Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty

E. Bisbe1,3*, L. Moltó1, R. Arroyo1, J. M. Muniesa2 and M. Tejero2

1 Department of Anaesthesia and 2 Rehabilitation Service, Hospital Mar-Esperança, Sant Josep de la Muntanya 12, 08024 Barcelona, Spain
3 IMIM Hospital del Mar Medical Research Institute, Barcelona, Spain
* Corresponding author. E-mail: 86927@parcdesalutmar.cat

Editor’s key points
- Anaemia is common after hip and knee arthroplasty and this may impair recovery.
- I.V. iron formulations restore perioperative haemoglobin levels more reliably than oral iron.
- This study identified some evidence that better treatment of postoperative anaemia could improve patient outcomes.
- I.V. iron therapy for pre- or postoperative anaemia is a promising option deserving further study.

Background. Despite preoperative anaemia treatment, a risk of postoperative anaemia remains. This randomized, controlled study evaluated the efficacy of i.v. ferric carboxymaltose (FCM) as postoperative anaemia treatment after total knee arthroplasty (TKA).

Methods. TKA patients with postoperative anaemia (haemoglobin (Hb) 8.5–12.0 g dl\(^{-1}\)) without prior transfusions were randomly assigned to FCM (700–1000 mg iron (according to calculate iron deficit on postoperative day 2)) or ferrous glycine sulphate (FS; 100 mg iron daily from day 7 onwards) and followed for Hb, iron status, quality-of-life (EQ-5D), and performance (6 min walk test) until day 30.

Results. Of 161 preoperatively non-anaemic patients, 122 (75.8%) developed anaemia after operation (within 24 h) and were enrolled in this study (60 FCM, 62 FS). Hb substantially decreased until day 4 in both groups, and partly recovered by day 30. FCM-treated patients achieved Hb ≥12.0 g dl\(^{-1}\) more frequently (42.3 vs 23.5%; \(P=0.04\)) and showed a trend towards higher Hb increase from day 4 to day 30 [+1.7 (1.2) vs +1.3 (1.0); \(P=0.075\)] compared with FS-treated patients. Patients with postoperative Hb <10 g dl\(^{-1}\) experienced better Hb increase with FCM [+2.4 (0.3) g dl\(^{-1}\)] than FS [+1.1 (0.4) g dl\(^{-1}\); \(P=0.018\)]. Patients being iron-deficient at enrolment (56.7%) had a higher Hb increase with FCM [+1.9 (0.3) g dl\(^{-1}\)] than FS [+1.2 (0.2) g dl\(^{-1}\); \(P=0.03\)]. Total EQ-5D and performance outcomes were comparable between the groups, but FCM was associated with better scores for ‘usual activities’. No i.v. iron-related adverse events were reported.

Conclusions. Preoperatively non-anaemic TKA patients are at high risk of postoperative anaemia. Postoperative i.v. FCM provided significant benefit over oral FS, particularly in patients with preoperative iron deficiency, severe postoperative anaemia, or both.

Clinical trial registration. EudraCT 2010-023038-22; ClinicalTrials.gov NCT01913808.

Keywords: anaemia; ferric carboxymaltose; iron deficiency; i.v. iron; patient blood management; surgery

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Both pre- and postoperative anaemia are common in patients undergoing major orthopaedic surgery.\(^1\)–\(^3\) The main consequence of perioperative anaemia is an increased risk of red blood cell (RBC) transfusions. Allogeneic RBC transfusion and anaemia are associated with higher postoperative mortality and morbidity.\(^5\)–\(^10\) Since blood transfusions increase haemoglobin (Hb) levels only transiently and come at the price of higher mortality and morbidity (e.g. postoperative infections),\(^6\)–\(^8\) the three-pillar concept of patient blood management (PBM) has been developed to reduce the risk of blood transfusions and improve patient outcomes.\(^11\)–\(^14\) Treatment or prevention of preoperative anaemia is the mainstay of PBM but also the second pillar, minimization of intraoperative blood loss,\(^15\) targets at least indirectly the patient’s Hb levels.

The third PBM pillar, use of a lower Hb cut-off as a transfusion trigger, implies that a certain degree of postoperative anaemia is accepted. However, it remains unclear whether a lowered transfusion threshold allows optimal functional recovery and quality of life.\(^15\)–\(^16\) Since patients undergoing total knee arthroplasty (TKA) are often elderly and have several comorbidities, prolonged exposure to low Hb levels may not be good for this population.\(^17\)–\(^18\) Furthermore, TKA patients should be mobilized...
as soon as possible after surgery which increases the metabolic demand. There is a high risk of postoperative anaemia, even among preoperatively non-anaemic patients.

Apart from blood loss, inflammatory processes associated with surgery can substantially affect Hb levels via impairment of iron homeostasis. Pro-inflammatory cytokines (e.g. IL-6, TNF-α) can increase hepcidin-expression which deactivates the iron export protein ferroportin and leads to iron sequestration in enterocytes and macrophages, a condition known as functional iron deficiency. Accordingly, postoperative anaemia in lower limb arthroplasty has often a multifactorial history of preoperative anaemia (~25%), blood loss (~30% of volume), and iron deficiency. Thus, rapid iron substitution, as recommended for preoperative anaemia management, should also be considered after operation.

Although, depending on the timescale before surgery, oral iron is suggested for preoperatively anaemic patients with absolute iron deficiency, oral iron showed no benefit over placebo in anaemic patients after lower limb arthroplasty. In patients at risk of functional iron deficiency due to chronic inflammation of different aetiologies, i.v. iron administration has proven its superiority over oral iron. Even in iron-deficient patients without established anaemia, i.v. iron improved physical performance and cardiac functional class. Thus, postoperative anaemia treatment with i.v. iron might not only reduce RBC requirements but also improve performance, rehabilitation, and outcomes.

The aim of this study was to compare the efficacy of postoperative i.v. ferric carboxymaltose (FCM) and oral ferrous glycine sulphate (FS) for early improvement of postoperative anaemia after TKA and recovery from surgery.

**Methods**

**Study design**

This study was designed as a prospective, single-blinded, randomized, controlled trial of patients who underwent TKA at the University Hospital Mar-Esperança, Barcelona, Spain. It was performed from January 2011 to January 2012 in compliance with the Declaration of Helsinki and the Guideline of Good Clinical Practice, registered (EudraCT 2010-023038-22, ClinicalTrials.gov NCT01913808), and approved by the hospital’s independent ethics committee.

**Patients**

Adult patients (≥18 yr of age) were recruited at the scheduled preoperative visit (21–30 days prior to surgery). Patients with known hypersensitivity or contraindications to iron, liver insufficiency (aspartate aminotransferase or alanine aminotransferase >60 IU litre⁻¹), bronchial asthma, presence of acute or chronic infection, severe heart disease, significant history of allergies (rash, etc.), or anti-anæmia treatment within 15 days before surgery were excluded from participation. Also pregnant or nursing women were excluded (negative pregnancy urine test within 7 days prior first study treatment or amenorrhoa for at least 12 months).

After signing informed consent, patients had aspects of their quality of life (EQ-5D questionnaire), independence in daily activities (Barthel Index), and physical performance (6 min walk test (6-MWT)) measured.

**Perioperative patient management**

Preoperative PBM included anaemia assessment 1 month before surgery. Anaemic patients were treated with iron, subcutaneous erythropoietin, or both according to the institutional standard protocol (Fig. 1). Patients received spinal anaesthesia unless contraindicated. Antithrombotic treatment was initiated 6 h after operation (subcutaneous bemiparin 3500 IU day⁻¹). During surgery, the patients could receive a dose of 1000 mg tranexamic acid before tourniquet release at the anaesthesiologist’s discretion. After operation, patients were equipped with an autotransfusion device (Bellovag ABT, Wellspect HealthCare, Mölndal, Sweden) for reinfusion of shed blood if the collected volume exceeded 400 ml. Analgesia was initiated in the immediate postoperative period, and comprised femoral and sciatic block supplemented with i.v. analgesics according to the institutional protocol. From 48 h after surgery, patients received conventional oral analgesia. Triggers of RBC transfusions were Hb <8.0 g dl⁻¹ or occurrence of acute anaemia symptoms (e.g. dizziness, chest pain, tachycardia, persistent hypotension). Drugs used for the control of surgery-related symptoms were permitted unless investigators considered the drug to influence the study endpoints (e.g. doxycillin in the FS group).

**Randomization, blinding, and intervention**

On the day after surgery, eligible patients with anaemia (Hb <12 g dl⁻¹), iron deficiency [transferrin saturation (TSAT) <20%], or both were randomly assigned 1:1 to receive either i.v. FCM or oral FS. Randomization was performed using a random number list that had been electronically generated before initiation of the study. Screening or treating physicians had no access to the randomization list. Treatment allocation was accessed only by the pharmacist after patient enrolment. Patients with an intraoperative or immediate postoperative transfusion, severe postoperative anaemia (Hb <8.5 g dl⁻¹), or a risk of transfusion within the next hours were not randomized to the study.

FCM (Ferinject®, Vifor France SA, France) was given the day after surgery as a single i.v. dose to correct the total iron deficit calculated by the Ganzoni formula (total iron deficit (mg) = 2.4 × patient’s weight (kg) × [current Hb (13 g dl⁻¹) − target Hb (g dl⁻¹)] + 500 (mg iron stores); SmPC update for FCM with simplified iron-dosing grid not approved that time). FS (Ferbisol, BIAL Industrial Farmacéutica, Spain) was given as a once daily oral dose of 100 mg iron from the day of discharge (day 7) to the rehabilitation visit 30 days after surgery. The recruitment team, physicians, and other medical staff involved in the conduct and evaluation of the questionnaires were blinded to the study treatment.

**Follow-up and outcome measures**

Data were collected via an online Case Report Form (CRF, available at www.awge.org). Primary efficacy endpoints were the
change in Hb level from postoperative day 4 to day 30 and the percentage of patients without anaemia (Hb > 12 g dl⁻¹). Patients with Hb increase ≥ 1.5 g dl⁻¹ were considered responders. Predefined secondary endpoints comprised Hb at day 30, changes in quality of life (EQ-5D and Barthel questionnaires) from before surgery to the end of the study period (day 30), distance in the 6-MWT, percentage of transfused patients, and adverse events (AEs).

**Adverse events**

AEs were recorded and evaluated daily during the hospitalization phase. At the rehabilitation visit, only surgical complications were recorded. Characterization of AEs included frequency, intensity/severity (categorized as ‘mild’, ‘moderate’, or ‘severe’), and relation to the study drug (‘related’ or ‘unrelated’).

**Statistical methods**

We powered our study to detect a difference between the groups in the change in Hb from baseline of 0.5 g dl⁻¹ (1) between days 4 and 30. Based on a predicted control group change of 0.5 (0.5), we required 51 cases per group (correlation between first and second measure was established to 0.6; 80% power; 5% significance level). Allowing for 15% loss to follow-up, we aimed to enrol 60 patients in each group.

Descriptive statistics comprised percentages of patients and mean (standard deviation, SD) of continuous variables. Missing data were excluded from the analyses. The χ² or the exact Fisher test was used for comparison of qualitative variables, and the analysis of variance test with the Bonferroni correction for quantitative variables. A linear regression was performed to evaluate the correlation of patient and treatment factors with Hb changes. The statistical analyses were done with the SPSS 16.0 software (Dynelytics AG, Zurich, Switzerland) considering P-values of < 0.05 for statistical significance.

**Results**

**Patient characteristics**

Of 197 pre-recruited patients, 161 underwent surgery, and of those, 122 (75.8%) fulfilling the inclusion criteria were enrolled (60 FCM, 62 FS) and analysed according to the intention-to-treat principle (Fig. 2). Baseline patient characteristics, clinical characteristics, and preoperative PBM measures were comparable in the two treatment groups (Tables 1 and 2). Most enrolled patients [102 (83.6%)] had complete data sets available at the end of the study period. The mean duration of surgery and blood loss were not significantly different (P = 0.16 and 0.7, respectively) between patients randomized to the FCM and FS groups.
Perioperative evolution of Hb and iron status

Hb and haematocrit

Before initiation of treatment, the preoperatively non-anaemic patients experienced a significant decrease in the mean Hb from 13.6 (0.9) g dL\(^{-1}\) at enrolment (day –30) to 10.5 (1.0) g dL\(^{-1}\) at 24 h after surgery (P<0.001 vs baseline; Table 3). The mean Hb further decreased to <10.0 g dL\(^{-1}\) before it increased to ≥11.0 g dL\(^{-1}\) until the end of the study (day 30) in both groups.

At the end of the study period, a significantly higher proportion of FCM- than FS-treated patients had normal Hb levels (42.3% vs 23.5%; P=0.04; n=52 and 51 evaluable patients, respectively; Table 3). Notably, only 50% of FS-treated patients had Hb levels ≥10 g dL\(^{-1}\) at study end, whereas 50% in the FCM group had Hb levels ≥11.4 g dL\(^{-1}\). The mean Hb increase from day 4 to day 30 and the rate of responders (Hb increase ≥1.5 g dL\(^{-1}\)) were greater in the FCM group; yet, the differences were not statistically significant.

In the subset of patients with Hb levels <10 g dL\(^{-1}\) at 24 h after surgery and available Hb levels at study end (n=23), Hb increase until day 30 was significantly better with i.v. FCM compared with oral FS (P=0.018) (Table 3). The length of stay was not different between patients with Hb <10 g dL\(^{-1}\) [7.8 (1.0) days] and Hb ≥10 g dL\(^{-1}\) [7.7 (1.5) days; P=0.7].

The mean haematocrit showed a similar time course to that of the Hb concentrations a decrease from preoperatively 41.6% to 31.5% at 24 h after surgery, followed by an increase to 35.7 (1.1)% (FCM) and 33.0 (1.4)% (FS) until day 30.

TSAT and serum ferritin

The mean TSAT increased significantly better until day 30 in FCM- compared with FS-treated patients (Table 3). Notably, 87.5% in the FCM group compared with only 35.1% in the FS group achieved normal TSAT until the end of the study (P<0.001). Preoperative ferritin levels (Table 1) increased to significantly higher levels in the FCM than the FS group (Table 3).

Patients with preoperatively low iron stores

Overall, 56.7% (n=68) of patients had a serum ferritin <100 ng mL\(^{-1}\) at enrolment; 61.7% (n=37) in the FCM and 51.7% (n=31) in the FS group. Among these patients, both Hb at day 30 and Hb increase from day 4 to day 30 were significantly higher with FCM than FS treatment (P=0.01 and 0.03, respectively) (Table 3). Normal Hb was achieved by 40.0% FCM- and 8% FS-treated patients (P=0.02).

Among preoperatively iron-deficient patients with a postoperative Hb <10 g dL\(^{-1}\) at 24 h post-surgery and available Hb levels at study end, only one of 12 FCM-treated patients
### Table 2: Applied PBM techniques

<table>
<thead>
<tr>
<th></th>
<th>FCM (n = 60)</th>
<th>FS (n = 62)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PREPARATIVE ANAEMIA TREATMENT</td>
<td></td>
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<tr>
<td>Preoperative anaemia treatment</td>
<td>7 (11.6)</td>
<td>12 (19.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>EPO</td>
<td>3 (5)</td>
<td>7 (11.3)</td>
<td></td>
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<tr>
<td>I.V. iron</td>
<td>1 (1.7)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>EPO+i.V. iron</td>
<td>3 (5)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Other haematinics</td>
<td>0</td>
<td>3 (4.8)</td>
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**PILLAR 2 [n (%)]**

<table>
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<tr>
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<th>FCM (n = 60)</th>
<th>FS (n = 62)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal anaesthesia</td>
<td>59/60 (98.3)</td>
<td>60/62 (96.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>20/60 (33)</td>
<td>26/62 (41.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>PSB reinfusion</td>
<td>9/60 (15)</td>
<td>11/62 (17.7)</td>
<td></td>
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</table>

**PILLAR 3 [n (%)]**

<table>
<thead>
<tr>
<th></th>
<th>FCM (n = 60)</th>
<th>FS (n = 62)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean nadir haemoglobin (g dl⁻¹)</td>
<td>7.6</td>
<td>7.6</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Outcomes of postoperative iron treatment (at day 30 unless otherwise indicated)

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>FS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysed patients (n=121)</td>
<td>59 FCM, 62 FS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb at 24 h post-surgery</td>
<td>10.5 (1.0)</td>
<td>10.5 (1.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hb at day 4 (g dl⁻¹)</td>
<td>9.7 (1.3)</td>
<td>9.7 (1.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Hb at day 30 (g dl⁻¹)</td>
<td>11.5 (1.2)</td>
<td>11.0 (1.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Delta Hb (g dl⁻¹)</td>
<td>1.7 (1.2)</td>
<td>1.3 (1.0)</td>
<td>0.075</td>
</tr>
<tr>
<td>Responders [n (%)]‡</td>
<td>20 (40)</td>
<td>13 (27.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Anaemia corrected [n (%)]</td>
<td>22 (42.3)</td>
<td>12 (23.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Delta MCV (fl)</td>
<td>2.9 (2.9)</td>
<td>1.5 (0.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Serum ferritin (ng ml⁻¹)</td>
<td>691 (340)</td>
<td>224 (183)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>27.3 (1.4)</td>
<td>21.1 (1.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TSAT ≥20% [n (%)]</td>
<td>28 (87.5)</td>
<td>13 (35.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelets (×10⁹ litre⁻¹)</td>
<td>322 (100)</td>
<td>385 (189)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total EQ-5D</td>
<td>0.6 (0.9)</td>
<td>0.6 (0.17)</td>
<td>0.3</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>7.9 (1.7)</td>
<td>7.6 (0.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Blood transfusions [n (%)]</td>
<td>3 (5)</td>
<td>2 (3.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>EQ-5D subscores</td>
<td></td>
<td></td>
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<tr>
<td>‘Usual activities’§</td>
<td>1.9 (0.3)</td>
<td>2.1 (0.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>‘Anxiety/depression’§</td>
<td>1.3 (0.6)</td>
<td>1.6 (0.7)</td>
<td>0.074</td>
</tr>
<tr>
<td>Patients with severe postoperative anaemia** [n=23 (12 FCM, 11 FS)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta Hb (g dl⁻¹)</td>
<td>2.4 (0.3)</td>
<td>1.1 (0.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Patients with severe postoperative anaemia and preoperatively low iron stores [n=19; 12 FCM, 7 FS]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta Hb (g dl⁻¹)</td>
<td>2.6 (1.02)</td>
<td>1.1 (1.23)</td>
<td>0.017</td>
</tr>
</tbody>
</table>
compared with four of seven FS-treated patients remained at Hb < 10 g dl⁻¹. The mean Hb levels at study end [11.4 (1.0) vs 10.0 (0.8) g dl⁻¹; P<0.005] and the mean Hb increase were significantly higher in the FCM group.

Quality of life and physical performance

EQ-5D

The total EQ-5D score and most subscores were comparable between the treatment groups at enrolment (Table 1) and the end of the study period (Table 3). Among preoperatively iron-deficient patients (ferritin < 100 ng ml⁻¹), FCM treatment was associated with better scores for ‘usual activities’ and ‘anxiety/depression’ at the end of the study period. Also, in patients with severe postoperative anaemia (Hb < 10.0 g dl⁻¹), those with FCM treatment had better subscores for ‘usual activities’ at the end of the study period (1.91 vs 2.27; P=0.04).

Barthel test and 6-MWT

Results of the Barthel test and the 6-MWT were similar between treatment groups at enrolment (Table 1) and at the end of the study period (Table 3).

Iron exposure and tolerability of i.v. iron

The mean total i.v. iron dose was 884 (125) mg per patient. The theoretical oral iron dose was 2.4 g (100 mg daily from days 7 to 30). Overall, five patients (4%) received an allogeneic blood transfusion (Table 3). In each of the two groups, AEs were reported for 20% of patients (Table 4). The events were almost entirely mild to moderate, and none of the AEs was considered related to the study drug. Wound disturbances were the most frequent group of AEs followed by a transient increase in transaminases and urine infections without significant differences between the groups. One allergic reaction and one severe hypotension were reported in the control group and one swelling in the FCM group. The mean CRP levels were <1 g dl⁻¹ at all time points and at day 30, only one patient per group had CRP levels between 5 and 10 mg dl⁻¹. Serious, but unrelated, AEs comprised cholangitis in a patient with unknown Caroli syndrome and deep venous thrombosis in the FCM group and also a tibia fracture in the FS group. All serious AEs resolved with standard treatment.

Discussion

The results of this study confirm that non-anaemic patients undergoing TKA are at high risk of postoperative anaemia. The mean Hb of anaemic patients after operation receiving iron treatment improved between day 4 and day 30 post-surgery, particularly among FCM-treated patients with low baseline ferritin levels, low Hb levels, or both the day after surgery.

Over the recent years, preoperative anaemia has been accepted as risk factor for RBC transfusion, postoperative complications, and death. Accordingly, the concept of perioperative PBM with a strong focus on treatment or prevention of preoperative anaemia has been developed. At our centre, a preoperative standard protocol including treatment with iron, subcutaneous erythropoietin, or both is applied and we have a very low transfusion rate in the range of 5%.

However, even in centres dedicated to the prevention of preoperative anaemia, the risk of postoperative anaemia should not be underestimated. A recently presented study showed an 87% prevalence of postoperative anaemia among preoperatively non-anaemic patients who underwent knee surgery, particularly among FCM-treated patients with low preoperative anaemia, the risk of postoperative anaemia should not be underestimated. A recently presented study showed an 87% prevalence of postoperative anaemia among preoperatively non-anaemic patients who underwent knee surgery, particularly among FCM-treated patients with low preoperative anaemia.

The fact that more than half of the non-anaemic patients in this study were iron-deficient at enrolment (TSAT < 20% or ferritin < 100 ng ml⁻¹) emphasizes that serious assessment and management of patients’ iron status should be as important as Hb management. Among available iron administration routes, i.v. iron treatment is characterized by high utilization of administered iron and good tolerability allowing the administration of high single doses. Thus, i.v. iron is the preferred option for rapid iron repletion in patients with large iron deficits, chronic diseases, or both where oral iron is ineffective due to poor absorption or inflammation-related iron sequestration (or both).

Accordingly, this study showed significantly better improvements in the iron parameters TSAT and serum ferritin of i.v. FCM-treated patients compared with oral FS-treated patients. The higher proportion of iron-deficient patients in the oral than the i.v. iron group (65% vs 12.5%) could be a reason for the significant difference in platelet counts at day 30. This would be in line with discussions about a link between iron deficiency and thrombocytosis in different patient populations.

| Table 4: AEs profile. Data shown as number of events and per cent of patients; no significant differences between the frequencies of shown AE categories between the study groups. “Control” group comprises the FS group; however, AEs not related to surgical complications were recorded only during the hospitalization phase (i.e. before initiation of FS). AE, adverse event; SAE, serious adverse event |
|-----------------|-----------------|-----------------|
|                | FCM (n = 60)    | Control* (n = 62) |
| Any AE (total) | 20 (33)         | 20 (32)         |
| Related         | 0               | 0               |
| Any mild or moderate AE | 18 (30) | 19 (30) |
| Most common AEs (in ≥5% of patients) | | |
| Wound disturbances | 7 (11) | 11 (17.7) |
| Transient transaminitis | 4 (6.6) | 3 (4.8) |
| Urine infections | 3 (5)          | 0 (0)           |
| Any severe AE   | 2 (3.3)         | 1 (1.6)         |
| Any SAE         |                 |                 |
| Cholangitis     | 1 (1.6)         | 0               |
| Deep venous thrombosis | 1 (1.6) | 0               |
| Tibia fracture  | 0               | 1 (1.6)         |
Furthermore, patients with preoperatively low iron stores experienced significantly better Hb increase with FCM than oral treatment. Moreover, 40% of FCM-treated iron-deficient patients compared with only 8% of FS-treated iron-deficient patients achieved normal Hb levels. Iron-deficient patients who developed postoperative anaemia with Hb levels below 10 g dl$^{-1}$ showed particular benefit from FCM; yet, the number of patients in this subgroup was already quite low. Notably, the low number of patients with both iron deficiency and severe postoperative anaemia might result from the thorough PBM programme established at our centre and should not be generalized. Conversely, this result shows that two easily available measures, preoperative serum ferritin and postoperative Hb, allow identification of patients that may benefit most from an i.v. iron administration after surgery.

Few published studies investigated the use of i.v. iron for the correction of postoperative anaemia and improvement of performance and quality of life. 23, 25, 32, 37, 38 However, most of them are retrospective observational studies focusing on the reduction in RBC transfusions in patients with severe anaemia and no preoperative blood management. Owing to the established PBM programme in our centre, it would require very large patient numbers to identify potential additional treatment effects on the RBC transfusions rate.

Despite patients not being blinded to the study treatment, overall quality-of-life scores neither changed over the study period nor differed between treatment groups. Significant differences in the EQ-5D subcategories, ‘usual activities’ and ‘anxiety/depression’, are meaningful for the patient’s self-esteem and subjective well-being. The aim of performing the 6-MWT was to characterize the study population more than to assess physical performance in response to iron. In general, selection and timing of this performance test should be reconsidered in studies involving this type of surgery.

Postoperative i.v. iron treatment was generally well tolerated and reported AEs primarily related to the surgical procedure or patients’ comorbidities and not to the iron treatment. Notably, AEs were recorded only during the hospitalization phase, that is, before the initiation of oral iron treatment. Since the rehabilitation visit on day 30 focused on the orthopaedic outcomes and wound disturbances, patient complaints has been observed and the aetiology of observed urinary tract infections remained unclear. Disturbances in wound healing were not significantly different between the treatment groups, but our study was underpowered to properly evaluate this outcome. No hypersensitivity reactions and no new safety findings were identified in the FCM group.

**Conclusions**

Patients undergoing TKA in a centre with an established PBM programme that corrects or prevents most cases of preoperative anaemia are still at high risk of postoperative anaemia. Therefore, both postoperative Hb and preoperative iron status should be routinely assessed in TKA and probably elective orthopaedic surgery in general. Postoperative FCM treatment resulted in more frequent correction of postoperative anaemia than oral iron. Patients with low iron stores before surgery, with significant postoperative anaemia the day after surgery, or both showed particular benefit of i.v. over oral iron, thus supporting the use of FCM in postoperative patient management.

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**Authors’ contributions**

E.B.: substantial contribution to conception and study design, preoperative visit (pre-selection and signed Consent), data analysis, and writing up of the first draft of the paper. L.M.: study design, patient recruitment and data collection, data analysis, and writing up of the first draft of the paper. R.A.: patient recruitment and data collection, revising the draft critically, and final approval of the version. J.M.: 30 day postoperative visit, EQ5 TEST, 6 WMT, Barthel evaluation, revising the draft critically, and final approval of the version. M.T.: 30 day postoperative visit, EQ5 TEST, 6 WMT, Barthel evaluation, revising the draft critically, and final approval of the version.

**Declaration of interest**

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