Optimization of the Dosing Schedule of Recombinant Human Erythropoietin for Perioperative Autologous Blood Donation in Patients undergoing Total Knee Arthroplasty

Zichuan Ding[1], Mingcheng Yuan[1], Qifeng Tao[2], Duan Wang[1], Haoyang Wang[1], and Zongke Zhou[1]

[1]Sichuan University West China Hospital
[2]Panzhihua Municipal Central Hospital

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Abstract

Aim: The purpose of this study was to optimize the dosing schedule of recombinant human erythropoietin (rhEPO) for perioperative autologous blood donation in patients undergoing total knee arthroplasty (TKA). Method: TKA patients receiving different dosing schedules of rhEPO were randomly divided into three groups. Group A patients were given 10,000 IU of subcutaneous rhEPO (1 ml) daily from preoperative day 5 to postoperative day 3 (9 doses); Group B patients were given subcutaneous normal saline daily from preoperative day 5 to day 3 and then subcutaneous rhEPO daily until postoperative day 3 (6 doses in total); Group C patients were given subcutaneous normal saline daily from preoperative day 5 to the day before surgery and then subcutaneous rhEPO daily from the surgery day to postoperative day 3 (4 doses). Results: A total of 180 TKA patients were included. On postoperative day 1 and 3, group A showed significantly higher Hb levels than group B and group C. The calculated blood loss was significantly greater in groups B and C than in group A on the day after surgery. Regarding total blood loss, groups B and C lost significantly more blood than group A. No case of allogeneic transfusion occurred during the trial in any of the three groups. Conclusions: A small dose of daily rhEPO from preoperative day 5 to postoperative day 3 could significantly increase perioperative autologous blood donation efficacy and slow the decline in postoperative Hb levels in TKA patients without causing extra complications.

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Running title: Optimal Dosing of rhEPO in TKA Patients

Zichuan Ding[1], Mingcheng Yuan[1], Qifeng Tao[2], Duan Wang[1], Haoyang Wang[1,*], Zongke Zhou[1,*]

[1] Department of Orthopedics, West China Hospital/West China School of Medicine, Sichuan University, 37# Wuhou Guoxue Road, Chengdu, P.R. China.

[2] Department of Orthopedics, Panzhihua Municipal Central Hospital Panzhihua, Panzhihua, People's Republic of China.

[*] Corresponding author: Department of Orthopedics, West China Hospital/West China School of Medicine, Sichuan University, 37# Wuhou Guoxue Road, Chengdu, P.R. China.

Zichuan Ding and Mingcheng Yuan contributed equally to this work.

Principal investigator statement: The authors confirm that the principal investigator for this paper is Zongke Zhou and that he had direct clinical responsibility for patients.

Key words: total knee arthroplasty, recombinant human erythropoietin, autologous blood donation, dosing schedule

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What is already known about this subject: The recombinant human erythropoietin (rhEPO) has demonstrated effectiveness in perioperative autologous blood donation in total joint arthroplasty but the optimal short-term daily dosing schedule of rhEPO for TKA patients still needs to be investigated.

What this study adds: A small dose of daily rhEPO from preoperative day 5 to postoperative day 3 could significantly decrease perioperative blood loss as well as slow the decline in postoperative Hb levels in TKA patients without causing additional complications.

Abstract

Aim: The purpose of this study was to optimize the dosing schedule of recombinant human erythropoietin (rhEPO) for perioperative autologous blood donation in patients undergoing total knee arthroplasty (TKA). **Method:**TKA patients receiving different dosing schedules of rhEPO were randomly divided into three groups. Group A patients were given 10,000 IU of subcutaneous rhEPO (1 ml) daily from preoperative day 5 to postoperative day 3 (9 doses); Group B patients were given subcutaneous normal saline daily from preoperative day 5 to day 3 and then subcutaneous rhEPO daily until postoperative day 3 (6 doses in total); Group C patients were given subcutaneous normal saline daily from preoperative day 5 to the day before surgery and then subcutaneous rhEPO daily from the surgery day to postoperative day 3 (4 doses). **Results:** A total of 180 TKA patients were included. On postoperative day 1 and 3, group A showed significantly higher Hb levels than group B and group C. The calculated blood loss was significantly greater in groups B and C than in group A on the day after surgery. Regarding total blood loss, groups B and C lost significantly more blood than group A. No case of allogeneic transfusion occurred during the trial in any of the three groups.**Conclusions:** A small dose of daily rhEPO from preoperative day 5 to postoperative day 3 could significantly increase perioperative autologous blood donation efficacy and slow the decline in postoperative Hb levels in TKA patients without causing extra complications.

Key words: total knee arthroplasty, recombinant human erythropoietin, autologous blood donation, dosing schedule

Background

Total knee arthroplasty (TKA), as one of the most common surgeries in orthopaedics, is routinely applied to treat end-stage knee diseases. It has been proven to be tolerable in correctly selected patients and can effectively alleviate pain, ameliorate function, and improve the quality of life of patients (1). As the proportion of aging adults increases in the general population so does the demand for TKA. It is estimated that the demand for primary TKA will grow to 3.48 million procedures by 2030 in the United States (2). Although the procedure has potential in facilitating the patient's functional recovery, substantial intraoperative and postoperative blood loss and consequential acute anaemia and transfusion are major concerns for orthopaedic surgeons. The TKA procedure is associated with substantial blood loss, leading to a high prevalence (82.5% in males and 84.3% in females) of postoperative anaemia (3), which may therefore cause the relatively high rate (nearly 45%) of postoperative allogeneic blood transfusion (4). In addition, most patients undergoing TKA are elderly and have a high prevalence (25.3-30.2%) of preoperative anaemia, which is widely accepted as a predictive factor of postoperative allogeneic transfusion. Allogeneic transfusion carries a substantial risk of transfusion-associated complications requiring additional treatment and increased length of stay (5).

To reduce blood loss and allogeneic blood transfusion requirements while accelerating haemoglobin and function recovery, many blood-saving strategies have been reported, of which recombinant human erythropoietin (rhEPO) has demonstrated effectiveness in perioperative autologous blood donation, reducing haemoglobin (Hb) level drop and blood transfusion requirements according to numerous randomized controlled trials (6-10). Currently, there are two main plans for the perioperative application of rhEPO in patients who are scheduled for total joint arthroplasty (TJA). One is the weekly administration of large-dose rhEPO for 2-4

weeks before surgery, which is called the long-term dosing schedule (10). The other is the daily administration of small-dose rhEPO from 0-5 days preoperatively to a few days (less than a week) postoperatively, which is called the short-term dosing schedule (6-9). However, the weekly dosing schedule has some known drawbacks; for instance, patients receiving the long-term dosing schedule and who had not undergone TKA are not allowed to visit the hospital for weekly injections, which is very inconvenient to the patients and will increase the preoperative waiting time and medical costs. The implementation of the dosing schedule is difficult in patients with poor compliance. In addition, initial high peak levels of erythropoietin caused by high weekly doses are likely considered to be wasteful, as erythropoietin receptors on progenitor cells in bone marrow may become saturated; when these receptors are again free for binding, the level of serum erythropoietin will fall (11). Compared with the weekly protocol, the short-term daily dosing schedule with small amounts of rhEPO could maintain a more constant low but relatively more effective level of serum erythropoietin without causing inconvenience or other potential risk to the patient (11). In addition, previous studies also reported that repeated administration of rhEPO is more effective in stimulating the reticulocyte response than the weekly large dose of the same total amount of rhEPO (12).

It has been reported that one daily dose (150 IU/kg) of rhEPO, starting from 3 days before arthroplasty, is more effective in increasing Hb levels and reducing blood loss without causing additional complications than starting on the day of surgery. In the same study, researchers also concluded that the initial application of rhEPO on the surgery day neither significantly reduced blood loss nor increased Hb level after arthroplasty when compared with the blank control group (7). In contrast, Na et al (9) administered 3000 IU of rhEPO subcutaneously to patients, starting on the surgery day through the postoperative period, and found that compared with the placebo group, starting rhEPO on the surgery day could effectively attenuate anaemia and decrease transfusion requirements in patients undergoing arthroplasty, which was comparable with the conclusion of a study by Bernabeu-Wittel et al (6) with a similar rhEPO dosing schedule. Moreover, in another study (8), researchers suggested that each patient undergoing arthroplasty receive a dosing schedule involving 10,000 IU of rhEPO daily subcutaneously from preoperative day 5 to postoperative day 3, which is also the same dosing schedule as our centre. Under this dosing schedule of rhEPO, researchers found a significant reduction of 94% in the need for allogeneic blood transfusion in patients.

As a result, the optimal short-term daily dosing schedule of rhEPO for TKA patients still needs to be investigated. This prospective double-blinded randomized placebo-controlled trial was conducted to compare three different types of short-term rhEPO-based treatment plans for perioperative autologous blood donation in TKA.

Patients and Methods

This double-blinded randomized placebo-controlled trial has been registered in the Chinese Clinical Trial Registry (ChiCTR1900026065). The Clinical Trials and Biomedical Ethics Committee of the local hospital approved this study. Written informed consent was obtained from all the participants prior to the trial.

Patients

Consecutive patients (18 to 85 years of age) scheduled for primary unilateral total knee arthroplasty from September 2019 to May 2020 were enrolled. The exclusion criteria included a diagnosis other than osteoarthritis (such as rheumatoid arthritis or bone tumour), a known allergy to rhEPO, an Hb level more than 130 g/L or less than 90 g/L, a history of a haematopoietic or haemorrhagic disorder, a history of deep venous thrombosis (DVT) or pulmonary embolism (PE), ongoing anticoagulant treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery, ongoing treatment with rhEPO within 3 months before admission, preoperative hepatic or renal dysfunction or other underlying diseases such as serious cardiac and/or cerebrovascular comorbidities, and refusal to participate.

Interventions and Randomization

The patients receiving different dosing schedules of rhEPO were randomly divided into three groups. The patients in group A received 10,000 IU of subcutaneous rhEPO (1 ml) daily from preoperative day 5 to

postoperative day 3 (9 doses); the patients in group B received 1 ml of subcutaneous normal saline daily from preoperative day 5 to day 3 and then 10,000 IU of subcutaneous rhEPO daily until postoperative day 3 (6 doses); and the patients in group C received 1 ml of subcutaneous normal saline daily from preoperative day 5 to the day before surgery and then 10,000 IU of subcutaneous rhEPO daily from the surgery day to postoperative day 3 (4 doses). If the Hb level exceeded 150 g/L, rhEPO was stopped. All patients received a daily dose of 100 mg intravenous ferric carboxymaltose when given subcutaneous rhEPO, which has been widely accepted as an effective partner with rhEPO for autologous blood donation in patients undergoing arthroplasty (9).

A random allocation sequence was computer-generated and concealed in consecutively numbered, opaque, sealed envelopes by a research statistician who was not involved in the data analysis. One experienced surgeon enrolled the patients, and another recorded the basic details. The envelope was opened after the patients were enrolled, and the study medication and placebo were prepared by a dedicated nurse who was not involved in daily patient care or outcome measurement. Patients, surgeons, anaesthesiologists, care providers, and data collectors were blinded to the allocation sequence. The placebo (normal saline) has the same appearance (colourless and clear liquid) as rhEPO.

TKA procedure and blood transfusion

All the TKAs were performed under general anaesthesia. All the operations were performed by the same senior surgeon in the same laminar air flow operation room. A midline skin incision, medial parapatellar approach, and a measured resection technique were performed in all the patients. Intramedullary guides were used for all the femoral preparations, and extramedullary guides were also used for the tibial preparations. All the patients received a cemented posterior-stabilized prosthetic with patellar resurfacing, and all the TKAs were conducted without a tourniquet. In addition, no blood salvage system or postoperative drain was used (13), and electrocautery and routine haemostasis were routinely performed during the surgery.

Blood transfusion was indicated for any patients with an Hb level of <70 g/L or an Hb level between 70 and 100 g/L and symptomatic anaemia (severe mental status changes, palpitations, and/or pallor)(14).

Outcome measurements

The primary outcomes consisted of Hb levels, allogeneic transfusion rate and blood loss (including intraoperative and total blood loss), of which blood loss was calculated according to the formula by Nadler et al and Gross plus the volume transfused (15, 16). Secondary outcomes included reticulocyte count and complications, including DVT, PE and other adverse effects related to rhEPO (nausea, fever, headache, etc.).

Statistical Analysis and Sample Size

The sample size calculation was performed in relation to the difference in the postoperative decrease in Hb level among the 3 groups using G*Power Version 3.1.7 (Franz Faul; UniKiel, Germany) software. On the basis of our preliminary data of 60 patients who underwent primary total knee arthroplasty and were assessed for the same measure, the mean decrease in Hb level (and standard deviation) was 39.3 ± 5.89 g/dL. A reduction of 10% (4 g/dL) in Hb level in patients who received a daily dose of 10,000 IU from preoperative day 5 to postoperative day 3 was recorded as a significant difference. In summary, 60 patients per arm were needed, with a power of 0.90 and a significance level of 0.05.

We compared the quantitative data between groups using 1-way analysis of variance and Tukey's post hoc test. The Pearson chi-square test or Fisher's exact test was used to analyse qualitative comparative parameters. All analyses were performed using SPSS for Windows, Version 19.0 (SPSS Inc, Chicago, IL). Significance was set at $P < 0.05$.

Result

During the recruitment period, from September 2019 to May 2020, 239 patients were scheduled to undergo a primary unilateral TKA because of osteoarthritis in our centre. Of them, 38 were ineligible, and 21 declined

to participate. Finally, 180 patients were enrolled and analysed; 60 were randomized to group A, 60 to group B, and 60 to group C (Fig. 1). The baseline data of the 3 groups were comparable (Table 1).

Primary outcome

Patients in group A had significantly higher Hb levels (108.4±11.4 g/L) than those in groups B and C (107.8±8.4 and 103.9±8.8 g/L, respectively) on the day after surgery, and the Hb level in group B was also higher than that in group C (p=0.0202). However, on postoperative day 3, no significant difference was found between groups B and C in Hb levels (97.4±10.5 and 93.5±10.8 g/L, respectively) (p=0.1192), even if the Hb level in group A (102.2±10.9 g/L) was still markedly higher than that in groups B and C. No difference was found among the three groups at other time points. (Fig. 2).

In terms of blood loss, no significant difference was found in intraoperative blood loss among groups A, B and C (88.6±19.5, 90.7±23.4, and 87.2±22.6 ml, respectively) (p=0.679), but on postoperative day one, the calculated blood loss was greater in groups B and C (378.9±123.1 and 436.4±147.4 ml, respectively) than in group A (313.4±118.5 ml) (p<0.05), and group C had more blood loss than group B (p=0.044). Regarding total blood loss, groups B and C had more total blood loss (611.0±227.5 and 751.4±301.5 ml, respectively) than group A (498.1±197.3 ml) (P<0.05), and group C had more blood loss than group B (p<0.01) (Table 2). There was no report allogeneic transfusion during the trial in any of the three groups.

Secondary outcome

The reticulocyte count grew rapidly after the use of rhEPO. From preoperative day 3 to postoperative day 3, reticulocyte counts in group A were always higher than those in groups B and C. From the day before surgery to the day after surgery, reticulocyte counts in group B were higher than those in group C (p<0.001) (Fig. 3). In terms of complications, no case of DVT or PE occurred in any group, and only a few cases of asymptomatic intermuscular vein thrombosis (IMVT) were observed in groups A (4, 6.7%), B (4, 6.7%) and C (5, 8.3%), without marked differences among the groups (P=0.92). The three dosing schedules of rhEPO were well-tolerated, with few adverse events: nausea in 11, pyrexia in 8, and headache in 4 patients, but there was no significant difference among the three groups (P>0.05) (Table 3). No deaths or readmissions occurred within 21 days postoperatively.

Discussion

RhEPO is widely recognized to be effective in perioperative autologous blood donation during TKA (6-11). Despite the common application of rhEPO in total joint arthroplasty during the last decade, with benefits including attenuated Hb drop, decreased blood loss, and reduced need for transfusion, no final consensus has been reached with respect to the optimal dosing schedule, which has yet to be investigated.

Previous studies have focused on the standard high-dose protocol (300-600 IU/kg) of rhEPO starting 2-4 weeks before surgery in TJA patients (10, 17). However, the long-term preoperative dosing schedule required patients to return to the hospital every week for injections, which was not only inconvenient to the patients but also increased the preoperative waiting time and medical costs. In contrast, some investigators reported that more frequent perioperative application of a small dose of rhEPO might be more effective. It was reported that high weekly doses of rhEPO might be considerable wasteful due to limited EPO receptors on progenitor cells in the bone marrow, which are easily saturated. When the receptors are saturated, no amount of rhEPO works until the receptors are free to bind again, but by then, the serum level of rhEPO has dropped. Therefore, frequent application of a small dose of rhEPO could maintain a more constant low but more effective serum rhEPO level (11). Similarly, another study found that repeated multiple doses of rhEPO were more effective than a single dose in stimulating the reticulocyte response, even when the total amount of rhEPO was the same (12). However, even if applied in repeated small doses, there is still no consensus on many dosing schedules.

In this study, we summarized and compared the main three types of perioperative rhEPO dosing schedules and found no significant difference in Hb levels among the three groups until the day after TKA, when the Hb level in group A was markedly higher than that in groups B and C (the Hb level in group B was

also significantly higher than that in group C). There was no need for transfusion in any group. Although the three groups had comparable intraoperative blood loss, the total blood loss in group A was still the lowest among the groups ($P<0.05$), while the total blood loss in group C was the highest ($P<0.05$). No treatment-related adverse events, such as DVT, PE or anaphylactic reaction, occurred throughout the trial, suggesting that the three dosing schedules of rhEPO were well tolerated, and no significant differences in other complication rates were observed among the three groups. Therefore, recommend initiating the dosing schedule of rhEPO starting from preoperative day 5.

rhEPO reduces the rate of Hb decline shortly after application in the postoperative period (9), with Hb reaching a recovery peak approximately 8-10 days later (18). We found that patients in group A had markedly higher Hb levels than those in groups B and C on the day after surgery, with higher Hb levels in group B than in group C, indicating that the dosing schedule of rhEPO from preoperative day 5 was better than that from day 3 and the day of surgery in reducing the rate of Hb decline in the early postoperative period. When the Hb level reached the lowest concentration on postoperative day 3, the day of which transfusions mostly occurred (19), patients in group A also had significantly higher Hb levels than those in groups B and C, which suggested that the drop in Hb level in group A was the mildest. The application of rhEPO in group A started 5 days before surgery, which meant that it was 8 days until postoperative day 3 when the erythropoiesis estimated by rhEPO reached the peak, which was comparable with prior studies (7). However, it was reported that patients who suffered a large blood loss in a short time would have a strong endogenous erythropoietin feedback (20). Another study also investigated that a linear–logarithmic relationship was found between the change in Hb level and endogenous erythropoietin feedback, which meant that the more the Hb dropped, the stronger the endogenous erythropoietin feedback, even if the effect is small when compared with the extraerythropoietin (21). Similarly, in this study, on postoperative day 3, the quick decline in Hb level in group C might be accompanied by a sharp increase in endogenous erythropoietin feedback, which could therefore stimulate erythropoiesis quickly, while the decline in Hb level in group B was not so fast that the exogenous rhEPO in group B still needed more time to stimulate erythropoiesis and promote the Hb level after surgery. This may be why the Hb levels between groups B and C became comparable on postoperative day 3.

Many studies have demonstrated that regardless of which kind of rhEPO dosing schedule is used, intraoperative blood loss is not influenced (7, 8), which is consistent with our study. In terms of total blood loss, we calculated the blood loss with the preoperative haematocrit (HCT) and the HCT tested on postoperative day 3 (19). The trend of HCT was consistent with the Hb level, so it was not surprising to find that total blood loss was significantly less in group A than in groups B and C, which suggested that the application of rhEPO 5 days before surgery could achieve the least total blood loss. However, the blood loss was net instead of actual because when losing blood, the body was still producing blood under the effect of haemopoiesis. Therefore, blood loss was calculated to compare the blood saving effect of different dosing schedules of rhEPO. With respect to transfusion requirements, prior studies all reported the application of rhEPO. In our study, no patients needed transfusion, which might be mostly due to the effective blood management in our centre, including the perioperative use of tranexamic acid (22), the intraoperative controlled hypotension and the application of rhEPO, leading to little blood loss and an extremely low transfusion rate.

Reticulocytes are generally released from the marrow 18 to 36 hours before their final maturation into erythrocytes, and they are regarded as a real-time assessment of erythropoiesis (20). It was reported that the blood reticulocyte count peaked 72 hours to day 5 after application of rhEPO (18). In this study, on preoperative day 1, the reticulocyte counts in groups A and B were markedly larger than those in group C, which was consistent with prior studies. We found that on postoperative day 1, the reticulocyte count in group C did not increase as much as those in groups A and B in group C, which may be because of the relatively late application of rhEPO from the day of surgery. However, on postoperative day 3, the reticulocyte count in group C caught up with the other two groups. After postoperative day 14, no significant difference was observed in the reticulocyte count among the three groups, which suggested that the marrow haematopoietic phase mobilized by exogenous rhEPO was over.

According to the instructions, rhEPO had the potential effect of increasing platelet count and blood viscosity, leading to hypercoagulability, thus increasing the risk of DVT and PE (23, 24). It was also reported that patients who underwent TJA were at high risk for developing DVT and PE, which relatively limited the clinical administration of rhEPO (23, 24). However, in this study, no episodes of DVT or PE occurred in any patient, which was attributed to not only the well-tolerated dosing schedules of the three groups but also the good perioperative thromboembolism prophylaxis in our centre.

However, there are also several limitations in our study. First, the sample size was calculated according to the decline in Hb level, which might not be sufficient to identify a significant difference in other indexes. In addition, we did not record the platelet count or any quantitative data related to coagulation function, such as D-dimer or fibrinogen/fibrinogen degradation products (FDPs), so it might be inaccurate to judge whether different dosing schedules had any influence on patients' risk of DVT or PE. Finally, it was reported by prior studies that the application of rhEPO perioperatively could significantly increase medical costs (25). However, in this study, we did not collect health economics indexes.

Conclusions

A small dose of daily rhEPO from preoperative day 5 to postoperative day 3 could significantly decrease perioperative blood loss as well as slow the decline in postoperative Hb levels in TKA patients without causing additional complications, which was better than the dosing schedule from preoperative day 3 or from the day of surgery. In summary, we recommend a more practical and highly effective therapeutic plan of a small dose of daily subcutaneous rhEPO from preoperative day 5 to postoperative day 3 in patients who have undergone TKA.

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None

Conflict of interest statement

The authors declare that they have no competing interests.

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Data availability statement

The datasets generated are available from the corresponding author on reasonable request.

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Table. 1 Baseline Demographic and Clinical Characteristics

Variable	Group A (n=60)	Group B (n=60)	Group C (n=60)	P Value
Demographic characteristic				
Age	68.36 ± 10.28	67.41 ± 9.96	68.77 ± 9.72	0.747
Female (no. [%] of patients)	48 (80.0)	46 (76.7)	50 (83.3)	0.659
Height	1.60 ± 0.09	1.62 ± 0.05	1.61 ± 0.07	0.316
Weight	65.24 ± 9.59	65.73 ± 9.83	66.31 ± 9.70	0.833
BMI	26.17 ± 3.43	25.94 ± 3.62	26.64 ± 3.89	0.565
ASA class (no. [%] of patients of grade I+II)	55 (91.7)	57 (95.0)	56 (93.3)	0.765
Preoperative hematological index				
Hb (g/L)	119.3 ± 9.7	119.9 ± 10.1	121.2 ± 9.9	0.562
Ret (×10ˆ12/L)	0.0724 ± 0.026	0.0737 ± 0.031	0.0698 ± 0.027	0.741

BMI, body mass index; ASA, American Society of Anesthesiologists; Hb: Hemoglobin; Ret: Reticulocyte

The p value represents the result of one-way analysis of variance for independent means for continuous variables or the chi-square test for independent proportions among the 3 groups

Table. 2 Blood loss during the postoperative period

Variable	Group A (n=60)	Group B (n=60)	Group C (n=60)	Pairwise Comparison (P valu
				Group A vs B
Intraoperative blood loss	88.6±19.5	90.7±23.4	87.2±22.6	0.8591
Blood loss till postoperative day 1	313.4±118.5	378.9±123.1	436.4±147.4	0.0178*
Total blood loss	498.1±197.3	611.0±227.5	751.4±301.5	0.0341*

The p value represents the result of one-way analysis of variance for independent means for continuous variables. * means significant difference.

Table. 3 Complications

Variable	Group A (n=60)	Group B (n=60)	Group C (n=60)	P Value
Complications				
DVT	0	0	0	NA
PE	0	0	0	NA
IMVT	4	4	5	0.920
Nausea	4	3	4	0.908
Pyrexia	2	3	3	0.877
Headache	1	2	1	0.774

NA, not applicable; DVT, deep vein thrombosis; PE: pulmonary embolism; IMVT, intermuscular vein thrombosis

The p value represents the result of the chi-squared test or Fisher's exact tests for categorical variables among the 3 groups.

Figure legends

Fig. 1 Patients flow chart

Fig. 2 Hb level through the trial

Fig. 3 Reticulocyte count through the trial

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`Fig. 1.docx` available at https://authorea.com/users/594742/articles/629069-optimization-of-the-dosing-schedule-of-recombinant-human-erythropoietin-for-perioperative-autologous-blood-donation-in-patients-undergoing-total-knee-arthroplasty