Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopedic surgery: a pooled analysis of observational data from 2547 patients

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BACKGROUND: Postoperative nosocomial infection (PNI) is a severe complication in surgical patients. Known risk factors of PNI such as allogeneic blood transfusions (ABTs), anemia, and iron deficiency are manageable with perioperative intravenous (IV) iron therapy. To address potential concerns about IV iron and the risk of PNI, we studied a large series of orthopedic surgical patients for possible relations between IV iron, ABT, and PNI.

STUDY DESIGN AND METHODS: Pooled data on ABT, PNI, 30-day mortality, and length of hospital stay (LHS) from 2547 patients undergoing elective lower-limb arthroplasty (n = 1186) or hip fracture repair (n = 1361) were compared between patients who received either very-short-term perioperative IV iron (200-600 mg; n = 1538), with or without recombinant human erythropoietin (rHuEPO; 40,000 IU), or standard treatment (n = 1009).

RESULTS: Compared to standard therapy, perioperative IV iron reduced rates of ABT (32.4% vs. 48.8%; p = 0.001), PNI (10.7% vs. 26.9%; p = 0.001), and 30-day mortality (4.8% vs. 9.4%; p = 0.003) and the LHS (11.9 days vs. 13.4 days; p = 0.001) in hip fracture patients. These benefits were observed in both transfused and nontransfused patients. Also in elective arthroplasty, IV iron reduced ABT rates (8.9% vs. 30.1%; p = 0.001) and LHS (8.4 days vs.10.7 days; p = 0.001), without differences in PNI rates (2.8% vs. 3.7%; p = 0.417), and there was no 30-day mortality.

CONCLUSION: Despite known limitations of pooled observational analyses, these results suggest that very-short-term perioperative administration of IV iron, with or without rHuEPO, in major lower limb orthopedic procedures is associated with reduced ABT rates and LHS, without increasing postoperative morbidity or mortality.

Postoperative nosocomial infection (PNI), especially surgical site infection, is a severe complication in surgical patients leading to increased rates of resource consumption and length of hospital stay (LHS).[1-4] Comorbidity burden, surgical complexity, and allogeneic blood transfusion (ABT) are well-known risks factors of PNI. Preoperative anemia, which is present in one-third to one-half of surgical patients, is one of the major predictive factors for ABT in surgeries with moderate to high perioperative blood loss (e.g., orthopedic surgery), which in turn induces postoperative anemia and/or aggravates existing anemia.[5] Moreover, preoperative anemia in itself has been linked to increased postoperative morbidity and mortality and decreased quality of life.[5-8] Preoperative anemia and even iron deficiency without anemia may also increase the rate of PNI.[9]

ABBREVIATIONS: ABT(s) = allogeneic blood transfusion(s); ASA = American Society of Anesthesiologist physiologic status classification system; HFR = hip fracture repair; IS = iron sucrose; LHS = length of hospital stay; PHF = pertrochanteric hip fracture; PNI(s) = postoperative nosocomial infection(s); RTI = respiratory tract infection; SHF = subcapital hip fracture; SWI = surgical wound infection; THR = total hip replacement; TKR = total knee replacement; UTI = urinary tract infection.

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Patients scheduled for major orthopedic surgery should have their hemoglobin (Hb) level and iron status (serum iron, ferritin, and transferrin saturation) tested, preferably 30 days before the scheduled surgical procedure.[10] For those more than 60 years of age, vitamin B_{12} and folic acid should also be measured.[10] This will allow for detection and differential diagnosis of anemia and implementation of appropriate therapy.

A recent consensus statement suggested perioperative administration of IV iron in patients undergoing major orthopedic surgery who are expected to develop severe postoperative anemia (GRADE recommendation 2B).[11] Perioperative treatment with intravenous (IV) iron, with or without recombinant human erythropoietin (rHuEPO), has been shown to reduce perioperative anemia and hasten the recovery of postoperative anemia, thereby reducing the risk of transfusion requirements in patients undergoing lower limb orthopedic surgery.[12-18] However, definitive conclusions regarding the efficacy and safety of very-short-term perioperative treatment with IV iron with or without rHuEPO in this clinical setting cannot be drawn due to the rather low numbers of patients included in each study. Therefore, we pooled all our observational data to ascertain whether the suggested benefits on ABT and PNI (primary outcome variables) remain when a large series of elective or nonelective, lower-limb orthopedic surgical procedures are included in the analysis. Postoperative 30-day mortality and LHS were secondary outcome variables.

MATERIALS AND METHODS

Patients and procedures

We performed a retrospective analysis of pooled clinical and analytical data from patients who underwent lower limb surgery for pertrochanteric hip fracture (PHF) repair, subcapital hip fracture (SHF) repair, primary total knee replacement (TKR), or primary total hip replacement (THR) between 2002 and 2011 at four different centers in Spain. Data were retrieved from databases of previous publications,[9,12-18] doctorate theses,[19,20] and unpublished databases (Table 1). This study was a retrospective observational study without any modification of treatment, using only nonidentifiable, disaggregated data, which maintained confidentiality; therefore, approval from an ethics committee was not necessary.

At all centers, standardized anesthetic (>90% locoregional) and surgical protocols, antibiotic and antithrombotic prophylaxes, and postoperative analgesia were used (Appendix S1, available as supporting information in the online version of this paper). All TKR procedures were performed using a pneumatic tourniquet, which was deflated after wound closure. No patient was operated on using minimally invasive techniques. Closed suction drains were placed in all operations and were removed at the

TABLE 1. Distribution of patients included in this study, according to type of surgery (period), and hospital of precedence

	Total hip arthroplasty		Total knee arthroplasty		Hip fracture	
Hospital (reference)	Number	Period	Number	Period	Number	Period
General Hospital of Barbastro (Huesca, Spain)[12,13]					234	October 2002 March 2003
University Hospital Miguel Servet (Zaragoza, Spain)[9,14-16,19,20]	95*	March 2006 April 2008	301	March 2003 June 2005	1148	March 2003 December 2008
University Hospital Virgen de la Victoria (Málaga, Spain)	250*	January 2005 December 2008	287*	January 2005 December 2008		
Hospital Santa Elena (Torremolinos, Spain)[17,18]	149†	January 2004 December 2011	108†	January 2004 December 2011	61†	January 2005 December 2010
Total patients‡	494		696		1443	

* Unpublished data.
† Published and unpublished data.
‡ Patients were excluded from data analysis if they presented with a Hb level of less than 10 g/dL on admission.

second postoperative day. All hip fracture repair (HFR) patients received a Foley catheter postoperatively.

Patients with any contraindication to receive IV iron (e.g., history of anaphylaxis, iron overload, active infection) were excluded. Patients presenting with preoperative Hb level of less than 10 g/dL were at very high risk for ABT and were also excluded. IV iron administration, with or without rHuEPO, was the study group, whereas those receiving standard therapy (oral iron or no iron) were controls.

IV iron supplementation

The IV iron formulations evaluated in the analysis were iron sucrose (IS, Venofer, Vifor France, Neully-sur-Seine, France), administered at doses of 100 to 200 mg in 100 to 200 mL of saline over 30 to 60 minutes up to three times perioperatively (either 2-5 days preoperatively and/or 2-3 days postoperatively) and ferric carboxymaltose (Ferinject, Vifor France), administered as 600 mg in 100 to 200 mL of saline over 15 to 30 minutes on the first postoperative morning. A single preoperative dose (40,000 IU, sc) of rHuEPO (Eprex, Janssen-Cilag SA, Madrid, Spain) was administered at the orthopedic ward to some patients presenting with preoperative Hb level of less than 13 g/dL.[21] Of those, HFR patients received rHuEPO on Postadmission Day 1, after Hb assessment,[14,15,19,20] whereas TKR patients received rHuEPO 24 to 48 hours before surgery.[16]

Blood management

Most patients were managed with a restrictive ABT trigger (Hb < 8 g/dL). However, in the presence of active cardiac disease or symptoms of acute anemia, a less restrictive transfusion trigger was used (Hb < 9 g/dL). This transfusion protocol was uniformly applied across all participating centers, anesthesiologists and surgeons at the operation theatre, the anesthesia recovery unit, and the ward for the entire duration of patients' hospitalization. ABT was given as buffy coat–reduced or leukoreduced red blood cells. No patient was in an autologous blood donation program, received salvaged blood or antifibrinolytic agents, or underwent acute normovolemic hemodilution.

Data collection

Demographics and clinical data including sex, age, weight, comorbidity, American Society of Anesthesiologist physiologic status classification system (ASA), type of procedure, hematinic treatment (IV iron, rHuEPO), ABT rate, ABT index (units per patient), perioperative Hb concentrations and compensated Hb loss, PNI rate, PNI type (urinary tract infection [UTI], respiratory tract infection [RTI], surgical wound infection [SWI], or other infections), 30-day mortality rate, and LHS (from surgery to hospital discharge) were collected for all patients. Compensated Hb loss was estimated as preoperative Hb minus Hb at Postoperative Day 7 plus units of ABT, assuming that 1 ABT unit will increase Hb by 1 g/dL. Infection was clinically diagnosed by a senior member of the orthopedic or medical team and was always confirmed by laboratory, microbiologic, or radiologic evidence.[22,23]

Statistical analysis

Data were expressed as percentage (%) or as the mean ± SD (n). In the univariate analysis, Pearson's chi-square test or Fisher's exact test was used for comparison of qualitative variables, and t test or Mann-Whitney's test for comparison of quantitative variables, according to the variable's distribution. Statistical tests were performed using computer software (SPSS 18, IBM-SPSS, Inc., Chicago, IL), licensed to the University of Málaga (Málaga, Spain). All p values reported are two-sided and are considered significant at less than 0.05.

RESULTS

A total of 2547 of 2633 patients who underwent major lower limb orthopedic surgery (1361 HFR, 492 THR, and 694 TKR) were included in this study (Fig. 1). Eighty-six patients presented with preoperative Hb level of less than 10 g/dL and were excluded, because these patients need to be referred to the hematologist (elective arthroplasty) and they usually receive a preoperative or intraoperative transfusion. In fact, 84% of hip fracture patients presenting with a Hb level of less than 10 g/dL received perioperative transfusion regardless of the treatment group (23/28, 82% vs. 46/54, 85%, for control and IV iron with or without rHuEPO, respectively). All four patients undergoing elective arthroplasty (three controls, one IV iron with or without rHuEPO) were transfused.

There were no differences in sex distribution, age, ASA scores, time to surgery (HFR only), or perioperative Hb levels between the study groups. Among the included patients, 1142 received IS, 45 received ferric carboxymaltose, 351 received IS plus rHuEPO, and 1009 received neither perioperative IV iron nor rHuEPO (Tables 2 and 4). No serious adverse events attributable to the administration of IV iron or rHuEPO were observed.

In the efficacy analysis, mean compensated perioperative Hb loss was 3.8 g/dL (95% confidence interval [CI], 1.0-6.5 g/dL), and 744 (29.2%) of 2547 patients received at least one ABT unit during their hospital stay. The PNI rate was 10.5%, distributed in UTI (52%), RTI (24%), SWI (17%), and others (7%); mean LHS was 10.8 ± 5.2 days; and 30-day mortality rate was 3.2% (all deaths occurring among HFR). Very-short-term perioperative treatment with IV iron, with or without rHuEPO, resulted in a significantly lower transfusion rate (24.2% vs. 36.9%; p = 0.001)

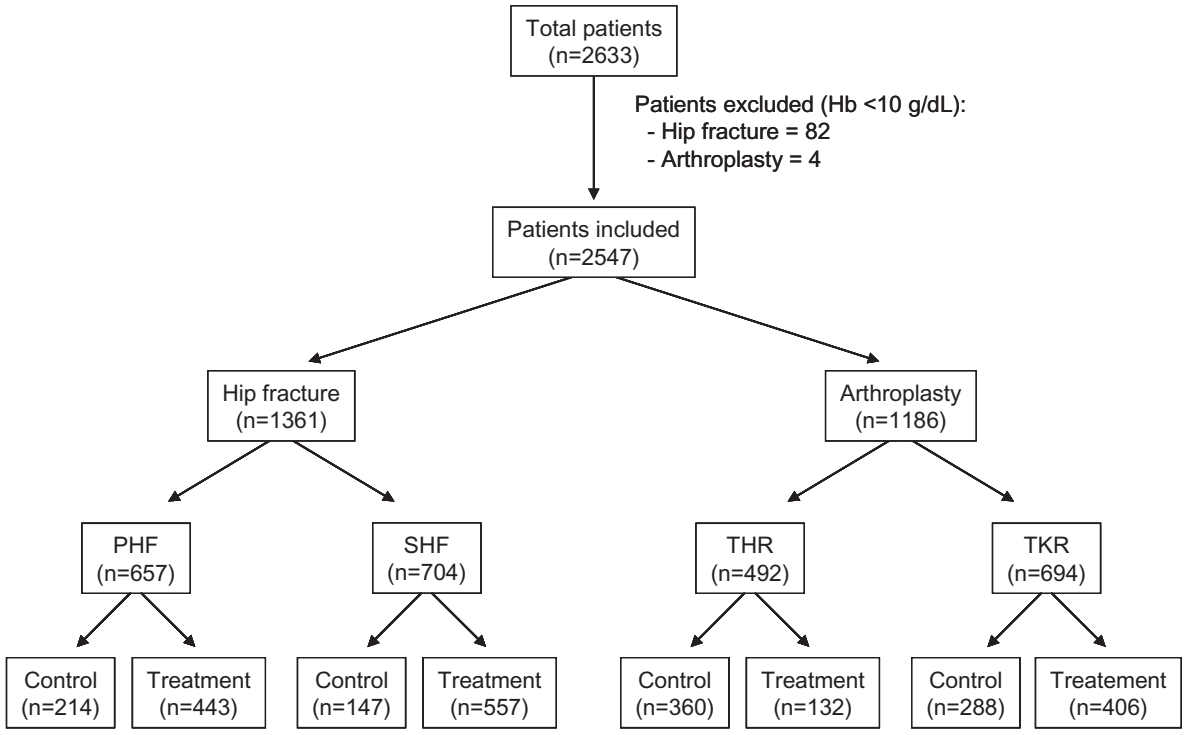

Fig. 1. Patient flow diagram. Treatment, 200 to 600 mg of iron IV ± 40,000 IU of rHuEPO, sc.

TABLE 2. Demographic and clinical data of patients undergoing surgery for PHF or SHF repair

	All patients		PHF		SHF	
	Control	Iron ± rHuEPO	Control	Iron ± rHuEPO	Control	Iron ± rHuEPO
Patients	361	1000	214	443	147	557
Age (years)	83 ± 7	83 ± 8	84 ± 7	84 ± 8	81 ± 7	83 ± 8
Sex (M/F)	63/298	161/839	37/177	81/362	26/121	80/477
ASA III/IV (n, %)	214 (59.3)	611 (61.1)	152 (71.0)	332 (74.9)	62 (42.2)	279 (50.1)*
Time to surgery (days)	4.5 ± 3.3	4.1 ± 2.4*	4.3 ± 3.4	4.3 ± 2.5	5.1 ± 3.2	3.9 ± 2.3†
Treatment, n (%)						
200-300 mg IV iron	0	100	0	65	0	35
400-600 mg IV iron	0	610	0	221	0	389
IV iron + rHuEPO	0	290	0	157	0	133
Hb (g/dL)						
Admission	13.0 ± 1.3	13.1 ± 1.4	12.9 ± 1.3	12.8 ± 1.4	13.3 ± 1.3	13.3 ± 1.4
PAD 1	11.4 ± 1.8	11.8 ± 1.8†	11.0 ± 1.8	11.3 ± 1.7	12.0 ± 1.5	12.2 ± 1.7
POD 1	10.0 ± 1.5	9.9 ± 2.6	9.9 ± 1.5	9.9 ± 3.3	10.1 ± 1.4	9.8 ± 1.8
POD 7	10.7 ± 1.1	10.3 ± 1.3†	10.8 ± 1.0	10.5 ± 1.2*	10.5 ± 1.1	10.1 ± 1.3*
Patients transfused, n (%)	176 (48.8)	324 (32.4)†	128 (59.8)	170 (38.4)†	48 (32.7)	154 (27.6)
Transfusion index (U/patient)	1.2 ± 1.5	0.7 ± 1.3†	1.5 ± 1.5	0.9 ± 1.4†	0.8 ± 1.3	0.6 ± 1.1
Postoperative infection, n (%)	97 (26.9)	107 (10.7)†	62 (28.9)	68 (15.3)†	35 (23.8)	39 (7.0)†
30-day mortality, n (%)	34 (9.4)	48 (4.8)†	23 (10.7)	32 (7.2)	11 (7.5)	16 (2.9)*
LHS (days)	13.4 ± 6.3	11.9 ± 6.1†	13.9 ± 6.6	12.6 ± 6.4*	12.7 ± 5.7	11.3 ± 5.8*

* $p < 0.05$, control versus treatment.
† $p < 0.01$, control versus treatment.
Iron ± rHuEPO = 200 to 600 mg of iron sucrose IV with or without 40,000 IU rHuEPO; PAD = postadmission day; POD = postoperative day.

and PNI rate (7.9% vs. 12%; p = 0.001) and a reduction of mean LHS (10.7 days vs. 11.7 days; p = 0.001). Despite the different ABT rates, there were no meaningful differences in Hb levels at Postoperative Day 7 between groups.

Data from patients undergoing elective or nonelective lower limb orthopedic surgery were analyzed separately. As depicted in Table 2, in subjects undergoing HFR, IV iron with or without rHuEPO treatment reduced the overall transfusion rate and index. Although these differences remained significant for postoperative and perioperative transfusion, they did not for preoperative and intraoperative transfusions (Fig. 2A). Similarly, although

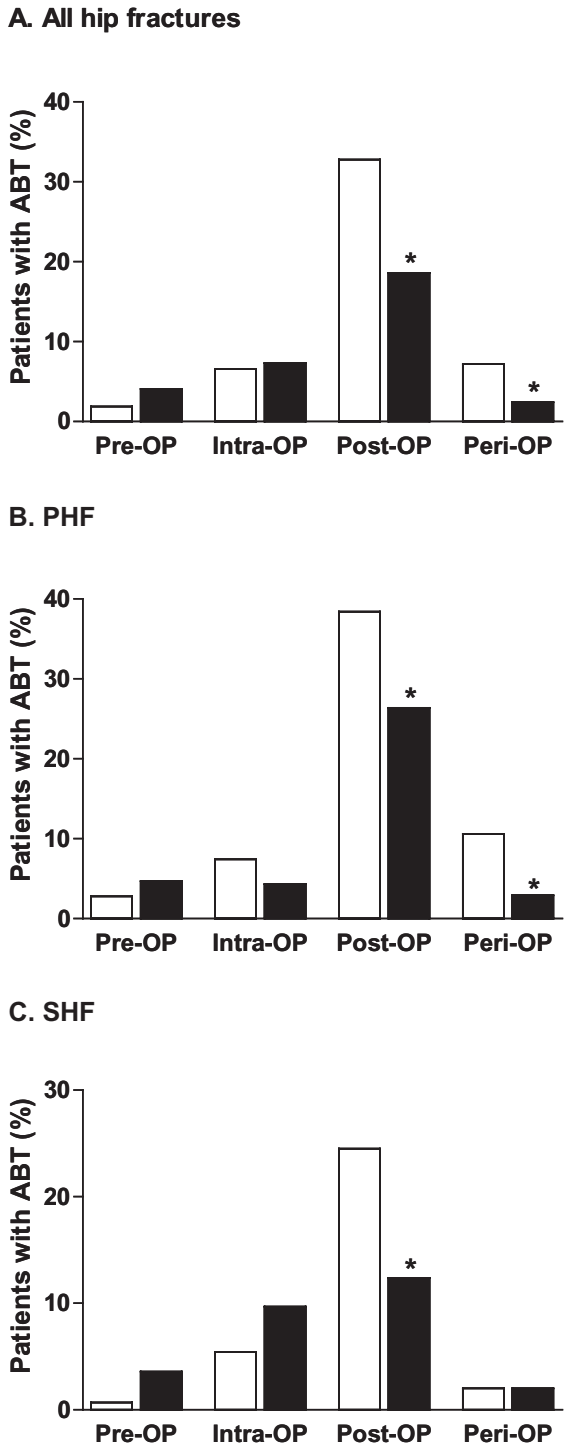

Fig. 2. Transfusion rates in patients undergoing surgery for hip fracture repair, according to the moment when they were transfused, the hematinic treatment, and the type of hip fracture. (A) All hip fractures (n = 1361); (B) PHFs (n = 657); (C) SHFs (n = 704). Pre-OP = preoperative; Intra-OP = intraoperative; Post-OP = postoperative; Perio-OP = preoperative and/or intraoperative plus postoperative; iron ± rHuEPO, 200 to 600 mg of iron sucrose IV ± 40,000 IU rHuEPO SC. *p < 0.05, iron ± rHuEPO (■) versus control (□).

overall transfusion rate and index were significantly decreased by treatment in PHF, the difference was no longer significant for SHF (Table 2). However, when only postoperative transfusions were considered, the administration of IV iron with or without rHuEPO compared to control treatment resulted in a significantly lower ABT rates in both PHF (Fig. 2B) and SHF (Fig. 2C).

In patients undergoing HFR, IV iron treatment also resulted in reduced PNI rate (Table 2), mostly due to reduction in ITU rate (Fig. 3A), and 30-day mortality rate and shorter LHS compared to control (Table 2). These differences remained significant when analyzing PHF and SHF separately (Table 2, Figs. 3B and 3C). There were no differences in PNI rates between IV iron alone or IV iron plus rHuEPO (10.4% vs. 11.4%; p = 0.653). Compared with nontransfused, patients receiving ABT showed higher rates of PNI (9.9% vs. 23.8%; p = 0.001) and 30-day mortality (3.7% vs.10%; p = 0.001) and longer mean LHS (11 ± 5 days vs. 14 ± 7 days; p = 0.001). In addition, the effect of ABT on PNI rates was dose dependent (1-2 units, 16.2% PNI; 3-4 units, 35.9%; >4 units, 66.7%; p = 0.001). This effect was more pronounced with buffy coat–reduced ABT than with leukoreduced ABT (37% vs. 14.4%; p = 0.001). To assess the contribution of the reduction in ABT rate on the observed beneficial effects of perioperative IV iron administration, these outcome variables were analyzed in transfused and nontransfused HFR. As shown in Table 3, for patients without ABT, a significant reduction in overall PNI (UTI, 3.1% vs. 11.7%, p = 0.002) and 30-day mortality rates, as well as in mean LHS, was observed in the IV iron group compared with control group. In contrast, this reduction in the patients receiving ABT was only significant for overall PNI rates (UTI, 5.9% vs. 15.2%; p = 0.001; Table 3).

In patients undergoing elective lower-limb joint replacement, perioperative administration of IV iron with or without rHuEPO resulted in a significant reduction of transfusion rate and index, both for the overall population and for THR and TKR separately, when compared to control (Table 4). For the overall study population, there were no differences in PNI rates (3.7% vs. 2.8%, respectively; p = NS), and no influence of rHuEPO was observed (TKR patients only; PNI rates, 2.8, 2.6, and 2.6%, for control, IV iron alone, and IV iron plus rHuEPO, respectively; p = NS). In TKR patients, treatment with IV iron with or without rHuEPO resulted in a significant improvement of LHS and SWI rate (Table 4). No patient died within 30 days after surgery.

The possible interaction between ABT and IV iron with or without rHuEPO treatment on PNI rate in TKR and THR patients was also investigated by analyzing this outcome variable in transfused and nontransfused patients. As depicted in Fig. 4, ABT increased rates of PNI, regardless whether they belonged to the treatment or the control group. Treatment with IV iron with or without

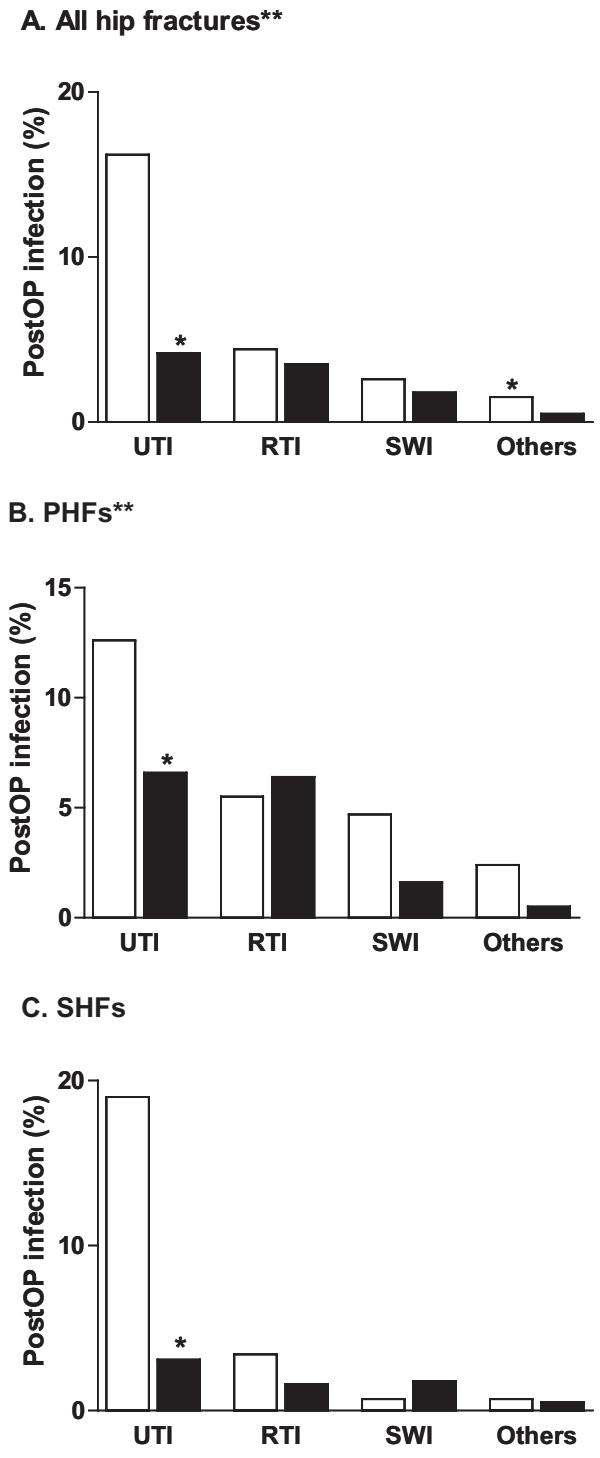

Fig. 3. Postoperative infection rates in patients undergoing surgery for hip fracture repair, according to the type of infection, the hematinic treatment, and the type of hip fracture. (A) All hip fractures (n = 1216); (B) PHFs (n = 512)**; (C) SHFs (n = 704). Others, septicemia, bacteremia, gastroenteritis, etc; Iron ± rHuEPO, 200-600 mg iron sucrose IV ± 40,000 IU rHuEPO sc. *p < 0.05, iron ± rHuEPO (■) versus control (□). **Type of infection was not recorded for 43 patients undergoing surgery for PHF repair.**

rHuEPO did not significantly affect the rates of PNI (1.8% vs. 2.2% without ABT, p = 0.818; 7.1% vs. 12.5%, with ABT, p = 0.242). Overall no difference was noted in PNI rate between buffy coat–reduced ABT versus leukoreduced ABT (11.9% vs. 8%; p = 0.446).

DISCUSSION

This pooled analysis of observational data, from a series of 2547 elective or nonelective major lower-limb orthopedic procedures, indicates that very-short-term perioperative administration of IV iron, with or without rHuEPO, is associated with reduced ABT rates and LHS. Moreover, for HFR, this treatment also resulted in reduced rates of PNI (mostly UTI) and/or 30-day mortality in both transfused and nontransfused, whereas in TKR and THR these outcome variables were not significantly influenced. Therefore, the findings from this pooled analysis seem to confirm those from smaller individual studies.

In lower-limb orthopedic surgery, perioperative blood loss and postoperative blunted erythropoiesis, due to surgery-induced inflammation, may lead to postoperative anemia in almost 90% of those procedures. ABT continues to be the most frequently used treatment for acute intra- and postoperative anemia, although its quick and effective increase of patient's Hb levels may last only transitorily.

In patients undergoing HFR, several studies have reported transfusion rates between 30 and 70% and mean ABT requirements of 1 to 3 units per patient. The level of ABT in HFR depends on the admission Hb level, the surgical technique, the type of prosthetic material employed, and the transfusion trigger, as well as on the localization of fracture.[24-30] Extracapsular hip fractures (pertrochanteric) showed higher transfusion requirements than intracapsular fractures (subcapital).[12-15] Similarly, there is large intercenter variability in both blood loss volume and percentage of patients who receive ABT when undergoing TKR (25%-50%) or THR (25%-60%).[31,32] These data mainly suggest differences in surgical techniques and physicians' opinions, rather than in patients' characteristics. In addition, data from different observational studies involving over 46,000 elective[31-36] and nonelective[24-30] orthopedic lower-limb procedures strongly suggest that ABT is associated with a dose-dependent increase in the risk of PNI and mortality, as observed in this study.

Therefore, the use of patient-based restrictive ABT protocols is recommended,[37] although many clinicians are still uncomfortable with low transfusion thresholds and may overuse blood transfusions after elective and nonelective orthopedic surgery. In this regard, our ABT protocol (transfusion trigger of Hb < 8 g/dL if there is no ischemia risk factors or Hb < 9 g/dL for those considered at cardiac risk) is in agreement with these recommendations. However, although a restrictive ABT protocol should

TABLE 3. Demographic and clinical data of patients undergoing surgery for hip fracture repair according to ABT status and treatment with IV iron with or without rHuEPO

	Patients without ABT		Patients with ABT	
Parameter	Control	Iron ± rHuEPO	Control	Iron ± rHuEPO
Patients, n	185	676	176	324
Age (years)	82 ± 7	83 ± 8	84 ± 7	84 ± 9
Sex (M/F)	37/148	118/558	26/150	43/281
ASA III/IV, n (%)	124 (67.0)	396 (58.6)*	90 (51.1)	215 (66.4)†
PHF/SHF (n/n)	86/99	273/403	128/48	170/154†
Admission Hb (g/dL)	13.6 ± 1.2	13.4 ± 1.3	12.5 ± 1.1	12.3 ± 1.4
Time to surgery (days)	4.3 ± 3.0	4.0 ± 2.3	4.7 ± 3.6	4.2 ± 2.6
Infection, n (%)	36 (19.5)	49 (7.2)†	61 (34.7)	58 (17.9)†
30-day mortality, n (%)	13 (7.0)	19 (2.8)†	21 (11.9)	29 (8.9)
LHS (days)	12.1 ± 5.7	11.1 ± 5.2*	14.7 ± 6.6	13.6 ± 7.4

* $p < 0.05$, control versus treatment.
† $p < 0.01$, control versus treatment.

be the cornerstone of any perioperative blood conservation program, it is not the only strategy to reduce both the frequency and the volume of ABT. Detection, evaluation, and management of perioperative anemia should be implemented.[10]

Preoperative administration of IV iron, with or without rHuEPO, for 3 to 4 weeks before surgery has been shown to correct anemia and reduce ABT requirements in most patients undergoing lower-limb arthroplasty.[21,38] If the time frame is not available, observational[9,12-18] and randomized studies[39-41] have shown that short-term IV iron treatment (with or without rHuEPO) may have a role in hastening the recovery of postoperative anemia and reducing transfusion requirements, postoperative morbidity, and LHS after orthopedic procedures. These benefits were achieved without reports of serious life-threatening adverse drug events. However, due to low numbers in each study, definitive conclusions regarding the efficacy and safety of very-short-term perioperative treatment with IV iron with or without rHuEPO in this clinical setting cannot be drawn. Therefore, we pooled all our observational data to ascertain whether the suggested benefits remain when more patients are included in the analysis.

The effectiveness of our blood-saving protocol is most probably due to the combined use of a restrictive transfusion threshold and the stimulation of erythropoiesis with IV iron with or without rHuEPO. IV iron overcomes the decreased iron availability after major surgery and rHuEPO that of endogenous EPO production and action.[42]

In addition to the reduction in the requirements for ABT, the most striking finding of this study has been the reduction in PNI, mostly in UTI (Fig. 3), and 30-day mortality in HFR patients receiving IV iron with or without rHuEPO (Table 2). As reported by others,[30] PNIs occurred more frequently in HFR receiving ABT (Table 3), especially in those with buffy coat–reduced ABT, but the observed lower rate of complications in patients receiving IV iron with or without rHuEPO cannot be entirely attributed to the lower ABT requirements. Notably, PNIs also occurred more frequently in TKR and THR patients receiving ABT, with no difference between buffy coat–reduced and leukoreduced ABT,[34] but were not influenced by treatment with IV iron with or without rHuEPO (Fig. 4). In this regard, it is well known that functional iron deficiency, which is present in many surgical and critically ill patients, leads not only to a blunted erythropoiesis but also to an impaired immune response as well.[43]

Consistent with prior reported smaller studies, significant reduction of LHS was observed in HFR and TKR patients (Tables 2 and 4). In critically ill patients with functional iron deficiency, systemic inflammatory response episodes last longer resulting in prolonged stay at the intensive care unit and increased morbidity.[44] Pagani and colleagues[45] have described two anti-inflammatory properties of hepcidin, iron sequestration and modulation of cytokine response, in an acute model of inflammation. These two properties are complementary and both are based on negative feedback loops. In iron balance, high hepcidin blocks both iron export and reduces interleukin (IL)-6 production by macrophages, thus limiting the potential damage of an excessive inflammatory response. In iron deficiency IL production by macrophages is exaggerated because of the lack of hepcidin-mediated anti-inflammatory response.[45] As iron deficiency is highly prevalent among HFR patients,[9,13] it is possible that administration of IV iron has not only contributed to reduce the requirements for ABT by improving the erythropoietic response, but also to reduce postoperative morbidity-mortality rate and LHS restoring an adequate immune response. Consistent with published evidence, no significant adverse drug events were noted in these patient populations receiving IV iron with or without rHuEPO and thromboprophylaxis with low-molecular-weight heparin.[11,46-48]

Some limitations of study are worth noting. First, because this is a pooled analysis of observational cohort studies, it does not provide unbiased results. Therefore, although perioperative patient management was homogenous, a cause-and-effect relationship between treatment with IV iron with or without rHuEPO and the observed clinical benefits cannot be inferred. Second, as we performed a retrospective analysis of different databases, the required sample size was not determined beforehand. To detect a 50% reduction in any postoperative complication with an 80% power and a 95% CI, at least 4064 patients are

TABLE 4. Demographic and clinical data of patients undergoing elective surgery for THR or TKR

	All patients		THR		TKR	
Parameter	Control	Iron ± rHuEPO	Control	Iron ± rHuEPO	Control	Iron ± rHuEPO
Patients	648	538	360	132	288	406
Age (years)	68 ± 10	70 ± 8*	66 ± 12	67 ± 10	71 ± 6	70 ± 7
Sex (male/female)	253/395	185/354	177/183	55/77	76/212	130/276
ASA II/III (n, %)	630 (97.2)	511 (94.8)	339 (94.2)	132 (100)*	288 (100)	398 (98.0)*
Treatment, n (%)						
IV iron	0	477	0	132	0	345
IV iron + rHuEPO	0	61	0	0	0	61
Hb (g/dL)						
Preoperative	13.7 ± 1.3	13.8 ± 1.3	13.7 ± 1.4	13.7 ± 1.3	13.7 ± 1.1	13.8 ± 1.3
POD 1	9.7 ± 1.8	10.7 ± 1.4*	9.5 ± 1.4	10.9 ± 1.5*	10.0 ± 2.2	10.6 ± 1.3*
POD 7	10.1 ± 1.1	10.3 ± 1.3	10.1 ± 1.1	10.7 ± 1.2*	10.3 ± 0.9	10.1 ± 1.3
Patients transfused, n (%)	196 (30.2)	48 (8.9)*	124 (34.4)	22 (16.7)*	69 (24.0)	25 (6.2)*
Transfusion index (U/patient)	0.7 ± 1.2	0.2 ± 0.6*	0.8 ± 1.2	0.3 ± 0.7*	0.5 ± 1.0	0.1 ± 0.5*
Postoperative infection, n (%)	24 (3.7)	15 (2.8)	16 (4.4)	5 (3.8)	8 (2.8)	10 (2.5)
UTI	11	12	8	4	3	8
RTI	2	1	1	0	1	1
SWI	7	1	3	1	4	0†
Other	4	1	4	0	0	1
LHS (days)	10.7 ± 5.3	8.4 ± 2.9†	8.9 ± 5.4	8.1 ± 2.4	13.0 ± 4.0	8.5 ± 3.0*

* $p < 0.01$, control versus treatment.
† $p < 0.05$, control versus treatment.
Iron ± rHuEPO = 300 to 600 mg iron sucrose or ferric carboxymaltose IV with or without 40,000 IU rHuEPO sc; POD = postoperative day.

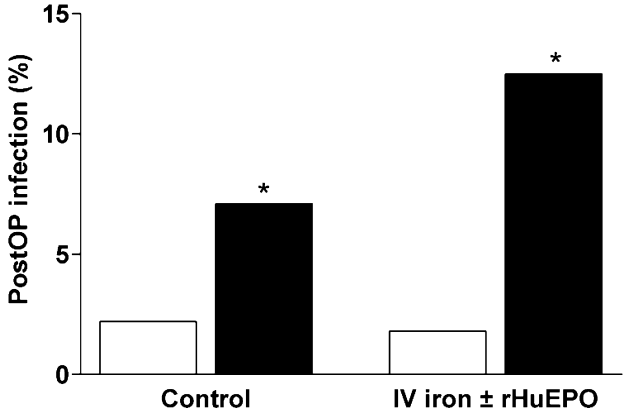

Fig. 4. Postoperative infection rates in patients undergoing elective surgery for THR or TKR, according to transfusion and hematinic treatment. (□) ABT (–) = nontransfused patients; (■) ABT (+) = transfused patients; iron ± rHuEPO = 300 to 600 mg iron sucrose or ferric carboxymaltose IV ± 40,000 IU rHuEPO sc. *p < 0.01, ABT (+) versus ABT (–).

needed for a complication rate of 2.5% in the control group, 1814 for 5%, 870 for 10%, and 558 for 15%.[49] Thus, this study may not be powered to detect significant differences in low-incidence postoperative complications, such as PNI (except for UTI), and no definitive conclusions regarding the role of IV iron with or without rHuEPO administration on PNI rate reduction in these patient populations can be drawn. Third, mean compensated perioperative Hb loss was 3.8 g/dL (95% CI, 1.0-6.5 g/dL), and approximately 200 mg of iron is needed to increase patient's Hb by 1 g/dL. Thus, the scheduled IV iron dose (400-600 mg) may not cover total iron loss, especially in patients with preoperative iron deficiency. The use of newer IV iron formulations (e.g., ferric carboxymaltose, ferumoxytol, or iron isomaltoside 1000), which allow the administration of single larger doses, will facilitate the implementation of a more accurate iron replacement therapy. In this regard, a randomized controlled trial to confirm the efficacy of postoperatively administered Ganzoni calculated doses of ferric carboxymatose in orthopedic patients is currently ongoing (EudraCT 2010-023038-22). Fourth, preoperative rHuEPO was only administered in 351 of 1059 patients presenting with Hb level of less than 13 g/dL and no contraindication. The main reasons for not administering rHuEPO were: 1) rHuEPO not included in the blood conservation protocol; 2) difficulties to obtain rHuEPO from the hospital pharmacy, especially during weekends; 3) patients not being transferred to the orthopedic ward, where rHuEPO was indicated and administered, staying at the emergency facilities until surgery was performed; 4) the presence of orthopedic trainees who were not aware of the existence of such a blood conservation protocol (for HFR at one center only); and 5) the introduction of an electronic system for laboratory data management in the emergency department resulting in patients arriving to the orthopedic ward without a printed blood count. Appropriate training, education, and awareness among the medical staff and nurses would be useful in increasing adherence to blood management protocol, thus limiting the exposure of anemic patients to ABT and ABT-related risks.

In conclusion, taking into consideration the limitations of pooled analyses of observational data from

different centers, these results suggest that very-short-term perioperative administration of IV iron, with or without rHuEPO, in patients undergoing major lower limb orthopedic surgery is associated with reduced ABT rate and LHS, without increasing the rates of postoperative morbidity or mortality. Large, prospective confirmatory studies are needed.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Characteristics of centers, patients and procedures.