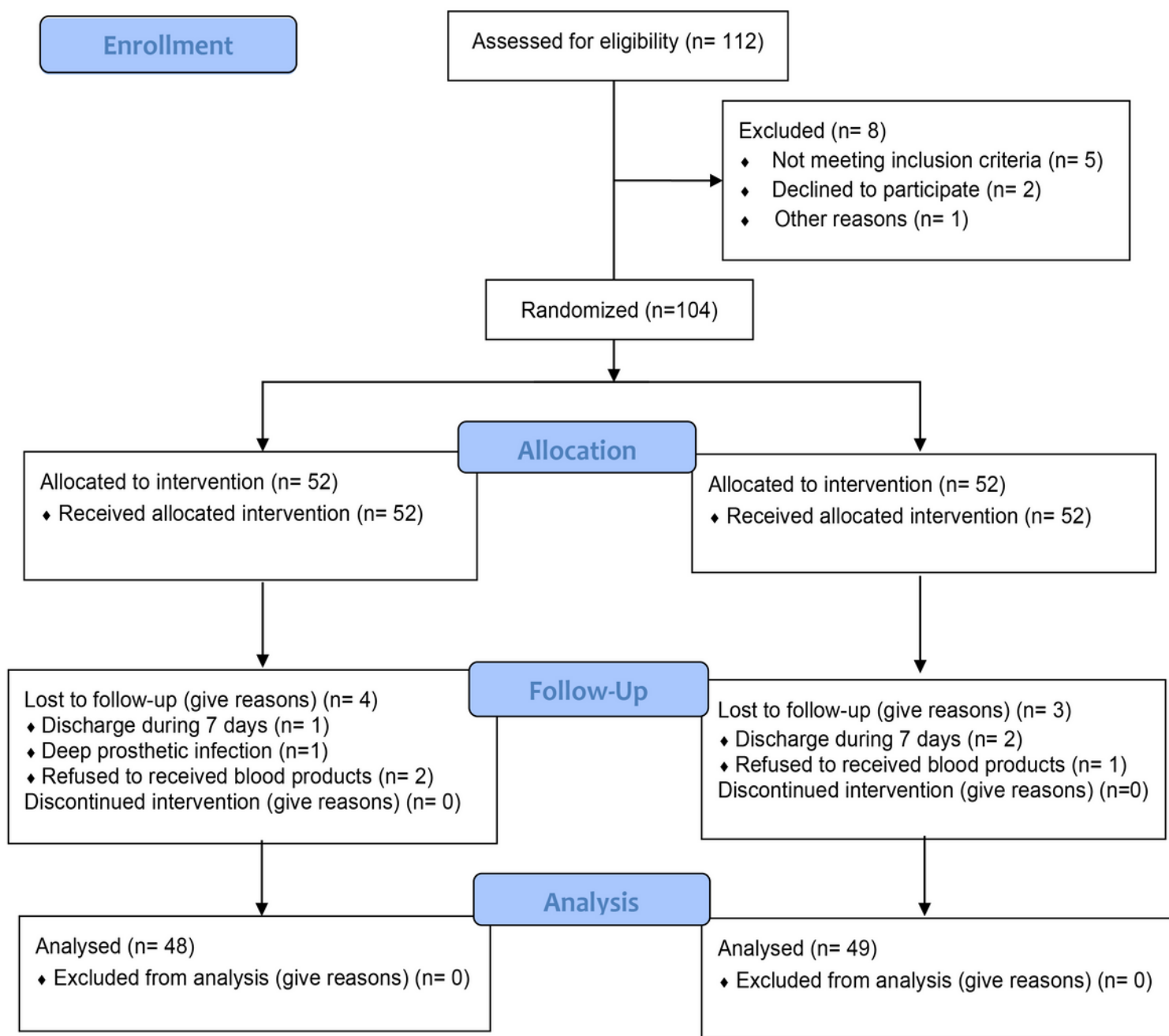
Figures

Figure 1

COMSORT (Consolidated Standards of Reporting) flow diagram. Name of the registry: Clinical observation of multiple doses use of tranexamic acid in patients with rheumatoid arthritis after total knee arthroplasty. Prospective registration, ChiCTR1900025013. Registered 7 August 2019, http://www.chictr.org.cn/showproj.aspx?proj=41375

Supplementary Files

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- datasharing.docx
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- flowchart.doc