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ORTHOPAEDIC SURGERY

A protocol avoiding allogeneic transfusion in joint arthroplasties

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Abstract
Introduction Arthroplasties of hip and knee are associated with blood loss, which may lead to adverse patient outcome. Performing arthroplasties in Jehovah's Witness patients who do not accept transfusion has been a matter of concern. We developed a protocol, which avoids transfusion in arthroplasties of Jehovah's Witness patients, and evaluated the feasibility and safety of the protocol.
Materials and methods The target of preoperative hemoglobin was more than 10 g/dL. When preoperative hemoglobin was lower than 10 g/dL, 4000 U erythropoietin (3 times a week) and 100 mg iron supplement (every day) were administered until the hemoglobin reached 10 g/dL. When the preoperative hemoglobin was higher than 10 g/dL, 4000 U erythropoietin and 100 mg iron supplement were administered once, before operation. During the operation, cell saver was used. Postoperatively, erythropoietin and iron supplements were administered until the hemoglobin reached 10 g/dL, similar to the preoperative protocol. We evaluated the feasibility of our protocol, perioperative complications and hematologic changes.
Results From 2002 to 2014, 186 Witness patients visited our department. In 179 patients (96.2 %), 77 total knee arthroplasties, 69 bipolar hemiarthroplasties and 33 total hip arthroplasties were performed. The mean hemoglobin level was 12.3 g/dL preoperatively, 9.4 g/dL on postoperative day 3 and 10.3 g/dL on postoperative day 7. One patient died immediately after the arthroplasty and the remaining 178 patients survived.
Conclusions Total joint arthroplasty could be done without transfusion using this protocol in most of our patients. The rates of infection and mortality were similar with known infection and mortality rates of arthroplasties. In patients who do not want allogeneic transfusions, our protocol is a safe alternative to perform joint arthroplasties.

Keywords Transfusion · Arthroplasty · Hip · Knee

Introduction

Orthopaedic surgeons and patients have increasing concerns regarding complications of blood transfusions [1–6]. Joint arthroplasties may be associated with a blood loss, which necessitates transfusion [7, 8]. Although various methods to reduce transfusions have been attempted in joint arthroplasties, a high percentage of patients require a transfusion during and after the procedures [3–6, 9–13]. Jehovah's Witnesses do not accept transfusion for religious reasons.

Several strategies have been proposed to reduce blood loss and to avoid transfusion in the care of Jehovah's Witnesses. These strategies include preoperative treatment of anemia [14–16]; erythropoietin therapy [17–20]; intravenous iron supplements; hemostatic agents [21, 22], autotransfusion [5, 23, 24] and tranexamic acid [11, 13, 21, 22]. However, there is no consensus about strategies for arthroplasties of Jehovah's Witness patients.

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We developed an alternative protocol to avoid transfusion and opened a bloodless arthroplasty center in March 2003.

The purpose of this study was to determine the feasibility and safety of our protocol, and to analyze complications and hematologic changes during and after joint arthroplasties in Witness patients.

Materials and methods

Developing a protocol for arthroplasty without transfusion

The design and protocol of this study were approved by the institutional review board at our hospital and all patients gave written informed consent regarding the risk of arthroplasties with the protocol. Prior to the study, the methods to be included in the protocol were selected from literature reviews and consensus by five panelists. Among the five panelists, two (YSS, HSC) were orthopaedic surgeons, who specialized joint arthroplasties; one was an anesthesiologist; one was a thoracic surgeon; and one was a nurse, who had a Christianity of Jehovah's Witness. One (YSS) of the authors was the moderator. Each decision was made on the basis of a consensus among the panelists.

Preoperative hemoglobin level is a major predictor of the risk for transfusion following total joint replacement [18, 25–27]. Thus, the first discussion focused on the safe hemoglobin level to attain before the arthroplasty.

We extensively reviewed studies about the relationship between preoperative hemoglobin level, operative blood loss, and mortality [25, 28–31]. Most studies reported that elective surgery can be done safely in patients with a preoperative hemoglobin level above 10 g/dL if estimated blood loss is more than 500 mL. Thus, we determined a 10 g/dL level of hemoglobin as the target level to attain before arthroplasty [32–34].

The second discussion focused on items to avoid transfusion. One of the authors (JHN) reviewed previous studies and selected the items that would be relevant to avoid transfusion [4–6, 11–13, 16–20, 25–28, 31, 32, 34–40]. We discussed the clinical efficacy and adverse effect of each item, and whether it was acceptable by the Jehovah's Witness patients. Finally, three methods: recombinant erythropoietin, iron supplements, and re-infusion of blood with use of a cell saver, were chosen.

The third discussion focused on whether to use pharmacological thromboprophylaxis. In East Asian countries, the occurrence of symptomatic venous thromboembolism after total joint arthroplasty is rare even without any thromboprophylaxis [41–45]. Considering risk/benefit of the prophylaxis, we decided not to use thromboprophylactic agents.

Preoperative pharmacological protocol consisted of the administration of 4000 units of recombinant erythropoietin (Darbepoetin; Aranesp®, Amgen Inc., Thousand Oaks, CA, USA) subcutaneously and 100 mg of iron supplements (Venoferrum: Venofer®, ferric hydroxide sucrose complex 100 mg, Vifor Pharma Ltd., Glattbrugg, Switzerland) intravenously.

When the preoperative hemoglobin level was higher than 10 g/dL, we administered recombinant erythropoietin and iron supplements, just once before the operation. However, when the preoperative hemoglobin level was lower than 10 g/dL, we administered the recombinant erythropoietin every other day (3 times a week), and iron supplements every day until the hemoglobin level reached 10 g/dL.

In this protocol, if the patient's hemoglobin reached over 10 g/dL, we performed the arthroplasties without any delay. However, if the patient's hemoglobin was lower than 10 g/dL, we maintained this protocol during minimum 14 days to maximum 18 days to elevate hemoglobin level as much as possible. Our maximal duration of using the preoperative protocol was 18 days (range 4–18 days) after admission. In the patients whose preoperative hemoglobin level did not reach 10 mg/dL despite of more than 14-day management of the preoperative protocol, the lower limit of hemoglobin to perform arthroplasty was 8.0 g/dL. During the operation, reinfusion of drainage blood using a cell saver and plasma expander were used. The cell saver device (Haemonetics Corporation, Braintree, MA, USA), which was used in our study, passed the collected blood through a filter and washed the blood to remove hemolyzed cells, free hemoglobin, and other impurities.

Postoperatively, recombinant erythropoietin and iron supplements were administered at the same manner with the preoperative protocol, and were continued until a hemoglobin level reached to 10 g/dL (Fig. 1).

Performing arthroplasties without transfusion

We included Jehovah's Witness patients, who visited our institution to receive primary arthroplasty of the hip or knee. These patients refused perioperative transfusion or transfusion substitutions, such as red blood cells pack, fresh frozen plasma, platelet, albumin, etc. for religious beliefs were included. Patients who visited for revision arthroplasties were excluded.

From March 2002 to December 2014, 186 Jehovah's Witness patients (total 232 cases) visited our department to receive hip or knee arthroplasty. All of them gave written informed consent regarding the risk and protocol for transfusion-free arthroplasty without allogeneic transfusion. They agreed the risk of surgery without transfusion, including death due to massive bleeding.

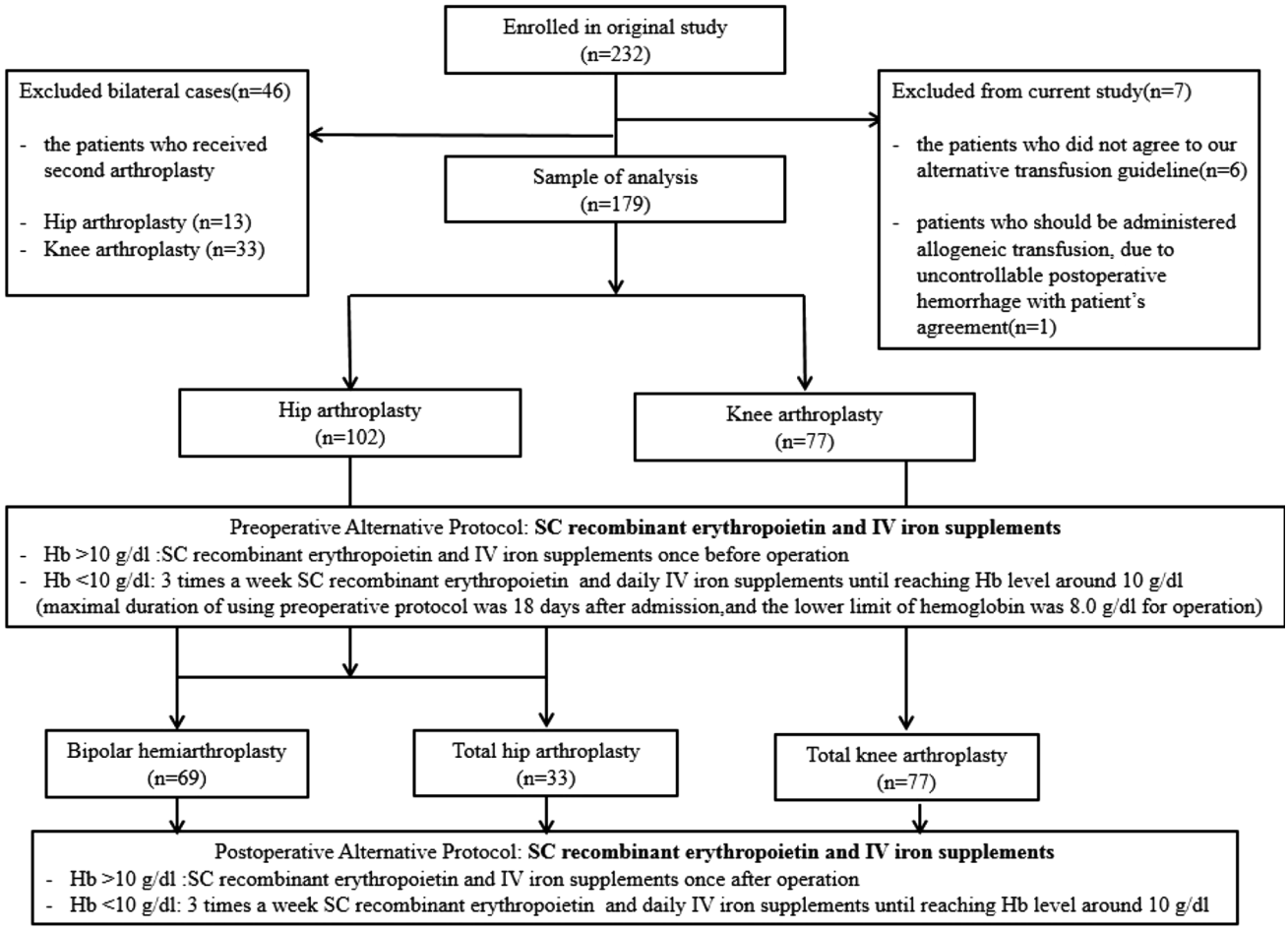


Fig. 1 A flowchart shows the flow of patients through the study

All operations were performed by one senior surgeon (YSS) under a spinal anesthesia and/or epidural anesthesia. The control of blood pressure could be difficult in old patients, if hypotensive anesthesia were used in combination with spinal anesthesia and/or epidural anesthesia [46, 47]. Thus, hypotensive anesthesia was not used in any patient.

In hip arthroplasties, the posterolateral approach was used. The hip prostheses were C2 stem and Delta-PF Cup (Lima, Udine, Italy) in 43 hips (25 bipolar hemiarthroplasties and 18 total hip arthroplasties (THAs)) and Bencox stem and Coren cup (Corentec, Seoul, Korea) in 59 hips (44 bipolar hemiarthroplasties and 15 THAs).

In total knee arthroplasties (TKAs), a tourniquet was applied at the proximal femur, and the medial parapatellar approach was used. Nexgen LPS prostheses (Zimmer, Warsaw, USA) were used in all knees. Both femoral and tibial components were fixed with bone cement, and patellar replacements were not performed in any cases. Meticulous hemostasis was performed using an electrocautery device after the tourniquet deflation. None of the patient underwent lateral retinacular release for patellar alignment.

The suction drainage was routinely inserted after the arthroplasty and removed on postoperative days 1–3. After removal of the suction drainage, patients started ambulation. Gradual weight-bearing was initiated by a crutch or walker.

Hemodynamic evaluation

We measured the amounts of intraoperative bleeding, blood infused by the cell saver, and postoperative drainage. The hemoglobin and hematocrit levels were measured immediately before the operation, immediately after the operation, and on postoperative days 1, 3, 5, and 7.

We evaluated the feasibility, perioperative complications, hematologic change, mortality and infection of our protocol.

In bilateral cases, there was an increased risk of serious bleeding and the left and right sides were possibly correlated with each other. Thus, we decided not to do simultaneous

bilateral arthroplasty, and to perform the second arthroplasty at least 3 months after the first arthroplasty. To keep the underlying principle of statistical independence and to avoid possible exaggeration of the levels of significance with narrowing the confidence intervals, only the first arthroplasty was included in the statistical analysis [48].

Statistics

Baseline patient characteristics and perioperative clinical data were analyzed for all patients, and by gender and operation type with descriptive statistics. Bi-variable tests of association were based on either Pearson's Chi-square or Fisher's exact tests for categorical variables. A robust analysis of variance (ANOVA) was used for continuous variables and the Kruskal–Wallis test was used for ordinal variables. After this analysis, the least significant difference method of post hoc multiple comparisons with Tamhane T2 were used to compare each group of operation types to determine significant differences before operation, immediately after the operation, and on postoperative days 1, 3, 5, and 7 postoperatively. All hemoglobin and hematocrit levels measured in this study were analyzed as continuous variables. All tests were two-sided, and statistical significance was accepted for a p value of <0.05, and statistical analysis was performed using SPSS statistical software (version 21.0; IBM, Armonk, New York).

Results

Among the 186 Jehovah's Witnesses, seven patients could not be operated due to poor medical conditions and comorbidities. The arthroplasty was successfully performed in the remaining 179 patients using the protocol without any transfusion. Thus, the feasibility of our protocol in patients, who refused transfusion, was 96.2 % (179/186) (Table 1).

In 46 patients, who received bilateral arthroplasty, only the first-operated joint was evaluated. The mean age of the 179 patients at the time of arthroplasty was 71.1 ± 12.8 years (range 27–98 years). The types of joint arthroplasty included 77 total knee arthroplasties, 69 bipolar hemiarthroplasties of the hip and 33 total hip arthroplasties (Table 1). Eight patients: two patients (two hips) with a history of a thromboembolic event and six patients (six hips) with cardiac disease before surgery were treated with heparin and/or warfarin for thromboprophylaxis.

The mean operating time was 58.6 ± 10.9 min in bipolar hemiarthroplasties, 84.4 ± 15.8 min in THAs, and 76.1 ± 14.7 min in TKAs.

The mean preoperative hemoglobin and hematocrit levels were 12.3 g/dL and 36.7 %, respectively.

Table 1 Demographic characteristics and baseline variables

Parameters	Number of arthroplasties
Number of patients	179
Male	25
Female	154
Age (years)	71.1. ± 12.8 (range 27–98)
Male	62.1 ± 15.9 (range 27–87)
Female	72.5 ± 11.7 (range 31–98)
Operations	Diagnoses
Bipolar hemiarthroplasty [69]	Femoral neck fractures [41]
	Intertrochanteric fractures [28]
Total hip arthroplasty [33]	Osteoarthritis [12]
	Osteonecrosis [21]
	Others [4]
Total knee arthroplasty [77]	Osteoarthritis [77]
Comorbidities	
Hypertension	74 (40.4 %)
Diabetes	32 (17.5 %)
Stroke	25 (13.7 %)
Cardiovascular disease	22 (12.0 %)
Pulmonary disease	17 (9.2 %)

In 41 patients: 31 with bipolar hemiarthroplasty, 6 with total hip arthroplasty, and 4 with total knee arthroplasty, the initial hemoglobin level before preoperative protocol was less than 10 g/dL (mean: 8.7 ± 0.9; range 6.6–9.9 g/dL). In these patients the preoperative protocol was applied during 4–18 days (mean, 7.8 days). In 23 patients: 15 with bipolar hemiarthroplasty, 4 with THA and 4 with TKA, the hemoglobin increased to 10 g/L within 4–18 days with the use of the preoperative protocol. In the remaining 18 patients: 16 with bipolar hemiarthroplasty and 2 with THA, the hemoglobin level did not reach to 10 g/dL (mean: 8.9 ± 0.5; range 8.0–9.9) even after the use of the preoperative protocol, during 14–18 days after admission. Although their hemoglobin level did not have been reached 10 g/dL, all of their hemoglobin level have been reached over 8.0 g/dL (the lower limit) with this preoperative protocol, during minimal 14 to maximal 18 days (mean 15.4 days). Then, we performed arthroplasties with perioperative and postoperative management of our protocol (Table 2).

During the first 3 days after arthroplasties, the mean hemoglobin level of hemoglobin reduced to 9.4 g/dL (mean decrease, 2.9 g/dL), and that of hematocrit to 28.6 % (mean decrease, 8.1 %). After then, the levels of hemoglobin and hematocrit gradually recovered. These level reached to 10.3 g/dL (mean decrease, 2.0 g/dL) and 31.2 % (mean decrease, 5.5 %), respectively on postoperative day 7 (Figs. 2, 3). The mean decrease of hemoglobin

Table 2 Summary and guideline for alternative blood management protocol without allogeneic transfusion

Preoperative period	Hb > 10 g/dL	SC recombinant erythropoietin 4000U(darbepoetin) and IV iron supplements (Venoferrum, ferric hydroxide sucrose complex 100 mg)/administration once before operation
	Hb < 10 g/dL	SC recombinant erythropoietin 4000 U (darbepoetin) and IV iron supplements (Venoferrum, ferric hydroxide sucrose complex 100 mg)/administration three times a week SC recombinant erythropoietin and daily IV iron supplements until reaching Hb level around 10 g/dL/maximal duration of using preoperative protocol was 18 days after admission and the lower limit of hemoglobin was 8.0 g/dL
Intraoperative period	Cell saver	Blood during operation was collected by cell saver suction and red blood cell washed and separated by the device was readministered
		Collection of blood with gravity
	Hemodilution	Crystalloid fluid was given to keep the systolic blood pressure above 90 mmHg. Typical ratio of fluid to blood collected was 1.5–2:1
		All collected blood was stored at room temperature at around 25 °C and infused after the operation
		Blood was collection with a goal of hematocrit 18 %
Postoperative period	Hb > 10 g/dL	SC recombinant erythropoietin 4000U (darbepoetin) and IV iron supplements (Venoferrum, ferric hydroxide sucrose complex, 100 mg)/administration once after operation
	Hb < 10 g/dL	SC recombinant erythropoietin 4000U (darbepoetin) and IV iron supplements (Venoferrum, ferric hydroxide sucrose complex, 100 mg)/administration three times a week SC recombinant erythropoietin and daily IV iron supplements until reaching Hb level around 10 g/dL

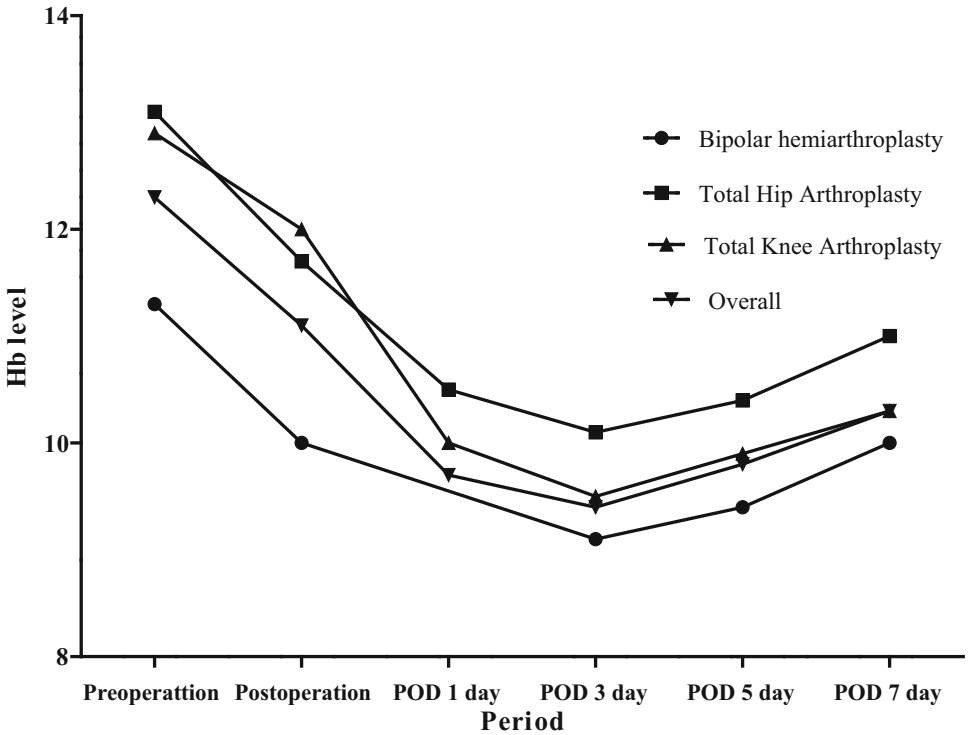


Fig. 2 Hemodynamic analysis with alternative blood management protocol after total joint arthroplasty using hemoglobin level

level during the postoperative 7 days was 1.3 g/dL in bipolar hemiarthroplasties, 2.1 g/dL in THAs, and 2.6 g/dL in TKAs. The mean decrease in bipolar hemiarthroplasty group was lower than THA and TKA groups ($p < 0.001$) (Figs. 2, 3) (Tables 3, 4).

The patients were categorized into three groups according to their preoperative hemoglobin level: group 1 (16 bipolar hemiarthroplasties and 2 THAs) with hemoglobin <10 g/dL, group 2 (32 bipolar hemiarthroplasties, 12 THAs, and 32 TKAs) with hemoglobin between 10 and 12.5 g/dL, and group 3 (21 bipolar hemiarthroplasties, 19 THAs, and 45 TKAs) with hemoglobin >12.5 g/dL.

The mean preoperative hemoglobin level was 9.1 ± 0.6 g/dL (range 8.0–9.8 g/dL) of the group 1. In group 2, the mean preoperative hemoglobin level was 11.5 ± 0.7 g/dL (range 10.1–12.5 g/dL). In group 3, the

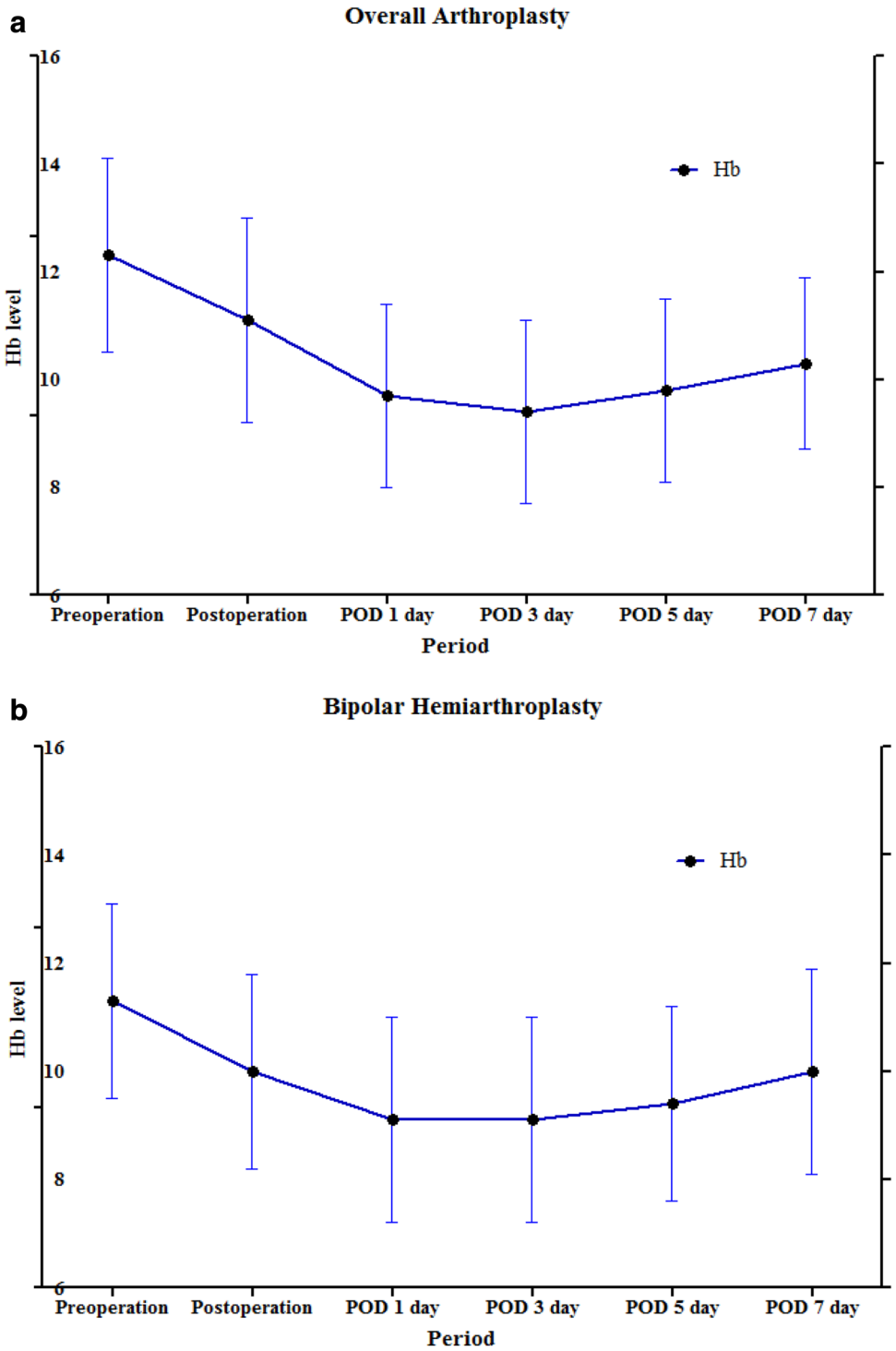
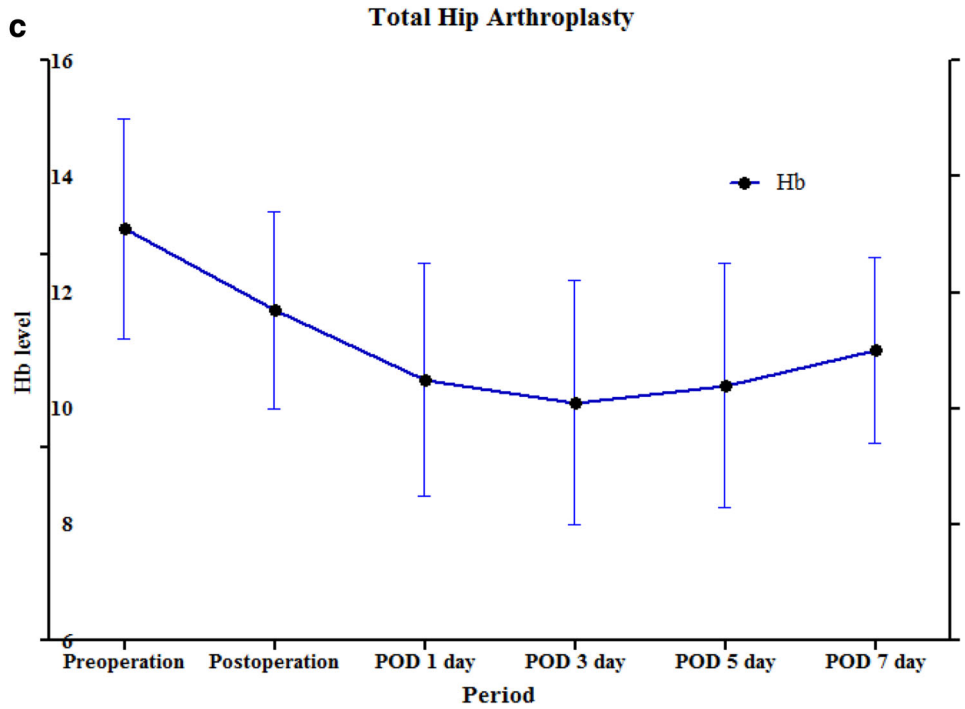


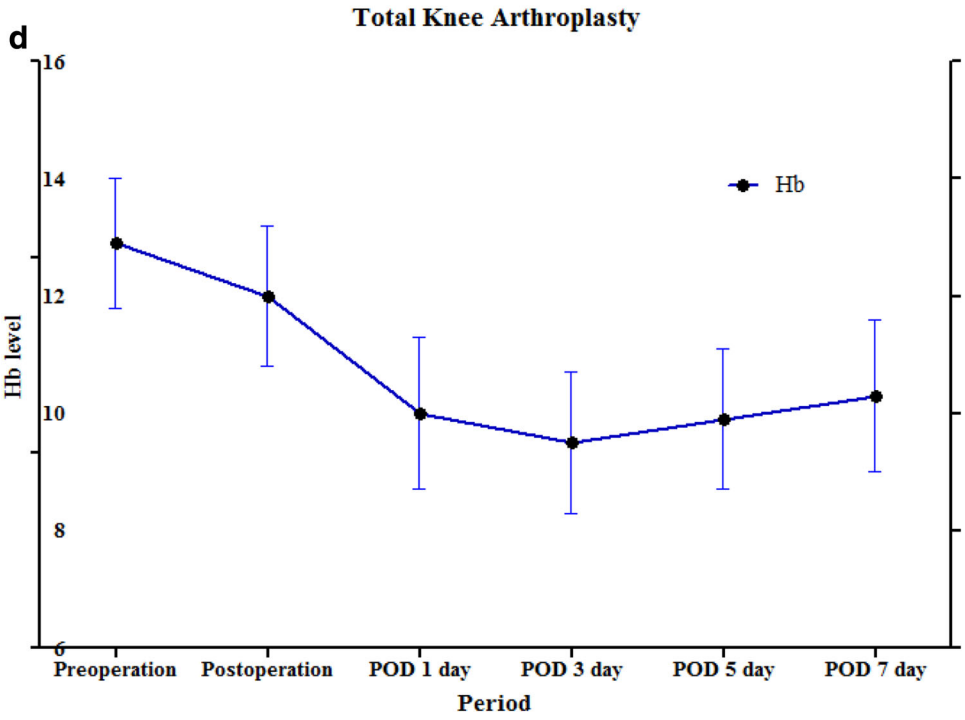
Fig. 3 Hemodynamic changes by perioperative period using alternative protocol for allogeneic transfusion by each operation. **a** Overall arthroplasty, **b** Bipolar hmeiarthroplasty, **c** Total hip arthroplasty, **d** Total knee arthroplasty

mean hemoglobin level was 13.7 ± 0.9 g/dL (range 12.6–16.5 g/dL). The mean decrease of hemoglobin level during the postoperative 7 days was 0.5 g/dL in group 1(hemoglobin level less than 10.0 g/dL), 1.6 g/dL in group 2 (hemoglobin level between 10 and 12.5 g/dL), and 2.0 g/dL in group 3(hemoglobin level over than 12.5 g/dL) ($p < 0.001$) (Fig. 4; Table 5).

The average blood loss during the operation was 431 ± 188 mL (range 50–1000 mL) in bipolar hemiarthroplasties, 581 ± 217 mL (range 50–1000 mL) in THAs, and 333 ± 204 mL (range 150–1500 mL) in TKAs ($p < 0.001$). The average volume of re-infused blood by the cell saver was 148 ± 65 mL (range 30–380 mL) in bipolar hemiarthroplasties, 164 ± 68 mL (range 57–250 mL) in THAs, and

Fig. 3 continued





137 ± 41 mL (range 110–250 mL) in TKAs ($p < 0.001$). The average of postoperative drainage was 478 ± 290 mL (range 200–1000 mL) in bipolar hemiarthroplasties, 576 ± 380 mL (range 250–1500 mL) in THAs, and 803 ± 422 mL (range 200–1800 mL) in TKAs ($p < 0.001$) (Table 6).

One patient died immediately after the operation. The patient was an 89-year-old woman, who was treated with bipolar hemiarthroplasty due to an intertrochanteric fracture. She had dyspnea, poor O_2 saturation and cardiac arrest at the recovery room. Despite of cardiopulmonary resuscitation, the patient died 2 h after the operation. The cause of death seemed to be a pulmonary embolism.

During the hospitalization, two patients had symptomatic deep vein thrombosis, 12 patients had postoperative delirium,

Table 3 Hemodynamic changes through the period from preoperation to postoperative 7 days among three groups (bipolar hemiarthroplasty, total hip arthroplasty and total knee arthroplasty)

	Bipolar hemiarthroplasty (69 cases)	THR (33 cases)	TKR (77 cases)	Overall (179 cases)	Sig.
Preoperation					
Hb (g/dL)	Hb 11.3 ± 1.8 (range 8.0–15.9)	Hb 13.1 ± 1.9 (range 9.6–16.2)	Hb 12.9 ± 1.1 (range 10.0–16.5)	Hb 12.3 ± 1.8 (range 8.0–16.5)	0.000
Hct (%)	Hct 33.4 ± 5.3 (range 24.3–47.2)	Hct 39.4 ± 5.7 (range 28.9–48.6)	Hct 38.3 ± 4.6 (range 31.3–49.8)	Hct 36.4 ± 5.9 (range 24.3–49.8)	0.000
Postoperation					
Hb (g/dL)	Hb 10.0 ± 1.8 (range 6.5–14.7)	Hb 11.7 ± 1.7 (range 6.9–14.3)	Hb 12.0 ± 1.2 (range 9.3–14.4)	Hb 11.1 ± 1.9 (range 6.5–14.7)	0.000
Hct (%)	Hct 30.0 ± 5.4 (range 20.5–42.2)	Hct 35.1 ± 4.7 (range 27.1–44.4)	Hct 35.9 ± 3.6 (range 28.1–44.0)	Hct 33.3 ± 5.6 (range 20.5–44.4)	0.000
POD 1 day					
Hb (g/dL)	Hb 9.1 ± 1.8 (range 6.2–14.3)	Hb 10.5 ± 2.0 (range 5.5–13.9)	Hb 10.0 ± 1.3 (range 6.0–12.9)	Hb 9.7 ± 1.7 (range 5.5–14.3)	0.002
Hct (%)	Hct 27.4 ± 5.4 (range 19.3–45.5)	Hct 31.3 ± 6.1 (range 16.5–42.8)	Hct 30.1. ± 3.8 (range 16.9–39.2)	Hct 29.2 ± 5.2 (range 16.5–45.5)	0.002
POD 3 day					
Hb (g/dL)	Hb 9.1 ± 1.9 (range 5.9–15.0)	Hb 10.1 ± 2.1 (range 4.8–14.3)	Hb 9.5 ± 1.2 (range 5.7–11.1)	Hb 9.4 ± 1.7 (range 4.8–15.0)	0.067
Hct (%)	Hct 27.4 ± 5.7 (range 17.7–46.2)	Hct 30.6 ± 6.6 (range 14.5–44.2)	Hct 28.8 ± 3.5 (range 16.5–34.8)	Hct 28.5 ± 5.1 (range 14.5–46.2)	0.032
POD 5 day					
Hb (g/dL)	Hb 9.4 ± 1.8 (range 6.3–14.6)	Hb 10.4 ± 2.1 (range 5.5–14.5)	Hb 9.9 ± 1.2 (range 6.5–12.9)	Hb 9.8 ± 1.7 (range 5.5–14.6)	0.045
Hct (%)	Hct 28.5 ± 5.4 (range 19.1–46.2)	Hct 31.6 ± 6.3 (range 17.5–44.3)	Hct 29.7 ± 4.0 (range 19.6–38.4)	Hct 29.6 ± 5.1 (range 17.5–46.2)	0.040
POD 7 days					
Hb (g/dL)	Hb 10.0 ± 1.9 (range 6.8–15.0)	Hb 11.0 ± 1.6 (range 6.4–14.5)	Hb 10.3 ± 1.3 (range 7.7–13.4)	Hb 10.3 ± 1.6 (range 6.4–15.0)	0.059
Hct (%)	Hct 30.0 ± 6.4 (range 19.2–50.2)	Hct 31.2 ± 5.8 (range 20.2–44.3)	Hct 31.3 ± 3.9 (range 23.1–41.1)	Hct 31.1 ± 5.2 (range 19.2–50.2)	0.039

one patient had neurogenic bladder and two patients had periprosthetic joint infection.

One hundred and seventy-eight patients survived the procedure and were discharged from the hospital. Two patients (1.1 %) died within 90 days after the operation: one due to myocardial infarct and the other due to gastrointestinal bleeding.

Discussion

Orthopaedic surgeons and their patients have been plagued with increasing concerns regarding complications from allogeneic blood transfusions [1–3]. Although various methods have been attempted to avoid or reduce transfusion, the transfusion rate still remains high in joint arthroplasties [3–6, 9, 10, 12, 13].

In this study, we obtained successful results with our programmed hemodynamic protocol using the combination of recombinant erythropoietin, iron supplements and cell saver without allogenic transfusion. Our protocol had no notable complications. The rate of infection and mortality were comparable to previous results of arthroplasties.

During total joint arthroplasty, bleeding is inevitable, caused by soft-tissue dissection, exposure of the hypervascular metaphysis, and bone resection. When the amount of actual blood loss is greater than the estimated volume of blood loss, various different blood transfusion methods are used to recover from intraoperative or postoperative bleeding.

Perioperative bleeding ranges from 900 to 1200 mL in primary THAs [16, 49] and from 800 to 1200 mL in TKAs [36]. Various methods had been developed to minimize blood loss and to avoid transfusion during surgery.

Concerns for the various problems related to blood transfusions are increasing, and Konishi et al. [50]. reported that 64 % of the 340 medical personnel they surveyed, including patients, nurses, and doctors, wanted to avoid

Table 4 Multiple comparision with Tamhane T2 for hemodynamic changes among three groups (bipolar hemiarthroplasty, total hip arthroplasty and total knee arthroplasty)

	Hb (g/dL)	Hct (%)
Preoperation		
BH-THA	0.000	0.000
THA-TKA	0.961	0.825
TKA-BH	0.000	0.000
Postoperation		
BH-THA	0.000	0.000
THA-TKA	0.747	0.713
TKA-BH	0.000	0.000
POD 1 day		
BH-THA	0.003	0.000
THA-TKA	0.513	0.696
TKA-BH	0.000	0.001
POD 3 day		
BH-THA	0.165	0.026
THA-TKA	0.663	0.570
TKA-BH	0.258	0.180
POD 5 day		
BH-THA	0.147	0.117
THA-TKA	0.656	0.553
TKA-BH	0.244	0.302
POD 7 days		
BH-THA	0.030	0.017
THA-TKA	0.167	0.152
TKA-BH	0.446	0.309

BH bipolar hemiarthroplasty, *THA* total hip arthroplasty, *TKA* total knee arthroplasty)

blood transfusions if possible. Furthermore, surgeons should be aware not only of viral infections resulting from transfusions, but also of hematogenous bacterial infections. Friedman et al. [2] reported that the rates of any infection, lower or upper respiratory tract, and lung infection, and wound inflammation or infection were significantly increased after elective total hip or total knee arthroplasty in patients receiving allogeneic blood transfusions compared with those receiving autologous blood transfusion or no blood transfusion. Newman et al. [1] reported that perioperative allogeneic transfusions were associated with a higher rate of reoperations for suspected acute infection. However, it is suggested that the fears associated with such problems are another reason to avoid allogeneic blood transfusions [1–3, 8, 10, 14, 15, 51–59].

Hypotensive anesthesia, autotransfusion and hemodilution, cell savers, and drug therapy using hemostatic agents have been introduced [11–13, 16, 23, 24, 32, 34, 37, 60]. However, the transfusion rate still remains high in joint arthroplasties [3, 9, 10].

In this study, erythropoietin could reduce the transfusion requirement significantly. Some studies have shown that erythropoietin can replace red blood cell transfusions in patients with end stage renal disease and aplastic anemia [19, 20, 55, 61–63]. Erythropoietin is essential for the proliferation, differentiation, and maturation of red blood cells in bone marrow. Moreover, erythropoietin is critical for the survival of RBC progenitors in bone marrow and may also have immunomodulatory activity. Erythropoietin functions by binding to the erythropoietin receptor, a 72–78 kDa glycosylated and phosphorylated transmembrane polypeptide. The erythropoietin receptor is a member of the superfamily of cytokine receptors. The number of erythropoietin receptors varies during RBC differentiation, with its peak presentation at the colony forming unit. The binding of erythropoietin to its receptor results in the homodimerization of the receptor, stimulating erythropoiesis [64–66]. With the injection of erythropoietin (15–500 μ/kg) approximately 2–3 times a week before an operation, the hematopoiesis of red blood cells could be accelerated, and the use of erythropoietin injections in patients who require transfusions has become as alternative transfusion method. Other studies report that the preoperative administration of erythropoietin is helpful in increasing hemoglobin levels, and the increase of hemoglobin was significantly associated with the amount of injected erythropoietin [17, 18, 55, 61–63, 67].

In addition, Harwin et al. used a special blood management protocol for 124 Jehovah's Witnesses patients who underwent total knee arthroplasty. Patients who had hemoglobin level less than 13 g/dL were initially treated with erythropoietin alone, and if their hemoglobin level remained to be less than 13 g/dL, they had additionally received combination therapy of intravenous iron and blood salvage. At a mean follow-up of 60 months (range 24–120 months), implant survivorship, with revision for aseptic component failure as an end point, was 98 % [56]. The same authors reported implant survivorship of 53 Witnesses undergoing primary THA. They adopted 12 g/dL as the criteria of preoperative hemoglobin level. When the level was 12 g/dL or less, they treated patients with erythropoietin alone, and if their hemoglobin level remained to be less than 12 g/dL, they added a combination therapy of intravenous iron and blood salvage. At a mean follow-up of 63 months (range 24–120 months), implant survivorship was 97 % [56]. In our study, we set a hemoglobin level over 10 g/dL before operation as the reference point for performing arthroplasty safely. The joint arthroplasty could be performed without allogenic transfusion in anemic patients whose hemoglobin level is less than 10 g/dL without protocol. Our study included 69 hip fracture patents, who were operated with bipolar hemiarthroplasty. In these patients, a surgical delay is

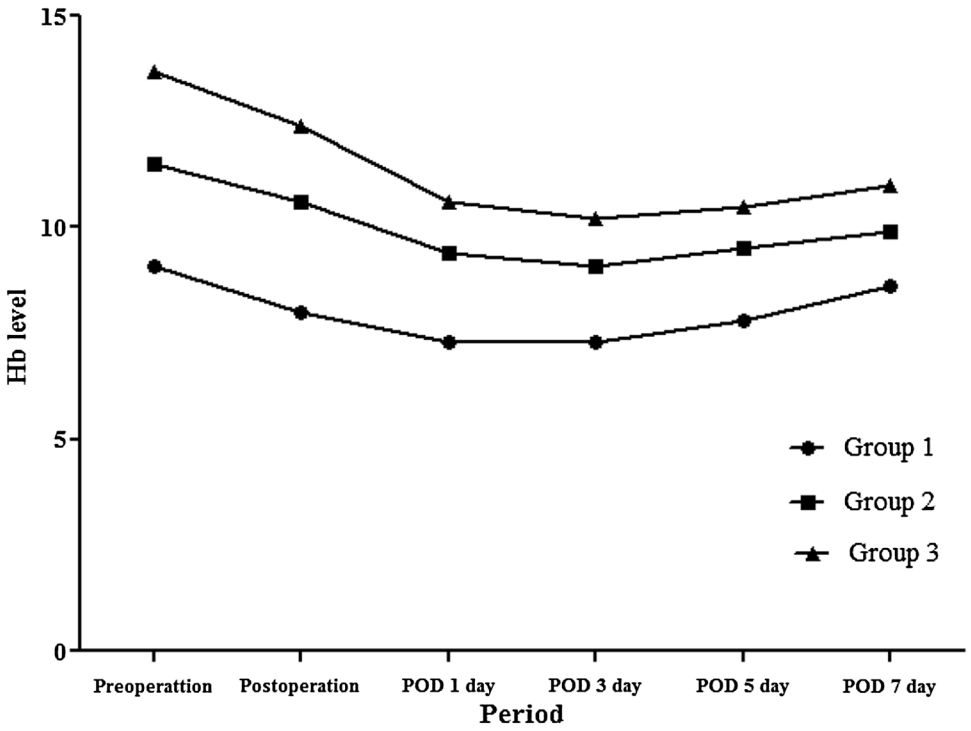


Fig. 4 Hemodynamic analysis with alternative blood management protocol after total joint arthroplasty using preoperative hemoglobin level (The group 1 is patients with a hemoglobin level under 10 g/dL, the group 2 is patients with a hemoglobin level between 10 and 12.5 g/dL, and group 3 is patients with a hemoglobin level over 10 g/dL, regardless of operation type)

associated with a risk of high morbidity and mortality. Thus, these patients necessitate an urgent use of higher dose of erythropoietin and iron supplements for a longer period before arthroplasty. Further investigations are warranted to determine whether to modify the protocol in hip fracture patients.

Some studies have demonstrated that iron therapy has no clinically relevant benefit when used to treat anemia associated with orthopaedic operations [35, 68]. However, several studies have advocated that IV iron supplements given perioperatively rapidly increase hemoglobin levels and reduce allogeneic blood transfusion requirements without serious side effects [69–75]. Perioperative IV iron with or without erythropoietin, plus a restrictive transfusion protocol has been shown to reduce allogeneic transfusion requirements after elective and non-elective orthopedic surgery [73, 76, 77].

During last 5 years, tranexamic acid has been used to reduce blood loss and transfusion rate in joint arthroplasties [4, 11–13, 21, 22]. However, our study was designed in 2002, when the efficacy of tranexamic acid on arthroplasty was not established. The using tranexamic acid has the potential to significantly reduce bleeding problems and decrease transfusion tendency as well as achieve larger cost saving tranexamic acid is the agent focusing on the method to reduce bleeding in operating field, however our protocol focused on the blood conservation management and reproduction as well as reducing bleeding, using erythropoietin, iron supplement and cell saver in this study.

There are several limitations in our study. First, it was not a randomized trial, and our study included three different arthroplasties: bipolar hemiarthroplasty, total hip arthroplasty, and total knee arthroplasty. However, randomized clinical with and without allogeneic transfusion is barely conductible. Second, all arthroplasties were done by a single high-volume surgeon. Low-volume surgeons could not reproduce our results. Third, the protocol was done only in Jehovah's Witness patients who do not accept transfusion for their religious belief. However, transfusion is a serious issue to non Jehovah's Witness patients as well as Jehovah's Witness patients. Our protocol could be applicable in non Jehovah's Witness patients. Fourth, we did not use medical thromboprophylaxis, because our study was performed in an in East Asian country, in which the occurrence of symptomatic VTE after THA is rare even without any thromboprophylaxis [41–45]. Thus, our protocol might not be applicable in Western patients who receive medical thromboprophylaxis. Fifth, the response to the preoperative protocol was various in our patients and the duration of preoperative protocol ranged 4–18 days. Thus, it was difficult to standardize the dose and duration of the preoperative protocol. Sixth, our study was not a randomized clinical trial and we could not compare the cost between the current protocol and blood transfusion. Accurate cost estimation is difficult because the difference of healthcare system among the countries. In South Korea, an ample of 4000 units of recombinant erythropoietin (Darbepoetin; Aranesp®, Amgen Inc., Thousand Oaks, CA,

Table 5 Hemodynamic changes through the period from preoperation to postoperative 7 days among three Groups (The group 1 is patients with a hemoglobin level under 10 g/dL, the group 2 is patients with a hemoglobin level between 10 and 12.5 g/dL, and group 3 is patients with a hemoglobin level over 10 g/dL, regardless of operation type)

	Group 1 (18 cases)	Group 2 (76 cases)	Group 3 (85 cases)	Overall (179 cases)	Sig.
Preoperation					
Hb (g/dL)	Hb 9.1 ± 0.6 (range 8.0–10.0)	Hb 11.5 ± 0.7 (range 10.1–12.5)	Hb 13.7 ± 0.9 (range 12.6–16.5)	Hb 12.3 ± 1.8 (range 8.0–16.5)	0.000
Hct (%)	Hct 26.9 ± 2.2 (range 24.3–30.1)	Hct 34.1 ± 3.1 (range 32.4–48.6)	Hct 41.0 ± 3.8 (range 34.4–49.8)	Hct 36.4 ± 5.9 (range 24.3–49.8)	0.000
Postoperation					
Hb (g/dL)	Hb 8.0 ± 1.0 (range 6.5–10.0)	Hb 10.6 ± 1.2 (range 8.1–12.7)	Hb 12.4 ± 1.1. (range 9.8–14.7)	Hb 11.1 ± 1.9 (range 6.5–14.7)	0.000
Hct (%)	Hct 22.2 ± 5.4 (range 20.5–42.2)	Hct 35.1 ± 4.7 (range 27.1–44.4)	Hct 35.9 ± 3.6 (range 28.1–44.0)	Hct 33.3 ± 5.6 (range 20.5–44.4)	0.000
POD 1 day					
Hb (g/dL)	Hb 7.3 ± 0.9 (range 5.7–8.8)	Hb 9.4 ± 1.2 (range 5.5–12.2)	Hb 10.6 ± 1.6 (range 6.0–14.3)	Hb 9.7 ± 1.7 (range 5.5–14.3)	0.000
Hct (%)	Hct 22.2 ± 2.9 (range 19.3–45.5)	Hct 31.3 ± 6.1 (range 16.5 –36.9)	Hct 30.1. ± 3.8 (range 16.9–45.5)	Hct 29.2 ± 5.2 (range 16.5–45.5)	0.000
POD 3 day					
Hb (g/dL)	Hb 7.3 ± 0.9 (range 5.7–9.1)	Hb 9.1 ± 1.1 (range 7.5–12.0)	Hb 10.2 ± 1.8 (range 4.8–15.0)	Hb 9.4 ± 1.7 (range 4.8–15.0)	0.000
Hct (%)	Hct 23.0 ± 2.9 (range 17.7–27.5)	Hct 27.6 ± 3.5 (range 24.5–44.2)	Hct 30.7 ± 5.1 (range 14.5–46.2)	Hct 28.5 ± 5.1 (range 14.5–46.2)	0.000
POD 5 day					
Hb (g/dL)	Hb 7.8 ± 1.1 (range 5.5–9.8)	Hb 9.5 ± 1.1 (range 7.9–12.2)	Hb 10.5 ± 1.7 (range 6.4–14.6)	Hb 9.8 ± 1.7 (range 5.5–14.6)	0.000
Hct (%)	Hct 24.5 ± 3.6 (range 17.5–29.8)	Hct 28.6 ± 3.5 (range 21.1–37.)	Hct 31.5 ± 5.6 (range 19.6–46.2)	Hct 29.6 ± 5.1 (range 17.5–46.2)	0.000
POD 7 days					
Hb (g/dL)	Hb 8.6 ± 1.2 (range 6.4–11.1)	Hb 9.9 ± 1.2 (range 8.0–12.8)	Hb 11.0 ± 1.6 (range 7.7–15.0)	Hb 10.3 ± 1.6 (range 6.4–15.0)	0.000
Hct (%)	Hct 26.8 ± 4.2 (range 19.2–34.1)	Hct 29.9 ± 4.6 (range 20.2–39.0)	Hct 33.1 ± 5.0 (range 23.1–50.2)	Hct 31.1 ± 5.2 (range 19.2–50.2)	0.000

Table 6 Hemodynamic comparison among bipolar hemiarthroplasty, total hip arthroplasty and total knee arthroplasty by perioperative period

	Bipolar hemiarthroplasty	THA	TKA	Sig.
Intraoperative blood loss (mL)	431 ± 188	581 ± 217	333 ± 204	0.000
Cell saver (mL)	148 ± 65	164 ± 68	137 ± 41	0.000
Postoperative drainage (mL)	478 ± 290	576 ± 380	803 ± 422	0.000
Hemodynamic changes (Hb, g/dL/Hct, %)				
Preoperation-POD 3 day Hb	2.3 ± 1.4	3.0 ± 1.9	3.3 ± 1.3	0.000
Preoperation-POD 3 day Hct	6.1 ± 4.1	8.6 ± 5.8	9.4 ± 5.2	0.000
Preoperation-POD 7 day Hb	1.2 ± 2.7	2.3 ± 1.6	2.7 ± 1.4	0.000
Preoperation-POD 7 day Hct	3.7 ± 5.8	5.8 ± 4.9	6.9 ± 5.9	0.000

USA) costs $55, a bottle of 100 mg of iron supplements (Venoferrum: Venofer®, Vifor Pharma Ltd., ferric hydroxide sucrose complex 100 mg, Glattbrugg, Switzerland) costs $5.8, a cell saver costs $166, and a pack RBC costs $60. From a healthcare system cost, blood transfusion might be the preferred strategy for arthroplasties than the current blood-sparing alternative. Future analyses are needed to assess the cost-effectiveness to individual patient and to society overall.

Our study showed that it is safe to perform joint arthroplasties without allogenic transfusion in anemic patients whose hemoglobin level is less than 10 g/dL, if our protocol

were used. The hemoglobin level was stable during and after the arthroplasty. The rates of infection, morbidity and mortality of our patients were similar with known rates of arthroplasties. In patients who do not want allogeneic transfusions, our protocol might be used as an alternative option of transfusion to perform joint arthroplasty.

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Compliance with ethical standards

Conflict of interest No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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