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# *Treatment of Iron Deficiency Anemia in Orthopedic Surgery with Intravenous Iron: Efficacy and Limits*

## *A Prospective Study*

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***Background:*** **Preoperative anemia is frequent in patients undergoing orthopedic surgery. The purpose of this study was to assess the preoperative increase of hemoglobin in iron deficiency anemia patients treated with intravenous iron.**

***Methods:*** **After obtaining written informed consent, 20 patients with iron deficiency anemia received 900 mg intravenous iron sucrose over 10 days starting 4 weeks before surgery. Changes of hemoglobin and iron status were measured over 4 weeks and at discharge. In the last 11 patients, endogenous erythropoietin was also measured. Data were analyzed using the Friedman test followed by pairwise Wilcoxon signed rank tests with Bonferroni correction.**

***Results:*** **Hemoglobin increased significantly ($P < 0.0001$) after intravenous iron treatment. Overall, the mean maximum increase was 1.0 ± 0.6 g/dl (range, 0.2–2.2 g/dl). Ferritin increased from 78 ± 70 to 428 ± 191 μg/l ($P = 0.0001$), ferritin index decreased from 2.7 ± 2.4 to 1.5 ± 1.0 ($P = 0.0001$), and soluble transferrin receptor decreased from 4.1 ± 2.3 mg/l to 3.7 ± 2.3 mg/l ($P = 0.049$), whereas transferrin saturation (20.5 ± 9.0 to 22.9 ± 9.0%) and serum iron (13.3 ± 4.6 to 13.1 ± 4.5 μM) did not change significantly after intravenous iron treatment. Endogenous erythropoietin decreased from 261 ± 130 pg/ml to 190 ± 49 pg/ml 2 weeks after intravenous iron treatment ($P = 0.050$, not significant after Bonferroni correction). No adverse events related to intravenous iron were observed. The maximum increase of hemoglobin was observed 2 weeks after the start of intravenous iron treatment, indicating that administration of intravenous iron 2–3 weeks before surgery may be optimal.**

***Conclusion:*** **Treatment with intravenous iron allows correcting iron deficiency anemia before elective surgery.**

PREOPERATIVE anemia is common among patients scheduled to undergo elective surgery and may be predictive of allogeneic blood transfusion. Although the prevalence varies according to surgical indication, reports demonstrate that up to 35% of patients scheduled to undergo joint arthroplasty have anemia.[1,2] Likewise, 34% of patients scheduled to undergo noncardiac surgery[3] and as many as 76% of patients with Dukes stage D colon cancer have low hemoglobin levels before surgery.[4] The prevalence of iron deficiency anemia among patients scheduled to undergo elective surgery seems to be around 30% among anemic patients.[5,6]

Preoperative anemia has significant consequences: Patients manifesting preoperative anemia are more likely to receive allogeneic blood transfusions than patients with a normal hemoglobin level.[2] In addition, preoperative anemia and blood transfusions are associated with a higher incidence of postoperative infections and a longer hospital stay.[3]

In patients with proven iron deficiency anemia, treatment with intravenous iron seems to be the specific treatment. However, the efficacy of high-dose intravenous iron to correct preoperative anemia in elderly patients scheduled to undergo orthopedic surgery has not been formally investigated so far.

The purpose of the current study was to assess the increase of hemoglobin preoperatively in patients with mild to moderate anemia and iron deficiency scheduled to undergo elective major orthopedic surgery when treated with intravenous iron.

## Materials and Methods

The protocol of this study was approved by the local ethics committee (President: Prof. Dr. M. Burnier, Commission éthique de la recherche clinique de la faculté de médecine of the University of Lausanne, Switzerland, January 9, 2006, under No. 205/05).

Patients scheduled to undergo major elective orthopedic surgery such as knee or hip arthroplasty or back surgery were screened for this study. They were seen consecutively 5–6 weeks before their intervention and were informed about this study. After written informed consent was obtained, all specific information was collected, and it was determined whether a patient met the inclusion criteria without violating any of the exclusion criteria. For each patient, the medical history, concomitant medications, body weight and height, physical examination including vital signs, hematologic parameters (hemoglobin, hematocrit, reticulocytes, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), vitamin $B_{12}$, folic acid, iron indices (serum

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ferritin, transferrin saturation [TSAT], serum iron, soluble transferrin receptor [sTfr]),[7,8] C-reactive protein (CRP), pregnancy test result (for premenopausal women), and erythropoietin for the last 11 patients were recorded.

The following inclusion criteria were used: age > 18 yr, hemoglobin level at baseline for males 10.0–13.0 g/dl and for females 10.0–12.0 g/dl, iron deficiency confirmed by either ferritin < 100 μg/l or 100–300 μg/l with TSAT < 20% or soluble transferrin receptor (Modular P®, Soluble Transferrin Receptor 2148315; Roche Diagnostics, Mannheim, Germany) for females > 4.4 and for males > 5.5 or a ferritin index for CRP < 5 of > 3.2 and for CRP ≥ 5 of > 2.0. Exclusion criteria were the participation in another trial in the previous month, pregnancy or lactation, known hypersensitivity to iron sucrose, significant cardiovascular disease, *e.g.*, unstable angina, immunosuppressive or myelosuppressive therapy, known history of hepatitis B or C or human immunodeficiency virus, folate or vitamin $B_{12}$ deficiency, CRP > 20 mg/l, active severe infection or malignancy, suspicion of iron overload (ferritin > 300 μg/l and/or TSAT > 50%), or autologous blood transfusion in the previous month. No patient received erythropoietin or any iron preparations in the previous month or during the study. All patients had a workup by their general practitioners in order not to miss a possible underlying malignancy to their anemia and iron deficiency.

Patients who where included (total of 20 patients) received three intravenous infusions of 300 mg iron as iron sucrose (Venofer®; Vifor International Inc., Sankt Gallen, Switzerland) over 90 min during a period of 10 days after baseline, except for male patients with a body weight < 70 kg and female patients with a body weight < 50 kg, for whom the total dose was calculated individually according to the formula total iron deficit (mg) = weight (kg) × (ideal hemoglobin [15 g/dl] – actual hemoglobin [g/dl]) × 2.4 + depot iron (500 mg)[9] not exceeding 900 mg. The infusion solution, consisting of 300 mg iron (III)–hydroxide sucrose, was diluted in 300 ml normal saline, 0.9%. Dilution took place immediately before infusion.

In Switzerland, the maximum dose of intravenous iron sucrose is 500 mg. Therefore, the dose of 300 mg intravenous iron sucrose is not off-label according to local regulation. We limited the dose to 300 mg to avoid adverse events.[10]

Hemoglobin was determined 1, 2, and 3 weeks after the start of intravenous iron treatment and at follow-up at hospital discharge or on postoperative day 14, whichever came first. sTfr was measured at 3 weeks after the start of intravenous iron treatment and at follow-up. In the last 11 patients, erythropoietin was measured at baseline and 2 and 3 weeks after the start of intravenous iron treatment. Transfusion needs and duration of stay were also documented.

*Statistical Analyses*

No sample size analysis was performed because of the lack of reliable data on the hematopoietic effect of high-dose intravenous iron in patients scheduled to undergo elective orthopedic surgery. A trial database within the PheedIt® database system (version 3.0; SAS Institute Inc., Cary, NC) was used to store study data. In this database, all records were entered from the case report forms and the laboratory results of erythropoietin, which were analyzed in an external laboratory. The statistical analyses were performed using SPSS® (version 13; SPSS Inc., Chicago, IL). Continuous variables are summarized as mean ± SD and median with range where appropriate. Changes of hemoglobin and endogenous erythropoietin were analyzed using the Friedman test followed by pairwise *post hoc* comparisons using the Wilcoxon signed rank test with Bonferroni correction. Continuous variables with two measurements were compared using the Wilcoxon signed rank test. *P* values of 0.05 or less are considered significant. Prevalence of anemia is presented with exact confidence interval (CI). Continuous variables were transformed to normal distribution, and CIs for the mean were computed. The limits of these CIs then were retransformed to the original units and interpreted as CIs for the median.

*Role of the Funding Source*

The authors, in collaboration with the funding sources, designed the study protocol. Data were collected on specially designated case report forms and entered into a database by a company assigned by Vifor International. All data were verified by the authors and Vifor International before the database was closed for analysis.

## Results

Over 7 months, 93 consecutive patients were screened after written consent, of whom 20 (21.5%; 95% CI, 14–31%) were entered into the study and treated. Eight subjects were male (40%), 12 were female (60%), 19 were white, and 1 was black. The mean age of the patients was 71 ± 10 yr, weight was 79 ± 23 kg, height was 169 ± 8 cm, and body mass index was 27 ± 6 $kg/m^2$.

All patients screened had a hemoglobin > 10 g/dl. We only found iron deficiency anemia in the screened patients; no other type of anemia was detected, such as folate or vitamin $B_{12}$ deficiency. Patients with hemoglobin between 10 and 13 g/dl (12 g/dl in women), indicating mild to moderate anemia, were enrolled into this study.

Hemoglobin increased significantly ($P < 0.0001$, Friedman test) at 1, 2, and 3 weeks after the start of the intravenous iron treatment (fig. 1A). Overall, the mean maximum increase was 1.0 ± 0.6 g/dl (range, 0.2–2.2

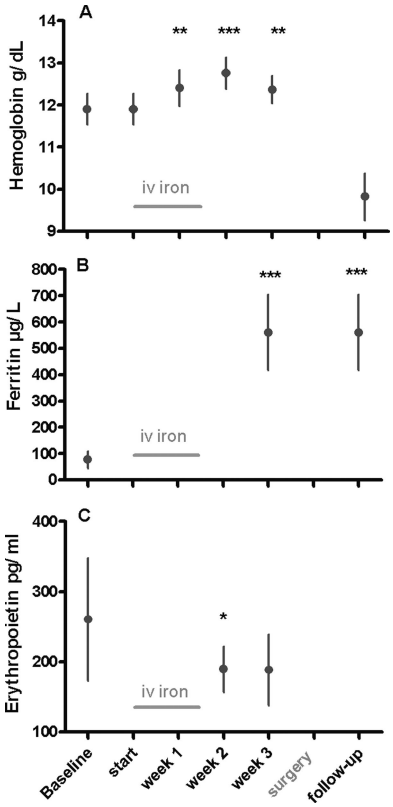


**Fig. 1. Changes of hemoglobin (*A*), ferritin (*B*), and erythropoietin (*C*) concentration over time. * $P = 0.050$, ** $P < 0.017$, *** $P < 0.001$ *versus* start. iv = intravenous.**

g/dl; 95% CI for the mean, 0.8–1.3 g/dl). The highest increase of hemoglobin was 2 weeks after the start of intravenous treatment ($P = 0.0001$, Wilcoxon signed rank test). Four patients (20%), 12 patients (60%), and 4 patients (20%) had a maximum increase in hemoglobin 1, 2, and 3 weeks, respectively, after the start of intravenous iron treatment.

Ferritin levels also increased significantly ($P = 0.0001$) from 78 ± 70 µg/l at baseline to 428 ± 191 µg/l (median increase, 638%; 95% CI, 523–958%) 3 weeks after the start of intravenous iron treatment (fig. 1B). Endogenous erythropoietin decreased after intravenous iron treatment from 261 ± 130 pg/ml at baseline to 190 ± 49 pg/ml 2 weeks after the start of intravenous iron treatment ($P = 0.050$). This is, however, not significant after Bonferroni correction. Median reduction of endogenous erythropoietin at 2 and 3 weeks after the start of the intravenous iron treatment was 11% (95% CI, 1–28%) and 21% (95% CI, 5% increase to 46% reduction). Overall, the median maximal reduction was 33% ($P = 0.02$; 95% CI, 13–50%; fig. 1C).

The ferritin index (ferritin index = sTfr/log ferritin) decreased significantly ($P = 0.0001$) from 2.7 ± 2.4 (range, 1–11) at baseline to 1.5 ± 1.0 (range, 1–5) 3 weeks after the start of intravenous iron treatment, and sTfr ($P = 0.049$) decreased from 4.1 ± 2.3 µg/ml at baseline to 3.7 ± 2.3 µg/ml at week 3. TSAT (20.5 ± 9.0 to 22.9 ± 9.0%) and serum iron (13.3 ± 4.6 to 13.1 ± 4.5 µM) did not change significantly after intravenous iron treatment (table 1).

**Table 1. Changes of Parameters and Their Significance**

| | Baseline | Week 2 | Week 3 |
|---|---|---|---|
| Hemoglobin, g/dl | 11.9 ± 0.8 | 12.8 ± 0.8‡ | 12.4 ± 0.7† |
| Ferritin, µg/l | 78 ± 70 | | 428 ± 191‡ |
| sTfr, µg/ml | 4.1 ± 2.3 | | 3.7 ± 2.3* |
| Epo, pg/ml | 261 ± 130 | 190 ± 49* | 189 ± 75 |
| Serum Fe, µM | 13.3 ± 4.6 | | 13.1 ± 4.5 |
| TSAT, % | 20.5 ± 9.0 | | 22.9 ± 9.0 |

Data are presented as mean ± SD.

* $P \leq 0.050$, † $P \leq 0.005$, ‡ $P < 0.001$ *vs.* baseline.

Epo = endogenous erythropoietin; Fe = iron; sTfr = soluble transferrin receptor; TSAT = transferrin saturation.

Eight of 20 patients (40%) required transfusions perioperatively. A total of 18 units of erythrocytes was transfused (0.9 ± 1.3 units per patient). The duration of hospital stay for all patients was 12.6 ± 3.8 days. Patients receiving blood transfusions were in the hospital for 13.0 ± 4.3 days and those not transfused were in the hospital for 11.5 ± 3.4 days.

There were three adverse events recorded, two urinary tract infections and one infection of a leg. Although there is concern that intravenous iron may increase the risk of infection, we did not think that the three events were related to the treatment with intravenous iron. The single serious adverse event was a postoperative death due to paralytic ileus with bronchial aspiration. This event was also considered not to be related to the intravenous iron treatment 5 weeks before.

## Discussion

We found a prevalence of iron deficiency anemia of approximately 20% in patients screened and scheduled to undergo major orthopedic surgery (knee and hip prothesis, back surgery). Intravenous iron therapy succeeded in increasing the hemoglobin concentration. However, because of the concomitant decrease in endogenous erythropoietin, this increase was not sustained.

The prevalence of preoperative anemia varies in different populations from 5% up to 76% depending on the underlying pathology, the population being screened, socioeconomic status, and age.[2,4,11–13] Furthermore, varying definitions of anemia add to the variability. In orthopedic surgery, one third of patients scheduled to undergo elective arthroplasty procedures for osteoarthritis are anemic. Goodnough *et al.*[5] found that one third of the anemic patients scheduled to undergo elective surgery had iron deficiency anemia, and Basora *et al.*[6] found, in 218 patients studied, 87 patients (39%) with hemoglobin levels between 10 and 13 g/dl, of whom

27% were anemic due to iron deficiency. Also, in a prospective study of 9,482 patients scheduled to undergo elective hip (n = 3,920) or knee (n = 5,562) replacement, Bierbaum *et al.*[1] reported that 35% had a preoperative hemoglobin level < 13 g/dl. Using a more conservative definition of anemia (men, hemoglobin < 12.5 g/dl; women, hemoglobin <11.5 g/dl), Meyers *et al.*[14] described a 15% prevalence of preoperative anemia in 225 patients undergoing hip arthroplasty. The clinical relevance of preoperative anemia is that anemic patients receive more allogeneic blood transfusions and may have a higher incidence of postoperative infections and a longer duration of hospitalization.[3,15] In addition, Gurson *et al.*[15] have shown that preoperatively, anemic patients had an elevated mortality rate at 6 and 12 months. Therefore, correction of preoperative anemia seems attractive.

Knowing the exact type of anemia allows physicians to treat anemia specifically. Laboratory values such as MCV, ferritin, and other parameters can help to classify and differentiate between the mechanisms of preoperative anemia such as nutritional anemia, iron deficiency anemia, or other types.[16] Microcytic anemia, most commonly caused by iron deficiency, is marked by reductions in erythrocyte parameters such as MCV, MCH, and MCHC. Macrocytic anemia, characterized by an increased MCV, is typically induced by medication, alcoholism, or deficiencies in vitamin $B_{12}$ or folate. Normocytic anemia, on the other hand, may be caused by nutritional deficiency, chronic kidney disease, hemolysis, anemia of chronic disease, or primary bone marrow disorders. With normocytic anemia, the MCV is within normal limits, but the hemoglobin and hematocrit levels are below normal.

Ioannou *et al.*[17] have shown that iron deficiency is not a sensitive marker for colorectal cancer, but the relative risk of colorectal cancer is increased in the combined presence of anemia and iron deficiency. For this reason, anemic patients should have a workup if the origin of anemia is undetermined.

Iron deficiency has an impact on mortality and morbidity,[18] and therefore, diagnostics and treatment are important. Diagnostics of iron deficiency anemia include hemoglobin, hematocrit, MCV, ferritin, TSAT, and CRP. This should detect most of the patients who are iron deficient. Because inflammation and infection modulate ferritin and transferrin concentrations, we also analyzed the sTfr, which is not modulated by infection or inflammation and allows by the ratio of the sTfr value to the logarithm of the ferritin value to determine iron deficiency anemia.[7] Of 93 screened patients, determining the sTfr was only helpful in one case. In all of the other cases, the sTfr did not provide any additional information. Determining the sTfr therefore does not seem to be required in the diagnosis of iron deficiency anemia on a routine basis, but may be helpful in special rare situations.

In the current study group, iron stores were empty and hemoglobin was low because of the lack of iron. The intravenous iron given was in part directed toward hematopoiesis and into the iron stores. This may explain why serum iron did not increase as a result of intravenous iron treatment. The decrease of serum iron postoperatively may be explained by perioperative blood loss.

Stable TSAT may indicate that for certain patients, the dose of 900 mg iron sucrose was insufficient, and certainly no iron overload was created.

Intravenous iron has been used in orthopedic surgery. Cuenca *et al.*[19] started with intravenous iron 3 days before the operation in patients with a pertrochanteric hip fracture and reported reduction in transfusion requirements, duration of hospital stay, and incidence of infections. However, the exact time course of the hemoglobin response due to intravenous iron was not described, and the described benefits were in the comparison with a historic control group.

There are two main limitations of this study, the lack of a control group and the limited number of patients enrolled. Because of the lack of a control group in our study, we compared our data with the data of the control group and the treated group of Cuenca *et al.*[19] The transfusion requirements in the control group of the study by Cuenca *et al.* were 1.3 ± 1.3 and 0.9 ± 1.2 units in the treated group. Our rate was 0.9 ± 1.3 units, which is similar. The percentage of patients transfused in the study by Cuenca *et al.* is 56% in the control group and 44% in the treated group, and we found a transfusion rate of 40%. The duration of hospital stay was 14.3 ± 3.6 and 12.6 ± 4.4 days, which is comparable to 12.6 ± 3.8 days for all patients in the current study. Interestingly, transfused patients were hospitalized for 13.0 ± 4.3 days *versus* 11.5 ± 3.4 days in patients without transfusions. With only 20 patients studied, we may have had limited power to detect an effect of intravenous iron treatment on hemoglobin concentration. However, the sample size was large enough to demonstrate that hemoglobin increased as a result of intravenous iron treatment and that this effect represented a mean maximum increase of 1.0 ± 0.6 g/dl (range, 0.2–2.2 g/dl; 95% CI for the mean, 0.8–1.3 g/dl).

Endogenous erythropoietin decreased in response to the hemoglobin increase, possibly as a result of intravenous iron; we speculate that this is why hemoglobin concentration was not sustained despite filled iron stores.

A similar decrease in endogenous erythropoietin has been observed in the treatment of inflammatory bowel disease with intravenous iron. This might be explained by the fact that the erythropoietic effect of intravenous iron seems to last 7–10 days, after which the iron is

sequestered by the reticuloendothelial system.[20] On the other hand, a simple negative feedback could be at the origin of the decrease of erythropoietin. However, the interplay between hemoglobin concentration, intravenous iron treatment, and endogenous erythropoietin is still incompletely understood.

## Conclusion

The prevalence of iron deficiency anemia is approximately 21% (95% CI, 14–31%) in patients screened and scheduled to undergo major elective orthopedic surgery (knee and hip prothesis, back surgery). Intravenous iron (iron sucrose, 900 mg) is an efficacious treatment. Ideal timing may be 2 weeks before surgery. Future randomized control studies are needed to assess the impact of such treatment on outcome.

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