Preoperative Epoetin-α with Intravenous or Oral Iron for Major Orthopedic Surgery

A Randomized Controlled Trial

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ABSTRACT

Background: Preoperative administration of epoetin-α with iron is commonly used in anemic patients undergoing major orthopedic surgery, but the optimal route of iron intake is controversial. The aim of this study was to compare the clinical effects of erythropoietin in combination with oral or intravenous iron supplementation.

Methods: This study was a prospective, randomized, single-blinded, parallel arm trial. Patients scheduled for elective hip or knee arthroplasty with hemoglobin 10 to 13 g/dl received preoperative injections of erythropoietin with oral ferrous sulfate or intravenous ferric carboxymaltose. The primary endpoint was the hemoglobin value the day before surgery.

Results: One hundred patients were included in the analysis. The day before surgery, hemoglobin, increase in hemoglobin, and serum ferritin level were higher in the intravenous group. For the intravenous and oral groups, respectively, hemoglobin was as follows: median, 14.9 g/dl (interquartile range, 14.1 to 15.6) *versus* 13.9 g/dl (interquartile range, 13.2 to 15.1), group difference, 0.65 g/dl (95% CI, 0.1 to 1.2; $P = 0.017$); increase in hemoglobin: 2.6 g/dl (interquartile range, 2.1 to 3.2) *versus* 1.9 g/dl (interquartile range, 1.4 to 2.5), group difference, 0.7 g/dl (95% CI, 0.3 to 1.1; $P < 0.001$); serum ferritin: 325 μg/l (interquartile range, 217 to 476) *versus* 64.5 μg/l (interquartile range, 44 to 107), group difference, 257 μg/l (95% CI, 199 to 315; $P < 0.001$). The percentage of patients with nausea, diarrhea, or constipation was higher in the oral group, 52% *versus* 2%; group difference, 50% (95% CI, 35 to 64%; $P < 0.0001$).

Conclusions: After preoperative administration of erythropoietin, body iron stores and stimulation of the erythropoiesis were greater with intravenous ferric carboxymaltose than with oral ferrous sulfate supplementation. **(Anesthesiology 2018; 129:710-20)**

PREOPERATIVE anemia is associated with increased morbidity and mortality in patients undergoing noncardiac surgery.[1–4] On the other hand, allogeneic erythrocyte transfusion *per se* increases perioperative morbidity, as well as septic risk and hospital stay.[5–7] Patient blood management is a key strategy to resolve this issue.[8–10] Patient blood management is based on three pillars: improvement of erythropoiesis, reduction of bleeding, and optimization of anemia tolerance. Patient blood management is effective in reducing blood transfusion, morbidity, mortality, and duration of hospitalization[11,12] but remains underused in major orthopedic surgery.[13] In order to improve erythropoiesis, preoperative epoetin-α is used. Originally described in nonanemic patients undergoing hip arthroplasty,[14] epoetin-α is used today in preoperative anemic patients undergoing major orthopedic surgery.[8,10] Its efficacy and safety have been evaluated in numerous studies.[15–17] Epoetin-α stimulates erythropoiesis and induces iron uptake, even though 75% of preoperative anemia in noncardiac surgery is related to absolute or functional iron deficiency.[18] It is therefore essential to combine iron supplementation with epoetin-α in order to optimize its effects.[8,19] Oral ferrous sulfate is widely used because of its simplicity and low cost. However, intestinal iron absorption is poor and frequently associated with digestive discomfort, which leads to a decrease in medication compliance.[20] IV ferric carboxymaltose ensures a rapid restoration of

Editor's Perspective

What We Already Know about This Topic

- Epoetin-α is often given to patients scheduled for major orthopedic surgery
- It remains unknown whether it is best to accompany epoetin-α with oral or intravenous iron

What This Article Tells Us That Is New

- Hemoglobin level the day before surgery was 1 g/dl greater in 50 patients randomized to intravenous iron than in those assigned to oral iron
- About half the patients given oral iron reported gastrointestinal symptoms
- Intravenous iron is preferable to oral iron as a supplement to epoetin-α

Part of this work was presented as the Cross Iron study, winner of the best abstract in anesthesia at the annual meeting of the French Society of Anesthesiology and Critical Care Medicine (Société Française d'Anesthésie et de Réanimation Congress), in Paris, France, September 21, 2017.

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iron stores. However, some rare but life-threatening hypersensitivity reactions have been described during iron infusions.[21] For this reason, IV iron administration should be carried out only in appropriately staffed sites to monitor patients and rapidly treat an adverse reaction.[18,21] Consequently, the benefit of an IV iron intake must be evaluated considering the logistic requirements. The aim of this study was to evaluate the clinical effect of oral or IV iron supplementation before hip or knee arthroplasty surgery, in combination with epoetin-α.

Materials and Methods

After ethics committee approval (Comité de Protection des Personnes, Sud Méditerranée III, Montpellier-Nîmes, France, No. 2014-05-05 bis), a prospective randomized trial was performed (Cross Iron study: Comparative Randomized Oral *versus* Systemic IRON, ClinicalTrials.gov: NCT02496377) at Lapeyronie University Hospital in Montpellier, France. Eligible participants were patients scheduled for elective primary or revision total hip or knee arthroplasty and examined by an anesthesiologist involved in the study. Exclusion criteria were underweight patients (less than 50 kg), pregnancy, age under 18 yr old, systemic infection, bilateral arthroplasty, time between anesthetic consultation and surgery greater than 5 weeks or less than 3 weeks, participation in a preoperative autologous donation program, iron therapy before enrollment, and contraindication to epoetin-α or to iron supplementation.

Preoperative Protocol

As per our routine protocol, within a 3-month period before the preoperative consultation with the anesthesiologist, an initial blood sample was drawn in all patients scheduled for total hip arthroplasty or total knee arthroplasty and examined for blood count, coagulation, renal function, electrolytes, serum ferritin level, serum iron, and transferrin saturation. During the anesthetic consultation, patients with a hemoglobin level between 10 and 12.9 g/dl, without iron overload disease (ferritin levels more than 800 μg/l or transferrin saturation more than 45%) and without exclusion criteria, were identified by the anesthesiologist and were enrolled after written informed consent. Included patients were then randomized either to the oral or the IV iron supplementation group. The allocation sequence was concealed from the anesthesiologist in sequentially numbered, opaque, and sealed envelopes. Block randomization by a computer generated a random number list, and an investigator of the Department of Medical Statistics (CHU Montpellier, University of Montpellier, Montpellier, France) without clinical involvement in the trial prepared the envelopes.

Patients with hemoglobin less than 10 g/dl or newly diagnosed iron overload were redirected to their physician to determine the cause of anemia or to exclude the diagnosis of hemochromatosis. For the patients included in the study, a baseline blood sample was drawn at the end of the anesthetic consultation and analyzed for blood count, serum ferritin level, serum iron, transferrin, transferrin saturation, and C-reactive protein.

According to our national recommendations,[22] all patients received 40,000 U epoetin-α (EPREX, Jansen-Cilag, France) subcutaneously by a registered nurse in the patient's home, on day −21, day −14, and day −7 before surgery. Patients randomized to the oral group received a prescription of ferrous sulfate (Tardyferon 80 mg of iron per tablet [247 mg of ferrous sulfate], Pierre Fabre, France), 160 mg of iron per day, two tablets, each morning, starting the day after the anesthesiologist's consultation. Particular attention was paid on treatments altering oral iron absorption as well as on side effects and the importance of treatment compliance. Patients randomized to the IV group received an injection of 1,000 mg of ferric carboxymaltose (Ferinject, Vifor, France) over a duration of more than 15 min. This infusion was carried out immediately after the anesthetic consultation and after the baseline blood sample, in an ambulatory care unit located close to the anesthetic consultation and the intensive care unit. Patients were monitored with noninvasive blood pressure and continuous heart rate recording during infusion and 30 min after.

The day before surgery, blood was drawn and analyzed in the same laboratory as the baseline blood sample had been, and was evaluated for complete blood cell count, serum ferritin level, serum iron, transferrin, and transferrin saturation. The produced erythrocyte mass was the difference between erythrocyte mass at day −1 and baseline erythrocyte mass. The erythrocyte mass was calculated according to the following formula: erythrocyte mass = estimated total blood volume × hematocrit, with estimated total blood volume = body surface area × α. The body surface area calculation used the Boyd formula,[23] and α was 2,430 for women and 2,530 for men.[24–26] The day before surgery, fatigue assessment using Pichot's scale (from 0, no fatigue, to 32, major fatigue)[27] and fitness evaluation using a visual analog scale (from 0 to 10, with a score of 10 representing a sensation of great physical shape) were performed. In the oral iron group, adherence to treatment was evaluated with the Morisky questionnaire (0 points for high compliance and 3 or 4 points for low compliance)[28] as well as a visual analog scale derived from the scale of Chesney (0 for low compliance and 10 for full compliance to treatment).[29] Finally, complications related to ferrous sulfate, ferric carboxymaltose, or epoetin-α therapy were recorded.

Intraoperative Protocol

Anesthesiologists and surgeons attending to the patient during surgery were blinded to patients' allocation. In the absence of contraindications, patients received 1,000 mg of tranexamic acid before skin incision and during wound closure. In case of revision surgery, a cell saver was used. The thresholds for homologous blood transfusion used during the intra- and postoperative period were 7 g/dl hemoglobin in healthy patients in the absence of physical activity, 8 g/dl in the presence of physical activity, especially postoperative rehabilitation, and 10 g/dl in patients with cardiac or coronary insufficiency.[30] At the end of the procedure, 300 mg

ferric hydroxide sucrose (Venofer, Vifor, France) were administered over the course of 2 h to all patients.

Postoperative Protocol

Postoperatively, low-molecular-weight heparin was administered in all patients. A blood count was performed the day after surgery (day 1) and on days 3 and 5 if the patient was still admitted. According to our national recommendations,[22] patients with hemoglobin less than 15 g/dl received on day 1 a subcutaneous injection of 40,000 U of epoetin-α. On day 2, all patients received 300 mg IV ferric hydroxide sucrose. The calculation of erythrocyte mass loss on days 3 and 5 was carried out according to the formula described in "Preoperative Protocol": erythrocyte mass at day −1 minus erythrocyte mass at day 3 or day 5. An average erythrocyte mass of 150 ml for each homologous erythrocyte unit was added in transfused patients, and an average hematocrit of 60% in the cell saver reinfusion bag (cell saver erythrocyte mass = volume of reinfused blood × 0.6) was considered.[24–26,31] The difference between erythrocyte mass produced during the preoperative period and the loss of erythrocyte mass during and after surgery was then calculated. Major complications, including thromboembolic events, cardiac or respiratory failure, and death during hospitalization, were reported on days 3 and 5 for inpatients. The occurrence of complications was further evaluated by a systematic telephone call 1 month after surgery. Postoperative lower limb ultrasonography was performed only in clinically suspected deep venous thrombosis. Finally, the cost of each iron treatment with epoetin-α was calculated.

Sample Size

The number of patients required was calculated from the study by Weber *et al.*, who found an increase in hemoglobin from 12.3 ± 0.7 g/dl to 14.3 ± 1.2 g/dl in 467 patients who received three injections of 40,000 U of epoetin-α in combination with oral iron.[32] The hypothesis of our study was a hemoglobin difference between the two groups of 1 ± 1.2 g/dl, as this difference was considered clinically significant.[14] With an α risk at 5% and a 90% power, 31 individuals per group were required. We increased the number to 50 per group to account for loss to follow-up.

Statistical Analysis

The primary outcome measure was the hemoglobin value the day before surgery to study the increase in hemoglobin from baseline. Secondary outcomes were serum ferritin level, produced erythrocyte mass the day before surgery, and postoperative hemoglobin.

The statistical analysis was carried out with intent to treat. Categorical variables were expressed as number and percentage, and quantitative variables were expressed as median and interquartile range. Differences between the two groups were expressed by Hodges–Lehmann median difference for continuous variables and the absolute difference for dichotomous variables. The Shapiro–Wilk test was used to test the normality of continuous variables.

For the primary outcome, in the univariate analysis the increase in hemoglobin the day before surgery (defined by the value of hemoglobin the day before surgery less baseline hemoglobin) was examined by group with the Student's *t* test. The increase in hemoglobin was also studied between patients with or without true iron deficiency, defined by a serum ferritin level less than 30 μg/l[18] on the baseline blood sample. A *post hoc* multivariable analysis was performed. The hemoglobin value the day before surgery was studied by stepwise multivariable linear regression, which included the baseline hemoglobin, the randomization arm, and variables identified in the univariate analysis as covariables (*i.e.*, associated to the outcome with a $P < 0.1$). To estimate the performance of our multivariable linear regression, we performed an internal validation (fivefold cross-validation), and the results were expressed as mean absolute percentage error of the prediction.

For secondary outcomes, univariate analysis was performed with the Student's *t* test between continuous variables or the Mann–Whitney test for the nonnormal variables. Categorical variables were compared with the chi-square test or Fisher exact test, as appropriate. Linear mixed models for repeated measures were performed to analyze change in hemoglobin over time. The model included time, group, and time–group interaction. Postoperative hemoglobin was analyzed using mixed-model regressions, with group and surgery as fixed effects and random intercepts for patients. A test was considered significant with $P < 0.05$. Statistical analyses were performed with SAS version 11 (SAS Institute, USA).

Results

From August 2014 to August 2016, 939 patients scheduled for total hip arthroplasty or total knee arthroplasty (primary or revision) had a consultation with an anesthesiologist involved in the study. In the initial blood assessment, 223 (24%) patients had a hemoglobin level between 10 and 12.9 g/dl. In addition, 123 patients (55%) had exclusion criteria or refused to consent. Ultimately, 100 patients (45%) consented to the study and were randomized to either the oral group or the IV group (50 patients each; fig. 1). Baseline characteristics, medical history, drugs, and baseline blood tests were similar in both groups (table 1).

From Inclusion to the Day before Surgery

One patient in the IV group presented a femoral vein thrombosis diagnosed the day before surgery; the procedure was cancelled. Two patients in the IV group received only two epoetin-α injections preoperatively because the date of surgery was expedited. One patient in the IV group presented prostatitis after three injections of epoetin-α, leading to surgery being delayed by 49 days. One patient's procedure in the oral group was postponed for 22 days for surgical reasons. All IV patients received 1 g of ferric carboxymaltose; in the oral group, 92% of the ferrous sulfate tablets prescribed

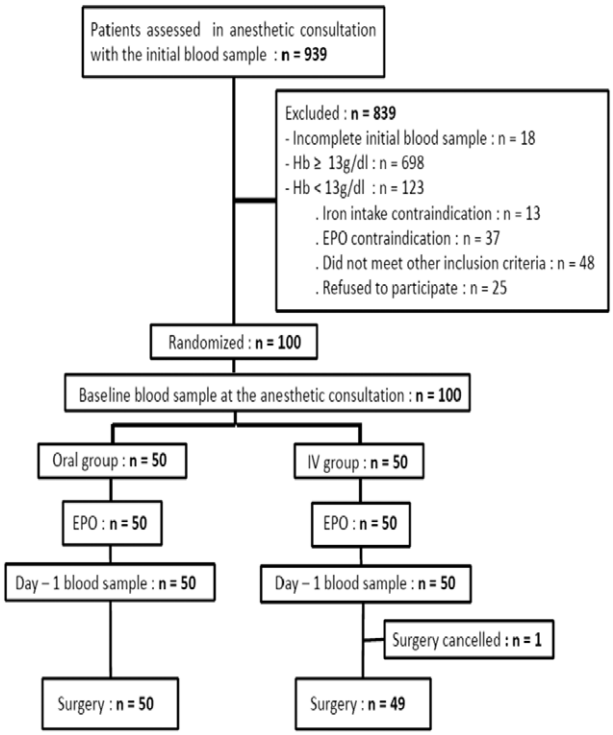

Fig. 1. Flowchart of study participants. EPO, erythropoietin; Hb, hemoglobin; IV, intravenous.

were reported taken. Patients with abdominal complications such as nausea, diarrhea, or constipation were higher in the oral group, 26 (52%) *versus* 1 (2%); group difference, 50% (95% CI, 35 to 64; $P < 0.0001$).

The Day before Surgery

The day before surgery, hemoglobin level and increase in hemoglobin were significantly higher in the IV group; for the IV and oral groups, respectively: median hemoglobin level, 14.9 g/dl (interquartile range, 14.1 to 15.6) *versus* 13.9 g/dl (interquartile range, 13.2 to 15.1); group difference, 0.65 g/dl (95% CI, 0.1 to 1.2; $P = 0.017$; table 2 and fig. 2); hemoglobin increase, 2.64 g/dl (interquartile range, 2.1 to 3.2) *versus* 1.95 (interquartile range, 1.4 to 2.5); group difference, 0.7 g/dl (95% CI, 0.3 to 1.1; $P < 0.001$). Serum ferritin level and produced erythrocyte mass were significantly higher in the IV group. The serum ferritin levels in the IV group and the oral group, respectively, were 325 μg/l (interquartile range, 217 to 476) and 64.5 μg/l (interquartile range, 44 to 107); group difference, 257 μg/l (95% CI, 199 to 315; $P < 0.001$); the produced erythrocyte mass in the IV group and oral group, respectively, were 353 ml (interquartile range, 294 to 450) and 299 ml (interquartile range, 217 to 357); group difference, 85 ml (95% CI, 38 to 133; $P < 0.001$).

The univariate analysis showed that the greatest rise in hemoglobin was reached in the subgroup of patients with true iron deficiency who benefitted from IV iron treatment (3.3 g/dl; interquartile range, 1.9 to 3.5; $P = 0.002$). This increase in hemoglobin was 2.5 g/dl (interquartile range, 2.2 to 3.2) in IV patients without true iron deficiency, 1.6 g/dl (interquartile range, 1.1 to 2.7) in oral patients with true iron deficiency, and 2 g/dl (interquartile range, 1.4 to 2.5) in oral patients without true iron deficiency. Multivariable linear regression showed associations between hemoglobin the day before surgery in the IV group (β = 0.7 [95% CI, 0.3 to 1.0]; $P < 0.0001$), baseline hemoglobin (β = 0.9 [95% CI, 0.1 to 0.7]; $P < 0.0001$), C-reactive protein (β = −0.36 [95% CI, −0.07 to −0.004]; $P = 0.039$), and body mass index (β= −0.03 [95% CI, −0.07 to −0.004]; $P = 0.029$) in the model that included baseline serum ferritin level as covariates (β = 0.001 [95% CI, 0 to 0.002]; $P = 0.057$). After the cross-validation of the multivariable linear regression, the mean (SD) absolute error was 4.8% (3.7). Figure 3 illustrates day −1 hemoglobin according to baseline hemoglobin and C-reactive protein by groups.

Intra- and Postoperative Periods

Intraoperative parameters did not differ between groups (table 3). No patient undergoing primary total hip arthroplasty, total knee arthroplasty, or revision total knee arthroplasty was transfused. Four patients were transfused, during or after total hip arthroplasty revision: one patient in the IV group and three patients in the oral group. The mixed-model analysis showed the negative independent association between postoperative hemoglobin and oral iron group (β = −0.64 [95% CI, −0.31 to −0.97]; $P = 0.0002$), primary total knee arthroplasty (β = −0.4 [−0.02 to −0.75]; $P = 0.03$); total knee arthroplasty revision (β = −1.7 [−1 to −2.42]; $P < 0.0001$) and total hip arthroplasty revision (β = −0.89 [−0.35 to 1.4]; $P = 0.001$). The erythrocyte mass loss at days 3 and 5 was similar in the two groups, but the difference between the produced erythrocyte mass and the erythrocyte mass loss was greater in the IV group ($P = 0.0004$; table 4). One patient in the IV group presented with deep venous thrombosis on day 7, secondary to accidental prolonged calf compression. No major complications were noted at 1 month in the two groups.

Cost of Each Iron Treatment with Epoetin-α

The flat rate of an in-hospital infusion of ferric carboxymaltose was 389 €, including the Ferinject price of 150 €. The cost of 60 ferrous sulfate tablets was 5.40 €. The cost of one dose of epoetin-α, 40,000 U, was 283 €, and that of the nursing act for the subcutaneous injection was 5.45 €. Therefore, the cost of three injections of epoetin-α with ferric carboxymaltose amounted to 1254 €, *versus* 871 € for oral iron, resulting in an additional cost of 383 € in the IV group.

Discussion

The day before surgery, hemoglobin level and increase in hemoglobin were higher in the IV group. In the oral group,

Table 1. Study Population

	Oral Group, n = 50	IV Group, n = 50	*P* Value
Age, yr	71 (61–78)	67 (60–75)	0.410
Women	38 (76)	42 (84)	0.317
Height, cm	163 (158–170)	163 (158–167)	0.606
Weight, kg	74 (62–86)	73 (62–84)	0.821
Body mass index, kg/m^2	27 (24–32)	28 (24–31)	0.856
Body surface area, m^2	1.9 (1.7–2)	1.9 (1.7–2)	0.636
Delay of surgery, day	28 (25–30)	28 (24–30)	0.802
ASA physical status			0.625
I	7 (14)	7 (14)	
II	39 (78)	36 (72)	
III	4 (8)	7 (14)	
Type of surgery			0.712
THA	20 (40)	25 (50)	
TKA	20 (40)	18 (36)	
rTHA	6 (12)	5 (10)	
rTKA	4 (8)	2 (4)	
Initial blood assessment			
Hemoglobin, g/dl	12.3 (11.8–12.6)	12.5 (11.8–12.7)	0.167
Ferritin level, µg/l	125 (54–211)	115 (62–248)	0.662
Transferrin saturation, %	22 (16.3–28)	20.2 (15.2–27.2)	0.633
Creatinine clearance	73.5 (58–101)	76.5 (58–99)	0.888
Baseline blood assessment			
Hemoglobin, g/dl	12.3 (11.8–12.8)	12.2 (11.6–12.8)	0.620
Hematocrit, %	37.3 (35.4–39)	36.6 (35.2–38.6)	0.313
Mean cell volume, µm^3	93 (90–96)	91.5 (87–95)	0.152
Ferritin level, µg/l	138 (71–246)	142 (66–246)	0.851
Serum iron, µmol/l	13.2 (9.3–15.2)	13.2 (9.6–16.8)	0.317
Transferrin, g/l	2.5 (2.3–2.7)	2.4 (2.2–2.7)	0.671
Transferrin saturation, %	22 (14–25)	22.1 (15–30)	0.300
True iron deficiency	3 (6)	5 (10)	0.714
C-reactive protein, mg/l	3.7 (1.8–9.6)	3.3 (2.1–9.2)	0.741
Erythrocyte mass, ml	1,704 (1,524–1,879)	1,668 (1,497–1,832)	0.301

Results are expressed as median (interquartile range) or number (%). Delay of surgery is the period between anesthetic consultation and surgery. Initial blood assessment was the results available at the anesthetic consultation. Creatinine clearance was estimated by Cockcroft–Gault equation (ml · min^{-1} · 1.73 m^{-2}). Baseline blood assessment was the results of the blood sample taken just after the anesthetic consultation and before iron supplementation. True iron deficiency was defined by serum ferritin level less than 30 µg/l.

ASA, American Society of Anesthesiologists; IV, intravenous; rTHA, revision total hip arthroplasty; rTKA, revision total knee arthroplasty; THA, primary total hip arthroplasty; TKA, primary total knee arthroplasty.

day −1 serum ferritin was decreased substantially from baseline, indicating the intense stimulation of erythropoiesis by epoetin-α, inducing an increased iron need not compensated by oral iron intake. In contrast, in the IV group, day −1 serum ferritin was elevated despite the administration of three preoperative injections of epoetin-α. The higher hemoglobin level in the IV group persists throughout the postoperative period despite infusion of ferric hydroxide sucrose on days 0 and 2 in both groups.

In the different steps of a patient blood management program, reduction of bleeding and optimization of anemia are gaining popularity.[33] Most patients received tranexamic acid because the hypothetical increased risk of thromboembolic complications is controversial,[34,35] and the thresholds for homologous blood transfusion are clearly defined. By contrast, the detection and treatment of preoperative anemia require a more complex and expensive organization. Therefore, assessing the best response to epoetin-α treatment is essential in clinical practice. To our knowledge, only one study compared oral iron intake and IV ferric carboxymaltose with epoetin-α in the context of perioperative blood management.[36] This before-and-after nonrandomized study included 51 patients and reported results similar to ours, with higher hemoglobin and ferritin levels in the IV group the day before surgery. Another study compared two preoperative injections of epoetin-α with an oral or an IV (iron saccharate 200 mg at days −14 and −6) iron intake in patients without iron deficiency.[37] In this selected population, there was a comparable erythropoietic response to epoetin-α, irrespective of the route of iron administration, but with a decrease in serum ferritin levels in the oral group and a slight increase in the IV group.[37] In our study, increase in hemoglobin was higher in patients with true iron deficiency supplemented with IV iron. This result emphasizes the effectiveness of IV iron supplementation

Table 2. Results the Day before Surgery

	Oral Group, n = 50	IV Group, n = 50	*P* Value
Iron received, tablets or mg	52 (42–56)	1,000 (1,000–1,000)	—
Duration of iron treatment, day	26 (22–28)	—	
Ratio prescribed iron/received	1 (0.95–1)	1 (1–1)	< 0.001
Morisky questionnaire	0 (0–1)	—	
Adherence to treatment VAS	10 (9–10)	—	
Pichot's scale	9.5 (4.5–15.5)	9 (4–14)	0.848
Fitness VAS	6 (5–7.5)	6.5 (5–8)	0.389
Digestive complications	26 (52)	1 (2)	< 0.0001
Blood assessment at day –1			
Hemoglobin, g/dl	13.9 (13.2–15.1)	14.9 (14.1–15.6)	0.017
Increase in hemoglobin	1.9 (1.4–2.5)	2.6 (2.1–3.2)	< 0.001
Hematocrit, %	43.1 (40.9–46.8)	44.7 (42.3–47)	0.043
Mean cell volume, μm^3	95 (92–99)	95 (91–99)	0.840
Ferritin level, µg/l	64.5 (44–107)	325 (217–476)	< 0.001
Serum iron, µmol/l	10.2 (6.8–21.9)	9.3 (6.2–11.3)	0.095
Transferrin, g/l	2.5 (2.3–2.7)	2 (1.8–2.3)	< 0.001
Transferrin saturation, %	15.5 (11–34)	17 (13–21)	0.837
Erythrocyte mass, ml	1,952 (1,823–2,137)	2,015 (1,833–2,169)	0.514
Produced erythrocyte mass, ml	298 (217–357)	353 (294–450)	< 0.001

Results are expressed as median (interquartile range) or number (%). Ratio iron prescribed/received is the ratio between the amount of iron prescribed in tablets for oral group or in mg for IV group and the amount of iron received by the patients. Morisky questionnaire is the score to assess adherence to an oral treatment (0 points for high compliance and 3 and 4 points for low compliance).[26] Adherence to treatment VAS is the score to assess compliance to an oral treatment by a VAS (0 for low compliance and 10 for full compliance to treatment). Pichot's scale is the score to assess fatigue (from 0, no fatigue, to 32, major fatigue).[25] Fitness VAS is the score to assess fitness using a VAS (a score of 10 representing a sensation of great physical form). Day –1 is the day before surgery. Increase in hemoglobin = hemoglobin the day before surgery – baseline hemoglobin.

IV, intravenous; VAS, visual analog scale.

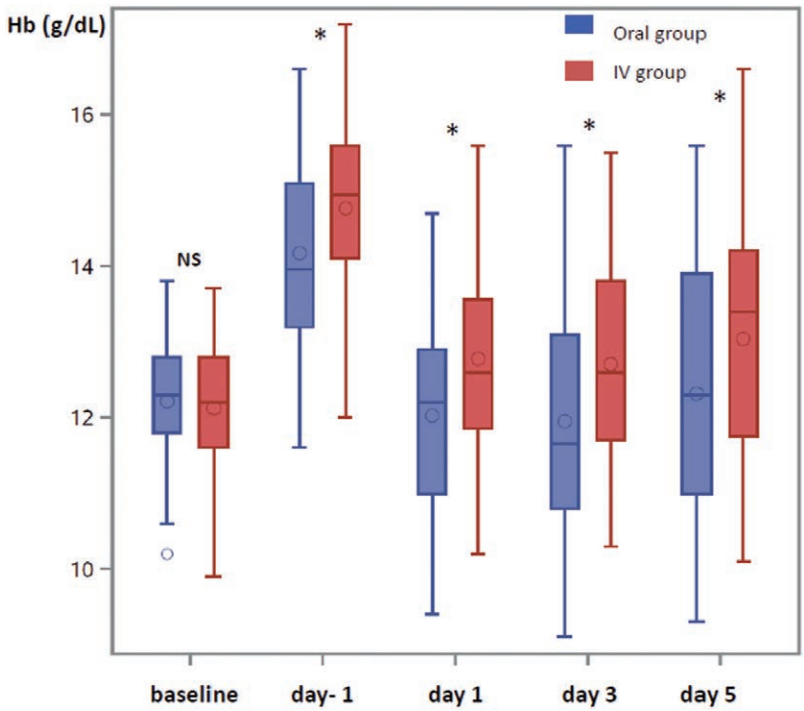

Fig. 2. Change in hemoglobin over time in the oral and intravenous groups. Baseline was the hemoglobin value the day of the anesthetic consultation; day –1 was the hemoglobin value the day before surgery, after erythropoietin administration with oral or intravenous iron intake; day 1 was the day after surgery. **P* value between groups at each time point. For the box and whisker plots, the *horizontal bar* indicates the median, the upper and lower limits of the boxes the interquartile range, and the ends of the whiskers the 95% CI.

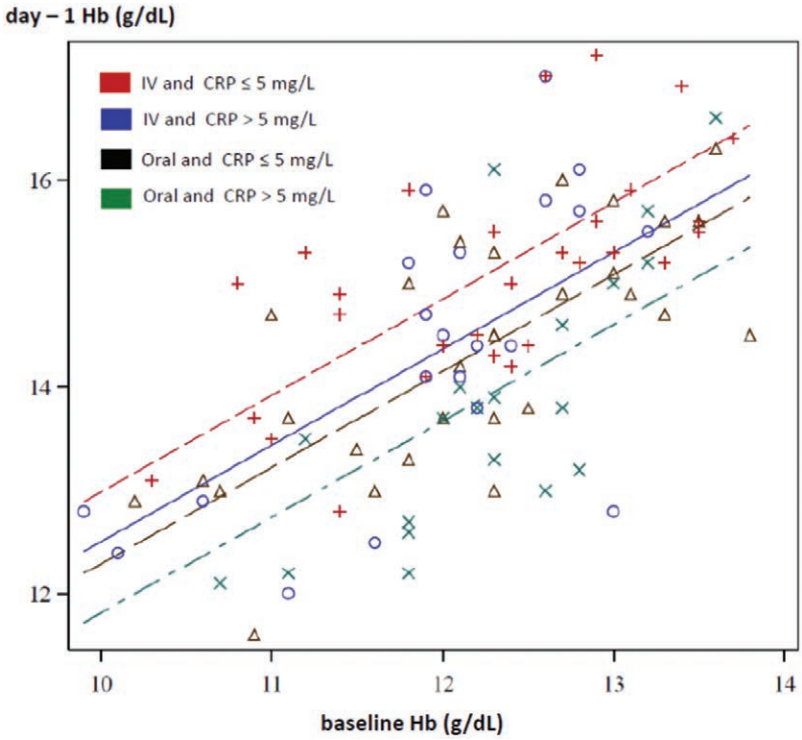

Fig. 3. Response to erythropoietin according to the baseline Hb level in the oral and IV groups with a CRP less than or equal to 5 mg/l or more than 5 mg/l. Baseline hemoglobin was the hemoglobin value the day of the anesthetic consultation; day −1 hemoglobin was the hemoglobin value the day before surgery, after erythropoietin administration with oral or IV iron intake. This figure illustrates the change in hemoglobin in the two groups, in patients with a CRP more than 5 mg/l or less than or equal to 5 mg/l. After the preoperative erythropoietin treatment, in both groups, there was an association between the baseline hemoglobin and the hemoglobin the day before surgery. The higher the baseline hemoglobin, the higher the hemoglobin at day −1. In both groups, the increase in hemoglobin was higher in patients with a CRP less than or equal to 5 mg/l compared to the patients with a CRP more than 5 mg/l. The increase in hemoglobin was always higher in the IV group than in the oral group, with or without a CRP more than 5 mg/l. CRP, C-reactive protein; Hb, hemoglobin level; IV, intravenous.

Table 3. Parameters during and after Surgery

	Oral Group, n = 50	IV Group, n = 49	*P* Value
General anesthesia	49 (98)	48 (98)	> 0.999
Spinal anesthesia	1 (2)	1 (2)	> 0.999
Peripheral nerve block	25 (50)	24 (49)	0.919
Tranexamic acid	48 (96)	48 (98)	> 0.999
Duration of surgery, min	90 (64–106)	88 (64–108)	0.851
Tourniquet in TKA and rTKA	11 (45.8)	9 (45)	0.920
Duration of tourniquet, min	80 (40–114)	100 (65–114)	0.847
Fluid management, ml	1,500 (1,000–2,000)	1,500 (1,000–2,000)	0.925
Ferric hydroxide sucrose at day 0	49 (98)	49 (100)	> 0.999
Ferric hydroxide sucrose at day 2	48 (96)	47 (96)	> 0.999
Epoetin-α at day 1	49 (98)	48 (98)	> 0.999
Patients transfused	3 (6)	1 (2)	0.617
Erythrocyte units per patient			
0	47 (94)	48 (98)	0.242
2	3 (6)	0	
3	0	1 (2)	

Results are expressed as median (interquartile range) or number (%). Tourniquet in TKA and in rTKA means the use of a tourniquet in primary total knee arthroplasty and in revision total knee arthroplasty. Day 0 is the day of surgery, day 1 is the first day after surgery, day 2 is the second day after surgery.
IV, intravenous; rTKA, revision total knee arthroplasty; TKA, total knee arthroplasty.

Table 4. Results after Surgery

	Day 1: Oral Group (n = 50) IV Group (n = 49)	Day 3: Oral Group (n = 50) IV Group (n = 49)	Day 5: Oral Group (n = 47) IV Group (n = 48)	*P* Value	
				Between Groups	Over Time
Hemoglobin, g/dl					
Oral group	12.2 (11–12.9)	11.6 (10.8–13.1)	12.3 (11–13.9)	0.0002	0.175
IV group	12.6 (11.9–13.6)	12.6 (11.7–13.8)	13.4 (11.8–14.2)		
Hematocrit, %					
Oral group	36.7 (33.5–39.9)	35 (32–39.9)	36.9 (33.9–41.6)	0.0003	0.147
IV group	38.1 (35.7–41.7)	38.3 (35.4–41.7)	40.2 (35.3–43.5)		
RBCM loss, ml					
Oral group		318 (223–453)	292 (196–403)	0.363	0.156
IV group		269 (138–397)	207 (57–405)		
RBCM, produced – loss, ml					
Oral group		–58 (–213 to 100)	13 (–164 to 131)	0.0004	0.109
IV group		65 (–50.5 to 236)	168 (–75 to 310)		

Results are expressed as median (interquartile range) or number. (%). Day 1 is the day after surgery.

RBCM, erythrocyte mass; RBCM loss, erythrocyte mass lost between day 1 and day 3 or day 5; produced RBCM, erythrocyte mass produced between baseline and day 1.

during epoetin-α treatment. The analysis of the produced erythrocyte mass had a high interindividual variability. The multivariable linear regression showed that oral iron supplementation, low baseline hemoglobin, C-reactive protein more than 5 g/l, or a high body mass index resulted in lower hemoglobin at day –1. In inflammation, interleukin 6 stimulates the hepatic synthesis of hepcidin, which binds to ferroportin, resulting in less intestinal absorption of iron and lower release of iron stored in hepatocytes and macrophages, leading to functional iron deficiency and decreased erythropoiesis.[38] A high body mass index has already been described as a factor in poor response to epoetin-α,[39] caused by obesity-induced chronic inflammation, which leads to preoperative iron deficiency and anemia.[40] Only 45% of patients with hemoglobin less than 13 g/dl were included in our study. This figure could be greatly increased by improvements in time between anesthetic consultation and surgery, use of brief protocols for administration of epoetin-α (300 $U \cdot kg^{-1} \cdot day^{-1}$ from day –10 to day 4,[41] or decreases in the unwarranted contraindications to epoetin-α in anemic patients.[15] The main limitation to preoperative epoetin-α therapy is its high cost,[42] and the additional cost of iron IV supplementation would be prohibitive. However, the cost of blood transfusion and the consequences of complications associated with perioperative anemia and/or transfusion must also be considered in an economic analysis. In our study, the increase in hemoglobin is lower with an oral iron supplementation in combination with epoetin-α. However, in the oral group, the day before surgery hemoglobin was 13.9 g/dl, with 298 ml of produced erythrocyte mass, and no transfusion occurred in primary arthroplasty. One can wonder if the statistically lower response to epoetin-α after oral iron is clinically relevant when considering the cost of the IV iron. To decrease the cost of preoperative anemia treatment, several measures could be considered. In this study, patients received the preoperative epoetin-α protocol recommended in France[22] and other countries,[32,39] but it has been demonstrated that only two preoperative epoetin-α injections could be sufficient to reach 40% hematocrit in 63% of enrolled patients.[31] With a better rise in hemoglobin than the oral route, IV iron might allow for only two preoperative injections of epoetin-α.[43] A blood count after the second injection would limit the third one to the weak responders, namely, according to our results, patients with inflammation, a high body mass index, and/or a low baseline hemoglobin. The fourth epoetin-α injection on day 1 could be restricted to anemic patients. Finally, the preoperative injection of ferric carboxymaltose could be restricted to major predictive blood loss as arthroplasty revision. IV ferric carboxymaltose infusion increases the hemoglobin at day 3 or day 5 compared to the baseline value noted the day of the anesthetic consultation. In contrast, patients in the oral group have a postoperative hemoglobin level lower than the baseline. This difference is important given that some studies have reported that higher postoperative hemoglobin was associated with better functional recovery after hip fracture repair[44,45] and improved quality of life after total hip arthroplasty.[46]

Some limitations of the study may deserve comments. The oral iron dose selected in our study was 160 mg per day, in a morning dose, according to the current recommendations in France.[47] In clinical practice, dose spacing and timing of oral iron supplementation vary widely. In a recent study, a twice daily iron supplementation seems to have limited additional effect on total iron absorption compared with daily administration.[48] Moreover, lower oral iron doses have been recommended because high oral iron intake increases hepcidin and decreases iron absorption.[48] Low doses may increase dosage efficacy, reduce gastrointestinal exposure to unabsorbed iron, and ultimately improve tolerance of iron supplements. However, the total iron absorbed was higher with high dose, and 160 mg daily provided the higher body iron stores.[48]

Therefore, our results might also be applied to lower oral doses. The degree of change in hemoglobin or in serum ferritin level could be related to the reliability of the measurements. However, this issue was minimized by randomization and by the fact that blood was analyzed in the same laboratory at baseline and the day before surgery. The effects of the higher serum ferritin level induced by IV iron intake could not be properly evaluated in this study. Iron deficiency *per se*, independently of anemia, is associated with fatigue and muscle weakness,[18,49] and iron treatment is used even in patients with heart failure.[47,50] The preoperative correction of iron deficiency, with or without anemia, could be effective in improving fatigue and physical performance[36,49] but, to our knowledge, has never been studied in a surgical context. We did not find any improvement in fatigue in the IV group. The subjective self-evaluation of fatigue used in our study is questionable. An objective evaluation by a strong and sustained preoperative effort, necessary to demonstrate the benefit of a high hemoglobin and/or serum ferritin level, was not applicable in these physically impaired patients. We did not perform a postoperative iron blood assessment because it would be strongly affected by the perioperative inflammatory state and by the postoperative IV iron systematically administered in our institution patient blood management program.[13,18] Finally, the studied population was too weak to properly evaluate the side effects of the preoperative anemia treatment. The 52% incidence of digestive discomfort in the oral group is consistent with the literature.[50] Despite this side effect, stated adherence to the oral treatment was good, probably improved by inclusion in a clinical research protocol. Anaphylactic reactions have been described during the administration of IV presentations associating iron with dextran.[21] Ferric hydroxide-sucrose and ferric carboxymaltose do not contain dextran. Ferric carboxymaltose has the advantage in that it can administer a large dose of iron in a very short time. With the current formulations of IV iron, serious adverse effects are very rare.[18,21] Patients should be closely monitored for signs of hypersensitivity during and for at least 30 min after each IV iron administration.[21] Regarding the complications of preoperative injection of epoetin-α, the risk of thromboembolism has been reported to be increased in spinal surgery patients who receive only mechanical antithrombotic prophylaxis; therefore, pharmacologic thromboprophylaxis is advised.[15] In a recent review, it has been demonstrated that, with correct use of prophylactic anticoagulation, there is not an increased risk of thrombotic events after preoperative epoetin-α treatment in major orthopedic surgery.[51]

In conclusion, both oral and IV iron treatments combined with epoetin-α resulted in increased hemoglobin levels, with a greater increase in the IV group before and after surgery. The IV iron supplementation led to a higher preoperative serum ferritin level. Given that the cost of an IV iron intake is higher, the IV supplementation could be used mainly in patients with inflammation, a high body mass index, a low baseline hemoglobin, and/or with anticipated major blood losses. Finally, the consequences of a high ferritin level and/or a high postoperative hemoglobin level in the context of early rehabilitation must be studied before the use of preoperative IV iron to a larger population can be suggested.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Biboulet: p-biboulet@chu-montpellier.fr. Raw data available from Dr. Biboulet: p-biboulet@chu-montpellier.fr.

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Address correspondence to Dr. Biboulet: Department of Anesthesiology and Critical Care Medicine, Lapeyronie University Hospital, 34295 Montpellier Cedex 5, France. p-biboulet@chu-montpellier.fr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Beattie WS, Karkouti K, Wijeysundera DN, Tait G: Risk associated with preoperative anemia in noncardiac surgery: A single-center cohort study. Anesthesiology 2009; 110:574–81

2. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, Khreiss M, Dahdaleh FS, Khavandi K, Sfeir PM, Soweid A, Hoballah JJ, Taher AT, Jamali FR: Preoperative anaemia and postoperative outcomes in non-cardiac surgery: A retrospective cohort study. Lancet 2011; 378:1396–407
3. Saager L, Turan A, Reynolds LF, Dalton JE, Mascha EJ, Kurz A: The association between preoperative anemia and 30-day mortality and morbidity in noncardiac surgical patients. Anesth Analg 2013; 117:909–15
4. Baron DM, Hochrieser H, Posch M, Metnitz B, Rhodes A, Moreno RP, Pearse RM, Metnitz P; European Surgical Outcomes Study (EuSOS) group for Trials Groups of European Society of Intensive Care Medicine; European Society of Anaesthesiology: Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth 2014; 113:416–23
5. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD: Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116:2544–52
6. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, Marrin CA, Helm RE Jr, Leavitt BJ, Morton JR, Charlesworth DC, Clough RA, Hernandez F, Frumiento C, Benak A, DioData C, O'Connor GT; Northern New England Cardiovascular Disease Study Group: The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 2009; 108:1741–6
7. Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith UW, Osler TM: Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011; 114:283–92
8. Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, Fergusson DA, Gombotz H, Habler O, Monk TG, Ozier Y, Slappendel R, Szpalski M: Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth 2011; 106:13–22
9. Spahn DR, Goodnough LT: Alternatives to blood transfusion. Lancet 2013; 381:1855–65
10. Kozek-Langenecker SA, Ahmed AB, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Haas T, Jacob M, Lancé MD, Pitarch JVL, Mallett S, Meier J, Molnar ZL, Rahe-Meyer N, Samama CM, Stensballe J, Van der Linden PJF, Wikkelsø AJ, Wouters P, Wyffels P, Zacharowski K: Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol 2017; 34:332–95
11. Kotzé A, Carter LA, Scally AJ: Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: A quality improvement cycle. Br J Anaesth 2012; 108:943–52
12. LaPar DJ, Crosby IK, Ailawadi G, Ad N, Choi E, Spiess BD, Rich JB, Kasirajan V, Fonner E Jr, Kron IL, Speir AM; Investigators for the Virginia Cardiac Surgery Quality Initiative: Blood product conservation is associated with improved outcomes and reduced costs after cardiac surgery. J Thorac Cardiovasc Surg 2013; 145:796–803; discussion 803–4
13. Lasocki S, Krauspe R, von Heymann C, Mezzacasa A, Chainey S, Spahn DR: PREPARE: The prevalence of perioperative anaemia and need for patient blood management in elective orthopaedic surgery: A multicentre, observational study. Eur J Anaesthesiol 2015; 32:160–7
14. Canadian Orthopedic Perioperative Erythropoietine Study Group: Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. Lancet 1993; 341:1227–32
15. Lin DM, Lin ES, Tran MH: Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: A systematic review. Transfus Med Rev 2013; 27:221–34
16. Alsaleh K, Alotaibi GS, Almodaimegh HS, Aleem AA, Kouroukis CT: The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: A meta-analysis of randomized clinical trials. J Arthroplasty 2013; 28:1463–72
17. Doodeman HJ, van Haelst IM, Egberts TC, Bennis M, Traast HS, van Solinge WW, Kalkman CJ, van Klei WA: The effect of a preoperative erythropoietin protocol as part of a multifaceted blood management program in daily clinical practice (CME). Transfusion 2013; 53:1930–9
18. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, Liumbruno GM, Lasocki S, Meybohm P, Rao Baikady R, Richards T, Shander A, So-Osman C, Spahn DR, Klein AA: International consensus statement on the perioperative management of anaemia and iron deficiency. Anaesthesia 2017; 72:233–47
19. Goodnough LT, Skikne B, Brugnara C: Erythropoietin, iron, and erythropoiesis. Blood 2000; 96:823–33
20. Goodnough LT, Nemeth E, Ganz T: Detection, evaluation, and management of iron-restricted erythropoiesis. Blood 2010; 116:4754–61
21. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, Szebeni J, Weiss G: Hypersensitivity reactions to intravenous iron: Guidance for risk minimization and management. Haematologica 2014; 99:1671–6
22. French National High Authority on Healthcare (HAS): The transparency commission, in its opinion of 6 October 2010 [in French]. Available at: https://www.has-sante.fr/portail/upload/docs/application/pdf/2010–11/eprex_-_ct-7457.pdf. Accessed April 15, 2018
23. Sendroy J Jr, Cecchini LP: Determination of human body surface area from height and weight. J Appl Physiol 1954; 7:1–12
24. Mercuriali F, Inghilleri G: Proposal of an algorithm to help the choice of the best transfusion strategy. Curr Med Res Opin 1996; 13:465–78
25. Rosencher N, Kerkkamp HE, Macheras G, Munuera LM, Menichella G, Barton DM, Cremers S, Abraham IL; OSTHEO Investigation: Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: Blood management in elective knee and hip arthroplasty in Europe. Transfusion 2003; 43:459–69
26. Brecher ME, Monk T, Goodnough LT: A standardized method for calculating blood loss. Transfusion 1997; 37:1070–4
27. Pichot P, Boyer P, Pull CB, Rein W, Simon M, Thibault A: A questionnaire for self-evaluation of depressive symptomatology, the QD2.II questionnaire: Abridged version QD2A [in French]. Rev Psychol Appl 1984; 34:323–40
28. Morisky DE, Green LW, Levine DM: Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986; 24:67–74
29. Chesney MA, Neilands TB, Chambers DB, Taylor JM, Folkman S: A validity and reliability study of the coping self-efficacy scale. Br J Health Psychol 2006; 11(Pt 3):421–37
30. French National High Authority on Healthcare (HAS): Homologous red blood cell transfusion: blood products, indications, transfusion avoidance 2014 [in French]. Available at: https://www.has-sante.fr/portail/upload/docs/application/pdf/2015-02/transfusion_de_globules_rouges_homologues_-_anesthesie_reanimation_chirurgie_urgence_-_fiche_de_synthese.pdf. Accessed April 15, 2018
31. Rosencher N, Poisson D, Albi A, Aperce M, Barré J, Samama CM: Two injections of erythropoietin correct moderate anemia in most patients awaiting orthopedic surgery. Can J Anaesth 2005; 52:160–5
32. Weber EW, Slappendel R, Hémon Y, Mähler S, Dalén T, Rouwet E, van Os J, Vosmaer A, van der Ark P: Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: The European Epoetin Alfa Surgery Trial (EEST). Eur J Anaesthesiol 2005; 22:249–57

33. Frank SM, Thakkar RN, Podlasek SJ, Ken Lee KH, Wintermeyer TL, Yang WW, Liu J, Rotello LC, Fleury TA, Wachter PA, Ishii LE, Demski R, Pronovost PJ, Ness PM: Implementing a health system-wide patient blood management program with a clinical community approach. Anesthesiology 2017; 127:754–64
34. Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG: Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: Retrospective analysis of effectiveness and safety. BMJ 2014; 349:g4829
35. Franchini M, Mengoli C, Marietta M, Marano G, Vaglio S, Pupella S, Mannucci PM, Liumbruno GM: Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: A meta-analysis of randomised controlled trials. Blood Transfus 2018; 16:36–43
36. Rineau E, Chaudet A, Carlier L, Bizot P, Lasocki S: Ferric carboxymaltose increases epoetin-α response and prevents iron deficiency before elective orthopaedic surgery. Br J Anaesth 2014; 113:296–8
37. Olijhoek G, Megens JG, Musto P, Nogarin L, Gassmann-Mayer C, Vercammen E, Hayes-Licitra SA: Role of oral *versus* IV iron supplementation in the erythropoietic response to rHuEPO: A randomized, placebo-controlled trial. Transfusion 2001; 41:957–63
38. Lasocki S, Longrois D, Montravers P, Beaumont C: Hepcidin and anemia of the critically ill patient: Bench to bedside. Anesthesiology 2011; 114:688–94
39. van Haelst IM, Egberts AC, Doodeman HJ, van Solinge WW, Kalkman CJ, Bennis M, Traast HS, van Klei WA: Occurrence and determinants of poor response to short-term pre-operative erythropoietin treatment. Acta Anaesthesiol Scand 2013; 57:350–7
40. Muñoz M, Botella-Romero F, Gómez-Ramírez S, Campos A, García-Erce JA: Iron deficiency and anaemia in bariatric surgical patients: Causes, diagnosis and proper management. Nutr Hosp 2009; 24:640–54
41. Faris PM, Ritter MA, Abels RI: The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. J Bone Joint Surg Am 1996; 78:62–72
42. So-Osman C, Nelissen RG, Koopman-van Gemert AW, Kluyver E, Pöll RG, Onstenk R, Van Hilten JA, Jansen-Werkhoven TM, van den Hout WB, Brand R, Brand A: Patient blood management in elective total hip- and knee-replacement surgery (Part 1): A randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. Anesthesiology 2014; 120:839–51
43. Rineau E, Stoyanov A, Samson E, Hubert L, Lasocki S: Patient blood management in major orthopedic surgery: Less erythropoietin and more iron? Anesth Analg 2017; 125:1597–9
44. Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL: Higher Hb level is associated with better early functional recovery after hip fracture repair. Transfusion 2003; 43:1717–22
45. Halm EA, Wang JJ, Boockvar K, Penrod J, Silberzweig SB, Magaziner J, Koval KJ, Siu AL: The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. J Orthop Trauma 2004; 18:369–74
46. Conlon NP, Bale EP, Herbison GP, McCarroll M: Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. Anesth Analg 2008; 106:1056–61
47. Arlet JB, Pouchot J, Lasocki S, Beaumont C, Hermine O: Iron therapy: Indications, limitations and modality [in French]. Rev Med Interne 2013; 34:26–31
48. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB: Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood 2015; 126:1981–9
49. Agarwal R: Nonhematological benefits of iron. Am J Nephrol 2007; 27:565–71
50. McDonagh T, Macdougall IC: Iron therapy for the treatment of iron deficiency in chronic heart failure: Intravenous or oral? Eur J Heart Fail 2015; 17:248–62
51. Zhao Y, Jiang C, Peng H, Feng B, Li Y, Weng X: The effectiveness and safety of preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2016; 95:e4122