Preoperative Intravenous Ferric Carboxymaltose Improves Recovery from Anemia in Patients Undergoing Revision Joint Arthroplasty: A Randomized Controlled Trial

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Article

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Abstract: (1) Background: Ferric carboxymaltose (FCM) is an intravenous (IV) high-dose iron that is effective in the treatment of iron deficiency anemia. This study was to determine if preoperative IV FCM administration could improve recovery from postoperative anemia in patients undergoing revision total joint arthroplasty. (2) Methods: This prospective randomized controlled study analyzed 82 patients undergoing revision total joint arthroplasty during a single hospitalization. Patients in the iron group (n = 41) were administered 1000 mg of IV FCM two weeks preoperatively, while those in the control group (n = 41) were not. Moreover, patients with anemia defined as a preoperative suboptimal Hb concentration <13.0 g/dl were compared according to IV FCM administration. The absolute Hb levels and changes in Hb levels, iron profiles, transfusion rate, and EuroQOL 5-dimension (EQ-5D) scores were compared. (3) Results: There were no significant differences in recovery of Hb levels at each timepoint between the two groups; however, the changes in Hb levels from baseline to four weeks postoperatively showed marginally significant differences favoring the iron group (p = 0.052). However, for preoperatively anemic patients, the change in hemoglobin (Hb) levels between baseline and four weeks postoperatively was significantly better in the iron group than in the control group (iron group [n = 26], −0.3 ± 0.7 g/dL vs. control group [n = 27], −0.9 ± 0.8 g/dL; p = 0.040), although the absolute Hb levels, transfusion rates, and patient quality of life were comparable (all p > 0.05). The iron group showed improved iron metabolite levels including serum ferritin and transferrin saturation four weeks postoperatively, and no adverse events associated with IV FCM administration occurred in either group. (4) Conclusions: Preoperative IV FCM in anemic individuals undergoing revision joint arthroplasty was effective in accelerating recovery from surgery-related anemia by improving Hb levels without any adverse events, despite similar actual Hb levels between the groups. Our findings are clinically relevant and can facilitate determination of the suitability of IV FCM as a safe and reliable protocol for iron supplementation for anemia correction.

Keywords: revision joint arthroplasty; iron supplementation; ferric carboxymaltose; hemoglobin; iron metabolism

1. Introduction

Orthopedic surgical procedures, particularly total knee arthroplasty (TKA) and total hip arthroplasty (THA), may result in moderate-to-high perioperative blood loss [1]. Perioperative anemia is an independent risk factor for increased morbidity, delayed hospital discharge, decreased quality of life (QOL), and poor recovery [2]. Hence, allogenic blood transfusion is commonly used to promptly correct anemia; however, its side effects, including periprosthetic joint infection,

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cardiovascular failure, deep vein thrombosis, and increased mortality, can adversely influence clinical outcomes [3,4]. Many blood conservation efforts have been made to reduce transfusion rates using preoperative erythropoietin (EPO), autologous transfusions, tranexamic acid, and subcutaneous Hemovac drains; however, these methods have varying success rates [5].

Accordingly, patient blood management (PBM) recommendations include early detection and treatment of anticipated perioperative anemia before orthopedic surgeries with iron replacement with or without erythropoiesis-stimulating agents (ESAs)6. Effective iron supplementation may decrease the incidence of postoperative anemia and the requirement for transfusion by optimizing hemoglobin (Hb) levels and correcting iron deficiencies to improve functional outcomes. Moreover, according to international treatment guidelines, patients undergoing major surgery with an expected blood loss of 500 mL or more should be checked for anemia two weeks preoperatively, which should be corrected with intravenous (IV) iron [6,7].

Recently, among several iron preparations, IV ferric carboxymaltose (FCM), which is a newer generation formulation with an excellent safety profile, has been recognized as an effective option to rapidly supplement iron storage and improve postoperative anemia for patients with iron deficiency with or without anemia [8,9]. Furthermore, due to the greater need for primary TKA and THA, their revision rates have increased [10–12]. Revision joint arthroplasty is technically difficult and requires better management of blood loss than primary joint arthroplasty [12–15]. Previous studies have demonstrated the effectiveness of perioperative IV FCM after lower limb total arthroplasty [2,16–19]; however, few studies have evaluated its role in revision joint arthroplasty.

Therefore, this prospective randomized study aimed to elucidate the effect of preoperative IV FCM administration in facilitating recovery from postoperative anemia in patients undergoing revision TKA or THA. We evaluated the efficacy of preoperative IV FCM administration on Hb recovery, changes in iron metabolite levels, transfusion rate, and QOL. We hypothesized that IV FCM administration would hasten anemia correction after revision TKA or THA.

2. Materials and Methods

2.1. Patients

Patients undergoing revision unilateral TKA or THA between February 2021 and May 2022 were screened and enrolled. This prospective, single-blinded, randomized, controlled, single-center trial was designed as a parallel-group study with balanced randomization. The study protocol was approved by the institutional review board (IRB number CNUHH-2020-275) and registered at Cris.nih.go.kr (KCT0005832). All eligible subjects were educated regarding the study requirements and provided informed consent.

The inclusion criteria were patients aged ≥20 and ≤80 years undergoing revision TKA or THA due to mechanical or septic complications with an American Society of Anesthesiologists grade 1–3. Patients were excluded if they had preoperative hematologic disease, chronic pulmonary disease, chronic renal disease, chronic hepatic disease, malignancy, a history of hypersensitivity and known anaphylaxis to iron, a history of a blood transfusion within the month prior to surgery, iron supplementation within six months prior to enrollment, or no available postoperative Hb data. Those who declined to participate were also excluded.

Among 90 eligible patients, 84 patients fulfilled all the inclusion and none of the exclusion criteria. These patients were included and randomly assigned to two groups using block randomization to generate balanced groups: 41 were included in the iron group after one was excluded from the analysis due to periprosthetic fracture, and 41 were included in the control group after one was excluded from the analysis due to periprosthetic joint infection (Figure 1). Patients in the iron group received 1000 mg of FCM (Ferinject®; Vifor Pharma, Flughofstrasse, Switzerland) as a single rapid IV infusion formula two weeks preoperatively. A total of 1000 mg of FCM was diluted in 100 ml of 0.9% sodium chloride solution and injected over 15 min.

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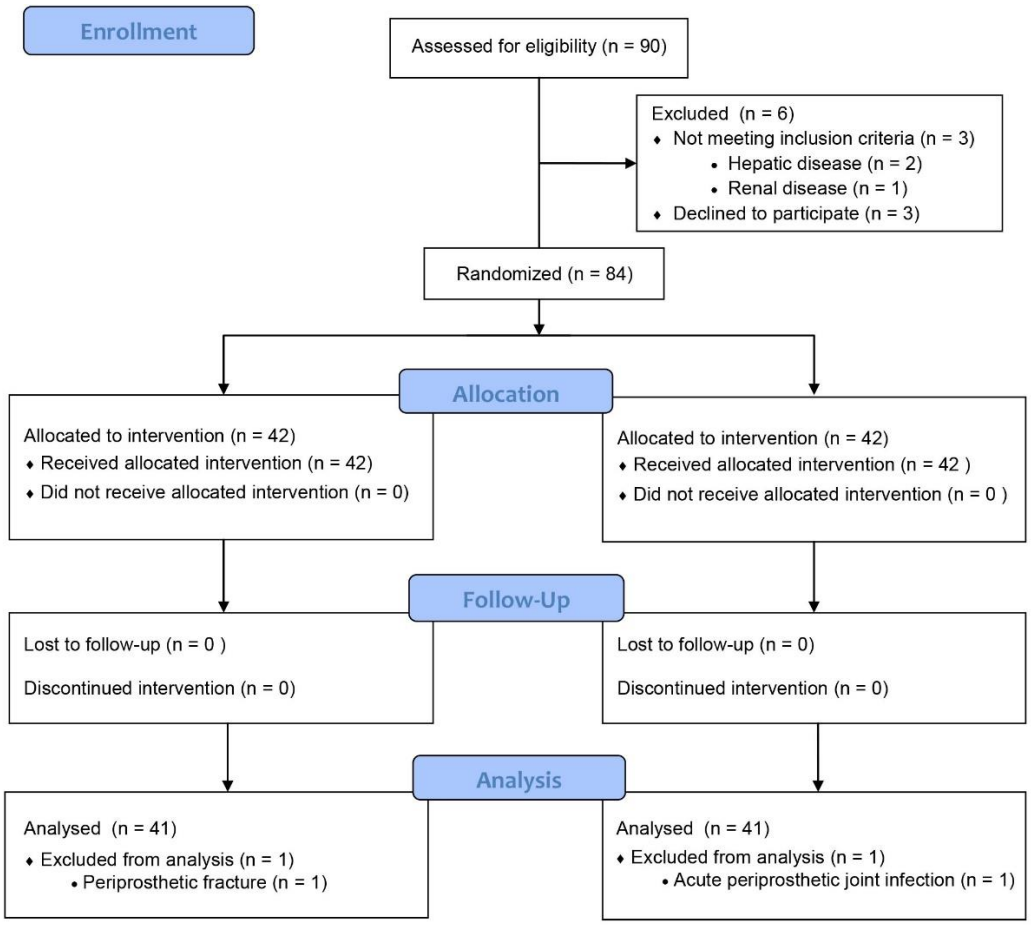

Figure 1. Flow diagram of patient enrollment.

2.2. Surgical Techniques

Revision TKA. Two-stage exchange arthroplasty was performed in all patients. All surgeries were performed by one senior surgeon (one of the authors) using the same surgical protocol via a medial parapatellar approach whenever possible with a tourniquet inflated to 280 mmHg. Extensive approaches such as quadriceps snip and tibial tuberosity osteotomy were performed when sufficient exposure could not be accomplished with the standard approach. All revision prostheses used in this study were the semi-constrained type and all prosthetic components were fixed with cement. Before tourniquet placement, 500 mg of IV tranexamic acid was administered intraoperatively. Intermittent pneumatic compression devices were used for thromboprophylaxis, and negative pressure blood drainage was routinely applied postoperatively, except in cases of a known contraindication.

Revision THA. All surgeries were performed by one senior surgeon (one of the authors) using the same surgical protocol. Revision THA surgeries were performed using a posterolateral approach in the lateral decubitus position. To reduce bleeding prior to skin incision, 500 mg of IV tranexamic acid of was administered intraoperatively, and a pneumatic compression device and subcutaneous closed suction drainage were also applied in the same manner as for revision TKA.

2.3. Clinical Investigations

The primary outcome was the change in Hb levels between baseline and four weeks postoperatively. Hb levels were recorded two weeks preoperatively, on the day of surgery, on postoperative days (PODs) 1, 3, and two weeks, four weeks, and three months postoperatively, and the change in Hb levels was compared between the two groups at each timepoint during the perioperative period. The secondary outcome measures were changes in iron metabolite levels including ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin saturation from

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baseline to PODs 1, 3, and four weeks and three months postoperatively; the number of patients requiring allogenic transfusion; and patient self-reported EuroQOL 5-dimension (EQ-5D)-3L questionnaire scores at four weeks and three months postoperatively.

Surgeons were encouraged to follow the standard restrictions for a transfusion trigger strategy of Hb <7.0 g/dl or perioperative symptoms of hemodynamic instability [20]. Anemia was defined as a suboptimal Hb concentration <13.0 g/dl in both females and males according to consensus guidelines [7].

2.4. Statistical Analysis

Based on a similar previous study, a 1.5 g/dL difference in Hb with a standard deviation of 2.5 g/dL was estimated [17]. The alpha error and power were set to 5% and 80%, respectively. The estimated sample size was 26 patients for each group. Therefore, a total of 84 patients with 42 patients per group were included to cope with possible losses. For normally distributed variables, paired and independent t-tests were performed. The chi-square test was used to compare differences in categorical variables. Repeated measures ANOVA followed by Bonferroni corrected post hoc analysis was performed to assess multiple comparisons of differences including Hb and iron metabolite profiles. The threshold for significance was set at $p < 0.05$.

3. Results

Patient demographics and clinical characteristics are summarized in Table 1. Forty-one pairs completed the trial, and there were no significant differences in demographic and hematologic findings between the two groups ($p > 0.05$). According to consensus guidelines, the iron and control groups had 26 and 27 anemic patients, respectively, with a preoperative Hb concentration < 13.0 g/dl.

Table 1. Baseline Patient Characteristics and Clinical Data Between the 2 Groups.

	Iron group (n = 41)	Control group (n = 41)	*P* Value†
Age (yr)	71.3 ± 7.2	71.5 ± 8.3	0.932
Women (no. [%])	29 (70.7)	24 (58.5)	0.248
BMI (kg/m^2)	25.2 ± 3.6	26.5 ± 4.2	0.132
ASA status			0.219
1 or 2	32 (78.0)	27 (65.8)	
≥3	9 (22.0)	14 (34.2)	
Cause of revision TKA (no. [%])			0.553
Septic	17 (41.5)	15 (36.6)	
Aseptic	17 (41.5)	11 (26.8)	
Cause of revision THA (no. [%])			0.654
Septic	2 (4.9)	3 (7.3)	
Aseptic	5 (12.1)	12 (29.3)	
Operative time (min)	132.9 ± 27.0	130.9 ± 37.9	0.777
Comorbidities (no. [%])			
Diabetes mellitus	14 (34.1)	11 (26.8)	0.472
Hypertension	28 (68.2)	30 (73.1)	0.627
Heart disease	10 (24.3)	8 (19.5)	0.594
Cerebrovascular disease	7 (17.0)	2 (4.9)	0.077
Bleeding tendency* (no. [%])			

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Aspirin therapy	10 (14.3)	8 (19.5)	0.594
Clopidogrel	3 (7.3)	3 (7.3)	0.999

Values are presented as the mean and standard deviation or n (%). *Patients with bleeding tendencies included those taking aspirin or other medication preoperatively with bleeding tendencies. No patients had underlying diseases causing a bleeding tendency such as a platelet defect or coagulation factor defect. Data are presented as numbers and percentages in the parentheses. BMI, body mass index; TKA, total knee arthroplasty; THA, total hip arthroplasty; ASA, American Society of Anesthesiologists.

3.1. Comparison of Clinical Results Between the Iron and Control Groups

The absolute Hb levels at each timepoint and changes in Hb levels from baseline to multiple postoperative timepoints were not different between the two groups, although the changes in Hb levels between baseline and four weeks postoperatively showed marginal significant differences favoring the iron group (iron group [n = 41], −0.6 ± 1.0 g/dL vs. control group [n = 41], −1.1 ± 0.9 g/dL; p = 0.052) (Table 2). The perioperative transfusion rate of each group did not vary (p = 0.364). However, for preoperatively anemic patients, the changes in Hb levels between baseline and four weeks postoperatively showed significant differences favoring the iron group (iron group [n = 26], −0.3 ± 0.7 g/dL vs. control group [n = 27], −0.9 ± 0.8 g/dL; p = 0.040). The changes in Hb levels at each timepoint are shown in Figure 2.

Table 2. Comparison of Hb Values and Changes in Hb Values Between the 2 Groups.

	Total set			Anemic patients*		
	Iron (n = 41)	Control (n = 41)	*P* Value†	Iron (n = 26)	Control (n = 27)	*P* Value†
Absolute Hb (g/dL)						
2 wks preop	12.6 ± 1.5	12.8 ± 1.3	0.433	11.7 ± 1.1	12.1 ± 0.6	0.144
Immediate postop	11.4 ± 1.3	11.4 ± 1.2	0.986	11.0 ± 1.2	10.9 ± 0.8	0.742
POD 1	10.3 ± 1.2	10.2 ± 1.3	0.986	9.8 ± 1.0	9.7 ± 0.9	0.547
POD 3	9.5 ± 1.2	9.1 ± 1.4	0.355	9.1 ± 1.1	8.8 ± 1.3	0.436
2 wks postop	10.5 ± 1.4	10.5 ± 1.2	0.825	10.2 ± 1.2	10.0 ± 0.9	0.789
4 wks postop	12.0 ± 1.4	11.7 ± 1.1	0.720	11.3 ± 1.0	11.2 ± 0.8	0.834
3 mo postop	12.5 ± 1.6	12.4 ± 1.1	0.813	12.0 ± 1.3	12.0 ± 0.8	0.574
Change in Hb (g/dL)						
Preop to immediate postop	−1.1 ± 1.0	−1.4 ± 0.9	0.287	−0.7 ± 0.6	−1.2 ± 0.8	**0.024**
Preop to POD 1	−2.3 ± 1.0	−2.6 ± 1.1	0.312	−1.8 ± 0.8	−2.4 ± 0.9	**0.034**
Preop to POD 3	−3.1 ± 1.3	−3.7 ± 1.3	0.076	−2.6 ± 0.9	−3.3 ± 1.2	**0.046**
Preop to 2 wks postop	−2.0 ± 1.1	−2.6 ± 1.0	0.073	−1.5 ± 0.9	−2.2 ± 0.6	**0.025**
Preop to 4 wks postop	−0.6 ± 1.0	−1.1 ± 0.9	0.052	−0.3 ± 0.7	−0.9 ± 0.8	**0.040**
Preop to 3 mo postop	0.0 ± 0.8	−0.2 ± 0.9	0.318	0.1 ± 0.8	−0.2 ± 0.8	0.256
Transfusion rate (n, [%])	5 (12.1)	8 (19.5)	0.364	3 (11.1)	5(12.1)	0.141

Values are presented as means and standard deviations or n (%). *Anemic individuals were defined as patients with a suboptimal Hb concentration <13.0 g/dL according to consensus guidelines; these patients were divided into two groups according to the administration of intravenous ferric carboxymaltose. †Bold indicates a p value <0.05 (statistically significant difference). Hb, hemoglobin; POD, postoperative day.

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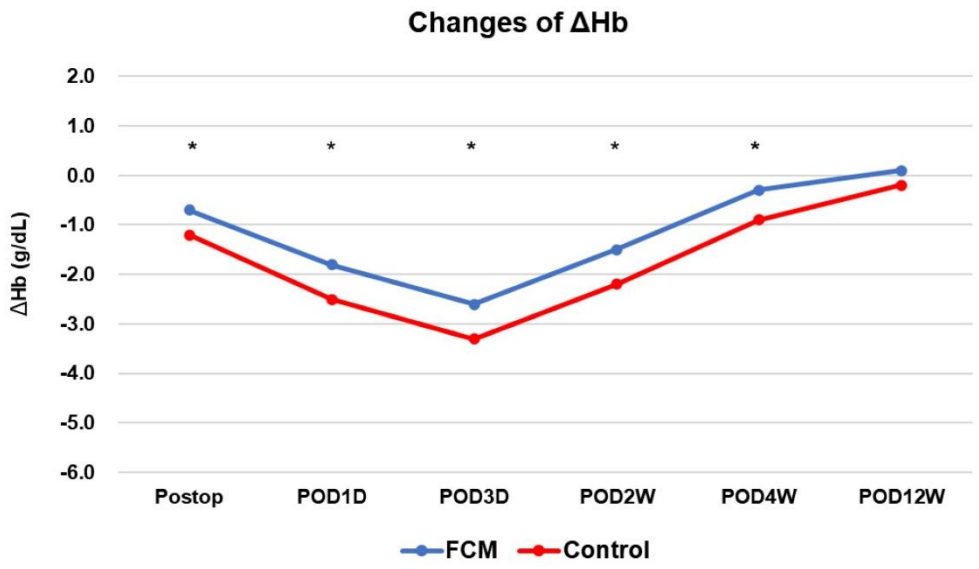

Figure 2. Changes in hemoglobin (ΔHb) from baseline to 12 weeks postoperatively between the two groups. The asterisks demonstrate a significance between groups. Hb, hemoglobin; POD, postoperative day.

The iron group showed improved iron metabolite levels including serum ferritin, TIBC, and transferrin saturation at multiple postoperative timepoints; however, preoperative iron storage testing showed no differences between the groups (Table 3). There were no differences in the EQ-5D scores between the groups preoperatively and at four weeks and three months postoperatively ($p > 0.05$) (Table 4). Moreover, there were no adverse events such as hypersensitivity, cardiovascular events, or infusion site reactions associated with IV FCM administration or postsurgical complications requiring additional treatment in either group.

Table 3. Comparison of Iron Metabolites at Each Timepoint Between the 2 Groups.

	Iron group (n=41)	Control group (n=41)	*P* Value*
Serum ferritin (ng/dL)			
2 wks preop	164.2 ± 182.5	104.0 ± 67.1	0.100
POD 1	1209.6 ± 520.7	206.7 ± 113.0	**<0.001**
POD 3	1200.2 ± 531.7	283.2 ± 184.6	**<0.001**
4 wks postop	603.4 ± 259.0	156.0 ± 98.0	**<0.001**
3 mo postop	352.0 ± 155.3	60.5 ± 53.7	**<0.001**
TIBC (ug/dL)			
2 wks preop	311.4 ± 58.8	323.2 ± 44.9	0.329
POD 1	214.2 ± 35.0	244.0 ± 44.0	**0.002**
POD 3	189.7 ± 36.2	236.0 ± 137.4	**0.051**
4 wks postop	251.9 ± 38.8	309.0 ± 55.6	**<0.001**
3 mo postop	272.7 ± 52.6	340.8 ± 52.9	**<0.001**
Iron (ug/dL)			
2 wks preop	86.1 ± 34.1	81.0 ± 33.4	0.523
POD 1	30.5 ± 12.6	32.8 ± 30.9	0.677
POD 3	35.8 ± 13.7	47.8 ± 138.7	0.603

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4 wks postop	80.1 ± 44.9	66.1 ± 23.4	0.115
3 mo postop	93.6 ± 27.0	69.6 ± 30.4	**0.002**
TSAT (%)			
2 weeks preop	29.0 ± 14.4	25.0 ± 9.6	0.169
POD 1	14.8 ± 6.8	13.2 ± 10.4	0.434
POD 3	19.3 ± 7.4	14.1 ± 12.0	**0.034**
4 wks postop	32.1 ± 19.1	21.9 ± 8.0	**0.007**
3 mo postop	35.5 ± 13.1	20.9 ± 9.6	**<0.001**

Values are presented as means and standard deviations. *Bold indicates a p value <0.05 (statistically significant difference). POD, postoperative day; TIBC, total iron binding capacity; TSAT, transferrin saturation.

Table 4. Comparison of Patient Reported Quality of Life Between the 2 Groups.

	Iron group (n = 41)	Control group (n = 41)	*P* Value*
EQ-5D-1 Mobility			
Preop	1.9 ± 0.1	2.0 ± 0.1	0.323
4 wks postop	1.9 ± 0.2	1.8 ± 0.3	0.751
3 mo postop	1.6 ± 0.5	1.5 ± 0.5	0.628
EQ-5D-2 Self Care			
Preop	1.6 ± 0.4	1.8 ± 0.5	0154
4 wks postop	1.8 ± 0.3	1.7 ± 0.5	0.182
3 mo postop	1.2 ± 0.4	1.3 ± 0.4	0.612
EQ-5D-3 Usual Activities			
Preop	1.9 ± 0.2	2.0 ± 0.1	0.570
4 wks postop	1.9 ± 0.1	1.8 ± 0.3	0.266
3 mo postop	1.5 ± 0.5	1.3± 0.4	0.179
EQ-5D-4 Pain/Discomfort			
Preop	2.8 ± 0.4	2.9 ± 0.2	0.145
4 wks postop	1.9 ± 0.2	1.8 ± 0.3	0.751
3 mo postop	1.6 ± 0.4	1.6 ± 0.4	0.734
EQ-5D-5 Anxiety/Depression			
Preop	1.6 ± 0.5	1.6 ± 0.4	0.831
4 wks postop	1.6 ± 0.4	1.6 ± 0.4	0.769
3 mo postop	1.4 ± 0.4	1.4 ± 0.5	0.587

Values are presented as means and standard deviations. *Bold indicates a p value of <0.05 (statistically significant difference). EQ-5D: EuroQOL 5-dimension.

4. Discussion

Preoperative IV FCM administration in anemic individuals undergoing revision joint arthroplasty was found to be effective in accelerating recovery from surgery-related anemia by improving Hb levels, despite similar actual Hb levels between the groups. IV FCM could be a safe and effective blood management protocol for improving anemia correction, which is supported by the previously reported efficacy of IV iron supplementation [2,17,19]. Moreover, postoperative iron

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metabolite levels were also improved in patients administered IV FCM, which was effective in replenishing iron, increasing circulation iron, and enhancing iron availability [21,22].

Significant differences in favor of the iron group were identified four weeks postoperatively, suggesting a potential "delayed effect" of iron supplementation after revision TKA and improved normal recovery process of Hb. Notably, in the control group, Hb levels three months postoperatively were still lower than preoperative levels, implying slower recovery from anemia without iron supplementation (1–3 months in the iron group vs. not until three months in the control group).

TKA and THA are established treatment methods for patients with end-stage osteoarthritis. However, they are associated with significant blood loss, and although the transfusion rate has steadily decreased due to procedural improvements, nearly one-third of patients still require a transfusion after TKA or TKA [5,18,23]. In their second Austrian benchmark study for blood use involving 3,164 patients undergoing TKA or THA, Gombotz et al. showed that transfusion rates decreased in TKA (41–25%) and THA (41–30%) [24]. In the National Surgical Quality Improvement Program (NSQIP) data from 13,662 TKA and 9,362 THA procedures evaluated by Hart et al., the transfusion rates after TKA and TKA were 18.3% and 22.2%, respectively. They demonstrated significant association between transfusion and high mortality (odds ratio: 2.7) after TKA [25]. Furthermore, systemic reviews of anemia and PBM joint arthroplasty have demonstrated that 24% of patients undergoing total joint arthroplasty are anemic, and more than half become anemic postoperatively due to intraoperative blood loss [14,15,18]. Accordingly, allogenic transfusions are needed to manage acute postoperative anemia, which may lead to several adverse outcomes [3,4]. Due to the rapid increase in lower limb total arthroplasties, the revision rates for TKA and THA are expected to increase proportionally by 2030 to 158% and 137%, respectively [10–12]. Revision joint arthroplasty after failure is technically demanding due to the loss of periprosthetic bone stock, and related complications, including more severe perioperative blood loss and damaged iron homeostasis affected by surgery-related inflammatory cytokines, which are more common than with primary joint arthroplasty13-15. Hence, clarifying ideal iron replacement strategies to minimize postoperative anemia after revision joint arthroplasty has clinically important relevance.

An association between iron supplementation and lower limb total arthroplasty outcomes has been reported [2,17,19,26]. Amato et al. evaluated the effect of IV FCM administered four weeks preoperatively on recovery from postoperative anemia after lower limb total arthroplasty and showed a quicker restoration of Hb concentration four weeks postoperatively in an FCM group [26]. Park et al. demonstrated the influence of intraoperative IV FCM on postoperative anemia recovery after TKA or THA and concluded that IV administration of 1000 mg of FCM accelerated Hb recovery without any adverse events; furthermore, this iron supplementation seemed to overcome surgery-related decreases in iron availability [17]. In contrast, Jeong et al. reported no significant differences in Hb levels and transfusion rates between patients treated with and without IV iron that was immediately administered after acute blood loss after staged bilateral TKA [27]. However, this was a retrospective, non-randomized study that used 300 mg of iron sucrose for IV iron supplementation, which has restrictive and time-consuming administration requirements. In contrast, FCM is a dextran-free complex with an excellent safety profile and is associated with less oxidative stress than other iron preparations [8,9]. Moreover, high doses of FCM show an advantage of rapid postoperative recovery of Hb levels compared with iron sucrose [17]. Based on these results, the newer generation IV FCM may facilitate recovery from anemia and avoidance of transfusions after major orthopedic surgery.

In their recent retrospective analysis, Maniar et al. demonstrated that IV FCM was an effective treatment for anemia recovery after TKA [19]. Improved Hb levels between baseline and five weeks postoperatively and actual Hb levels five weeks postoperatively weeks were both significantly increased in the iron group. Although the changes in Hb levels between baseline and four weeks postoperatively showed marginally significant differences favoring the iron group, patients in the iron group did not show significant recovery of Hb levels at each timepoint. However, when narrowing the included subjects to those with preoperative anemia (Hb < 13 mg/dl), those in the iron group showed significant changes in Hb levels between baseline and four weeks postoperatively,

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reflecting postoperative recovery from anemia in specific patients. Indeed, the Hb values in the iron group showed faster recovery to normal ranges. In their prospective randomized controlled study, Khalafallah et al. recently reported results consistent with our findings that patients with functional iron deficiency in an FCM group showed improved Hb levels four weeks postoperatively [28]. Patients with iron deficiency anemia have an increased risk of medical and surgical complications after total joint arthroplasty according to the national Medicare database; therefore, recovery from anemia is necessary. The iron group also showed improved iron metabolite levels including serum ferritin, and transferrin saturation at multiple postoperative timepoints. The reason for higher ferritin levels and transferrin saturation could be due to increased stored iron from IV FCM, which is effective in replenishing iron, increasing circulating iron, and enhancing iron availability, thus accelerating the recovery of Hb levels [21,22].

Iron supplementation leads to improved clinical outcomes and reduces the length of hospital stay after lower limb joint arthroplasty by correcting postoperative anemia [29]. This also affects QOL and functional recovery, leading to improved wound healing and decreased rehabilitation after joint arthroplasty [30]. We found no association between postoperative anemia and QOL in the two groups. However, a larger study with a longer follow-up period is needed for a more comprehensive analysis because it might be difficult to determine QOL among elderly patients 12 weeks after joint arthroplasty. Moreover, our findings failed to support the hypothesis that preoperative iron supplementation could decrease the need for postoperative transfusion, and there was no difference in the transfusion rates between the two groups, consistent with previous findings [2,17,19].

This study has some limitations. First, the number of recruited patients was relatively small to compare clinical outcomes between the groups, which may have underpowered the detection of all relevant outcomes. Second, as we enrolled patients undergoing major lower limb joint arthroplasty, changes in Hb levels or iron profiles may be different according to the surgery type. However, we performed stratified randomization for operative characteristics to enable a solid conclusion. Third, iron profiles were not measured in a serial longitudinal manner similar to Hb levels, making comparing the details of iron metabolism and evaluating iron availability between the groups impossible. Despite these limitations, we believe that our study provides a reasonable evaluation of the effectiveness of IV FCM for hemodynamic recovery in patients undergoing revision joint arthroplasty.

5. Conclusions

In conclusion, preoperative IV FCM in anemic individuals was effective in facilitating resolution of postoperative anemia by improving Hb levels without any adverse events in patients undergoing revision joint arthroplasty, despite similar actual Hb levels between the groups. Moreover, postoperative iron metabolite levels were also improved in patients treated with IV FCM. Our findings are clinically relevant and can facilitate determination of the suitability of IV FCM as a safe and effective protocol for iron supplementation for improving hemodynamic recovery and iron availability.

Author Contributions: Data curation, H.H.S., J.H.C.; Investigation, H.Y.Y., K.S.P., J.K.S.; Supervision.; Visualization, K.S.P.; Writing—original draft, H.Y.Y.; Writing—review & editing, K.S.P., J.K.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Seoul St. Mary's Hospital (CNUHH-2020-275). The trial was registered with Cris.nih.go.kr (KCT0005832).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data collected for this study, including individual patient data, will not be made available.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Larocque BJ, Gilbert K, Brien WF. Prospective validation of a point score system for predicting blood transfusion following hip or knee replacement. Transfusion 1998;38:932-7.
2. Kim MS, Koh IJ, Choi KY, Yang SC, In Y. Efficacy and Safety of Intravenous Ferric Carboxymaltose in Patients with Postoperative Anemia Following Same-Day Bilateral Total Knee Arthroplasty: A Randomized Controlled Trial. J Clin Med 2021;10.
3. Rosencher N, Kerkkamp HE, Macheras G, et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. Transfusion 2003;43:459-69.
4. Shander A. Emerging risks and outcomes of blood transfusion in surgery. Semin Hematol 2004;41:117-24.
5. Della Valle CJ, Buvanendran A, Mont MA, Callaghan JJ. Contemporary Blood Conservation in Hip and Knee Arthroplasty: Tranexamic Acid is an Important Piece of the Puzzle! J Arthroplasty 2018;33:3063-4.
6. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient Blood Management: Recommendations From the 2018 Frankfurt Consensus Conference. Jama 2019;321:983-97.
7. Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233-47.
8. Scott LJ. Ferric Carboxymaltose: A Review in Iron Deficiency. Drugs 2018;78:479-93.
9. Keating GM. Ferric carboxymaltose: a review of its use in iron deficiency. Drugs 2015;75:101-27.
10. Sibanda N, Copley LP, Lewsey JD, et al. Revision rates after primary hip and knee replacement in England between 2003 and 2006. PLoS Med 2008;5:e179.
11. Kim TW, Kang SB, Chang CB, Moon SY, Lee YK, Koo KH. Current Trends and Projected Burden of Primary and Revision Total Knee Arthroplasty in Korea Between 2010 and 2030. J Arthroplasty 2021;36:93-101.
12. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
13. Bozic KJ, Katz P, Cisternas M, Ono L, Ries MD, Showstack J. Hospital resource utilization for primary and revision total hip arthroplasty. J Bone Joint Surg Am 2005;87:570-6.
14. van Iperen CE, Kraaijenhagen RJ, Biesma DH, Beguin Y, Marx JJ, van de Wiel A. Iron metabolism and erythropoiesis after surgery. Br J Surg 1998;85:41-5.
15. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23.
16. Bisbe E, Moltó L, Arroyo R, Muniesa JM, Tejero M. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. Br J Anaesth 2014;113:402-9.
17. Park HS, Kim TY, Kim HJ, Ro YJ, Jang HY, Koh WU. The Effect of Intraoperative Ferric Carboxymaltose in Joint Arthroplasty Patients: A Randomized Trial. J Clin Med 2019;8.
18. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology 2010;113:482-95.
19. Maniar AR, Mishra A, Sanghavi N, Maniar RN. Does Postoperative Intravenous Ferric Carboxymaltose Hasten the Recovery of Hemoglobin in Patients Post Total Knee Arthroplasty? J Arthroplasty 2022;37:S155-s8.
20. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion 2002;42:812-8.
21. Muñoz M, Breymann C, García-Erce JA, Gómez-Ramírez S, Comin J, Bisbe E. Efficacy and safety of intravenous iron therapy as an alternative/adjunct to allogeneic blood transfusion. Vox Sang 2008;94:172-83.
22. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol 2008;103:1182-92.
23. Mistry JB, Gwam CU, Naziri Q, et al. Are Allogeneic Transfusions Decreasing in Total Knee Arthroplasty Patients? National Inpatient Sample 2009-2013. J Arthroplasty 2018;33:1705-12.
24. Gombotz H, Rehak PH, Shander A, Hofmann A. The second Austrian benchmark study for blood use in elective surgery: results and practice change. Transfusion 2014;54:2646-57.
25. Hart A, Khalil JA, Carli A, Huk O, Zukor D, Antoniou J. Blood transfusion in primary total hip and knee arthroplasty. Incidence, risk factors, and thirty-day complication rates. J Bone Joint Surg Am 2014;96:1945-51.
26. D'Amato T, Kon E, Martorelli F, et al. Effect of intravenous ferric carboxymaltose supplementation in non-anaemic iron deficient patients undergoing hip and knee arthroplasty. J Biol Regul Homeost Agents 2020;34:69-77. Congress of the Italian Orthopaedic Research Society.
27. Jeong JH, Chang MJ, Kang SB, Park HJ, Lee KH, Chang CB. Postoperative Intravenous Iron Supplementation Does Not Improve Hemoglobin Level and Transfusion Rate Following Staged Bilateral Total Knee Arthroplasty. J Arthroplasty 2020;35:2444-50.

 doi:10.20944/preprints202312.1984.v1

28. Khalafallah AA, Hyppa A, Chuang A, et al. A Prospective Randomised Controlled Trial of a Single Intravenous Infusion of Ferric Carboxymaltose vs Single Intravenous Iron Polymaltose or Daily Oral Ferrous Sulphate in the Treatment of Iron Deficiency Anaemia in Pregnancy. Semin Hematol 2018;55:223-34.
29. Farley KX, Anastasio AT, Premkumar A, Boden SD, Gottschalk MB, Bradbury TL. The Influence of Modifiable, Postoperative Patient Variables on the Length of Stay After Total Hip Arthroplasty. J Arthroplasty 2019;34:901-6.
30. Cuenca J, García-Erce JA, Martínez F, Cardona R, Pérez-Serrano L, Muñoz M. Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. Int J Surg 2007;5:89-94.