Patient Blood Management in Major Orthopedic Surgery: Less Erythropoietin and More Iron?

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Erythropoietin (EPO) is proposed preoperatively to reduce blood transfusion in anemic patients (hemoglobin < 13 g/dL) scheduled for a major orthopedic surgery. New intravenous iron formulations allow infusion of higher doses, increasing EPO response. In that context, we evaluated in a before-after study (n = 62 and 65 patients for each period) a new EPO administration protocol (2 injections 4 and 3 weeks before surgery, and a third if hemoglobin <13 g/dL instead of <15 g/dL 2 weeks before surgery). After this protocol implementation, the mean (standard deviation) number of EPO injections decreased from 2.8 (0.5) to 2.2 (0.4)/patient ($P < .0001$) without changing transfusion rates (3% in the 2 periods). (Anesth Analg 2017;XXX:00–00)

Preoperative anemia is associated with both increased blood transfusion rate and morbidity-mortality in the perioperative period[1,2]; its correction is therefore recommended before major elective orthopedic surgery,[3,4] as part of patient blood management (PBM) protocols. Erythropoietin (EPO) is one of the available treatments proven to reduce perioperative blood transfusion,[4,5] and it is commonly used in PBM programs, in association with iron therapy.[6,7] The recent French guidelines on blood transfusion also strongly recommend to treat preoperative anemia using EPO in the context of major orthopedic surgery,[8] but without clear hemoglobin (Hb) targets.

Ideally, EPO should be initiated 1 month before surgery in patients with an Hb < 13 g/dL at the anesthesia visit, but the Hb to be targeted is not precisely defined. In the context of elective orthopedic surgery, marketing authorizations only state to stop EPO administration when Hb exceeds 15 g/dL. Because EPO is indicated only when Hb is <13 g/dL, this value could represent an appropriate preoperative threshold (ie, instead of 15 g/dL). Nowadays, the use of tranexamic acid allows a reduction in perioperative blood losses, and thus the preoperative Hb target to be reached may be lowered, without increasing the risk of being transfused.[9] Moreover, a lower target may necessitate fewer EPO injections, and thus help to reduce costs, especially if EPO is used with intravenous (IV) iron, as we previously shown that the use of IV ferric carboxymaltose (FCM) together with EPO improves erythropoiesis in comparison with oral iron and increases preoperative and postoperative Hb values.[10]

We have thus modified our PBM protocol, targeting an Hb ≥ 13 g/dL (instead of 15 g/dL) 1 week after the second EPO injection. The objective of this before-after study was to evaluate blood transfusion rates, EPO injections number, and Hb levels in patients scheduled for a total hip or knee replacement, after modification of our PBM protocol.

METHODS

In a retrospective study, before and after modification of our PBM protocol, all patients scheduled for a primary knee or hip prosthetic surgery between June 2012 and January 2015, and preoperatively treated with EPO and FCM, were included. The study was approved by the local Ethics Committee ("Comité d'Ethique du Centre Hospitalier Universitaire d'Angers," Ref: 2011/42), which waived patients' consent for this study, according to French law.

All patients scheduled for a primary knee or hip prosthetic surgery and having an Hb <13 g/dL at the anesthesia visit 1 month before surgery were eligible for a preoperative treatment with EPO and FCM in the absence of contraindication (for EPO: hypersensitivity to epoetin-α or derived products, uncontrolled hypertension, severe or recent arterial disease [coronary, cerebral, or peripheral disease], and uncontrolled seizure; for FCM: hypersensitivity to any IV iron). Our protocol was associated with 2 EPO injections (40,000 IU subcutaneous on day_{-21} and day_{-14}) and 1 FCM injection (1 g on day_{-21}). An additional EPO injection was given on day_{-7} and day_{-1} if Hb remained <15 g/dL during the first phase (group "EPO <15"), as previously published,[6] and if Hb remained <13 g/dL during the second phase (group "EPO < 13"). Surgical techniques and transfusion Hb triggers (ie, an Hb < 8 g/dL in the presence of comorbidities or <7 g/dL without comorbidity) did not change between the 2 phases, as well as thromboprophylaxis (using low-molecular-weight heparin from the day of surgery, 6 to 12 hours after the end of surgery).

Demographic data, perioperative treatments and Hb levels, length of hospital stay, and complications were collected from patients' files. Anemia was defined according to the World Health Organization criteria: Hb < 13 g/dL for men or < 12 g/dL for women. The iron deficit was calculated using the modified Ganzoni formula as previously described[11]: iron deficit (mg) = subject weight in kg × (Hb target − current Hb [g/dL]) × 2.4 + 500.

The primary outcome was the transfusion rate (proportion of transfused patients during hospitalization in orthopedic surgery unit) in the 2 phases. Secondary outcomes

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Accepted for publication February 17, 2017.

Funding: This work was solely supported by the University Hospital of Angers, France.

Conflicts of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000002086

were the number of EPO injections per patient, perioperative Hb levels, length of hospital stay, and complications. Data are expressed as mean (standard deviation), median [25th to 75th percentiles], or n (%). The 2 groups ("EPO < 15" and "EPO < 13") were compared for primary and secondary outcomes and for baseline characteristics using the Mann-Whitney *U* test or the Fisher exact test as appropriate. Odds ratios [95% confidence intervals] are presented for each binary outcome for "EPO < 13" group (versus "EPO < 15" group), before and after adjustment for sex, using a logistic regression. Tests were 2-sided, and *P* values <.05 were considered statistically significant.

Table 1. Baseline Characteristics of Patients in Whom EPO Was Continued If Hb Remained <15 g/dL ("EPO < 15" Group) or If Hb Remained <13 g/dL ("EPO < 13" Group)

	"EPO < 15" Group (n = 62)	"EPO < 13" Group (n = 65)	*P* Value
Age (y)	74 (10)	73 (14)	.692
Female sex	49 (79%)	62 (95%)	.007
Weight (kg)	74 (15)	72 (16)	.464
Body mass index (kg/m^2)	28.5 (5.0)	28.6 (6.0)	.924
Renal insufficiency	5 (8%)	3 (5%)	.485
Diabetes	8 (13%)	12 (19%)	.469
Hypertension	42 (68%)	38 (59%)	.358
Atrial fibrillation	5 (8%)	6 (9%)	1
Valvular heart disease	4 (6%)	4 (6%)	1
Ischemic heart disease	1 (2%)	3 (5%)	.619
Usual medications			
Warfarin or Coumadin	4 (7%)	6 (9%)	.744
Aspirin	16 (26%)	14 (22%)	.677
Clopidogrel	1 (2%)	3 (5%)	.619
Antiulcer	20 (32%)	22 (34%)	1
Preoperative Hb levels (g/dL)			
Anesthesia visit	12.0 (0.9)	12.1 (0.9)	.508
Day$_{-8}$	13.8 (1.0)	13.8 (1.0)	.75
Type of surgery			
Total knee arthroplasty	31 (50%)	26 (40%)	.288
Total hip arthroplasty	31 (50%)	39 (60%)	.288

Data expressed as mean (SD) or number (%).
Abbreviations: day$_{-8}$, the eighth day before surgery; EPO, erythropoietin; Hb, hemoglobin.

RESULTS

During the study period, 1322 patients had a total hip (n = 752) or knee (n = 570) replacement at the CHU d'Angers. Among them, 127 (10%) patients received EPO and FCM preoperatively and were included in the analysis (62 for the first phase and 65 for the second phase). Fifty (39%) patients had an anemia at the anesthesia consultation, according to the World Health Organization criteria. Patients' characteristics were not significantly different between the 2 phases except for the percentage of women (Table 1). Fifty (89%) patients had an available Hb value at day$_{-1}$ in the first phase and 61 (94%) in the second phase. Among them, 20 (40%) patients had reached the desired Hb target in the first phase (15 g/dL) vs 55 (90%) patients in the second phase (13 g/dL).

No difference was found on the primary outcome, with a low transfusion rate of 3% in the 2 phases (odds ratio [95% confidence interval] = 1.17 [0.14–9.72], *P* = .883). As expected, the number of preoperative EPO injections per patient was lower during the second period (Table 2) as well as the number of patients who received more than 2 injections (11 [17%] vs 52 [84%], *P* < .001). Hb levels were significantly higher in the group "EPO < 15" from day$_{-1}$ until hospital discharge (0.7 g/dL in mean), but rate of patients with severe anemia (ie, with an Hb < 10 g/dL) at hospital discharge, complications rate, and length of hospital stay were not significantly different between the 2 phases (Table 2). One deep venous thrombosis was diagnosed in the group "EPO < 15" on postoperative day$_{+6}$ (preoperative Hb: 14.1 g/dL), despite thromboprophylaxis using low-molecular-weight heparin.

The calculated iron deficit was 604 [595–668] mg on day$_{-8}$ in patients who did not reach 13 g/dL and 646 [588–728] mg on day$_{-1}$.

DISCUSSION

After changing the Hb target from 15 to 13 g/dL in patients scheduled for a major orthopedic surgery and treated by EPO + IV iron 4 weeks before surgery for an Hb < 13 g/dL, a lower number of EPO injections was needed, without increasing the transfusion rate.

The systematic use of IV iron (in combination with EPO) plays probably an important role in this PBM protocol.

Table 2. Primary and Secondary Outcomes: Univariate Analysis and Logistic Regression After Adjustment for Sex

	"EPO < 15" Group (n = 62)	"EPO < 13" Group (n = 65)	OR [95% CI]	*P* Value	After Adjustment for Sex	
					OR [95% CI]	*P* Value
Primary outcome						
Transfused patients	2 (3%)	2 (3%)	1.05 [0.14–7.69]	.962	1.17 [0.14–9.72]	.883
Secondary outcomes						
Perioperative complications	3 (5%)	3 (5%)	0.95 [0.19–4.90]	.953	1.02 [0.18–5.59]	.986
Anemia at discharge	33 (53%)	40 (62%)	1.41 [0.69–2.85]	.344	1.88 [0.89–3.98]	.098
Hb < 10 g/dL at discharge	3 (5%)	7 (11%)	2.37 [0.59–9.63]	.226	2.40 [0.56–10.24]	.24
Preoperative EPO injections	2.8 (0.5)	2.2 (0.4)		<.0001		
Perioperative Hb values (g/dL)						
Day$_{-1}$	14.4 (1.3)	13.6 (1.0)		.005		
Day$_{+1}$	12.4 (1.5)	11.7 (1.2)		.003		
Hospital discharge	12.1 (1.3)	11.4 (1.3)		.003		
Nadir Hb	11.5 (1.3)	11.1 (1.2)		.039		
Length of hospital stay (d)	10 (5)	9 (4)		.21		

Data are expressed as mean (SD) or number (%). ORs [95% CIs] are presented for each binary outcome for "EPO < 13" group" (vs "EPO < 15" group), before and after adjustment for sex.
Abbreviations: CI, confidence interval; day$_{-1}$, the day before surgery; day$_{+1}$, the day after surgery; EPO, erythropoietin; Hb, hemoglobin; OR, odds ratio.

Indeed, it has been shown that the use of iron (oral or IV) improves the response to EPO, in patients with "functional" iron deficiency observed in anemia of inflammation such as in cancer[12] or chronic kidney disease anemias.[13] Furthermore, the use of IV iron, in comparison with oral iron, accelerates EPO-induced erythropoiesis, not only in hemodialysis patients[13] but also in orthopedic surgery patients,[10] except when doses are insufficient.[14] Thus, the use of 1 g IV iron (FCM here) probably explains that 90% of our patients treated with EPO (whose causes of anemia can be multiple and sometimes entangled: true iron deficiency, chronic kidney, or inflammatory diseases) reached the Hb target of 13 g/dL, with only 2 EPO injections for a majority of them (83%).

However, a lower Hb target is associated with lower postoperative Hb levels too, about 0.7 g/dL in our study. By calculating the iron deficit, it seems that an additional IV iron injection after the second EPO injection might be needed to further improve the EPO response. This result is consistent with analyses showing that the median iron deficit is around 1500 mg in different IV iron trials, suggesting that these patients should have received more iron.[11] Studies that will involve a second iron injection, according to the iron status of the patient (eg, 1 week after the second EPO injection), are needed to confirm these results.

DISCLOSURES

Name: Emmanuel Rineau, MD.
Contribution: This author helped collect and analyze the data, design the study, and write the manuscript.
Conflicts of Interest: None.
Name: Alexandra Stoyanov, MD.
Contribution: This author helped collect the data and write the manuscript.
Conflicts of Interest: None.
Name: Emmanuel Samson, MD.
Contribution: This author helped collect the data.
Conflicts of Interest: None.
Name: Laurent Hubert, MD.
Contribution: This author helped review the manuscript.
Conflicts of Interest: None.
Name: Sigismond Lasocki, MD, PhD.
Contribution: This author helped design the study, and review and write the manuscript.
Conflicts of Interest: This author received consulting fees from Vifor Pharma.
This manuscript was handled by: Marisa B. Marques, MD.

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