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

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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 $\geq$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.

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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.[4–10] 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.[19] There is a high risk of postoperative anaemia, even among preoperatively non-anaemic patients.[15 20]

Apart from blood loss, inflammatory processes associated with surgery can substantially affect Hb levels via impairment of iron homeostasis.[21 22] 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.[22] Accordingly, postoperative anaemia in lower limb arthroplasty has often a multifactorial history of preoperative anaemia (~25%),[3] blood loss (~30% of volume),[23] and iron deficiency. Thus, rapid iron substitution, as recommended for preoperative anaemia management,[24–26] should also be considered after operation.[26–28]

Although, depending on the timescale before surgery, oral iron is suggested for preoperatively anaemic patients with absolute iron deficiency,[24–26] oral iron showed no benefit over placebo in anaemic patients after lower limb arthroplasty.[29] 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.[30] Even in iron-deficient patients without established anaemia, i.v. iron improved physical performance and cardiac functional class.[31] Thus, postoperative anaemia treatment with i.v. iron might not only reduce RBC requirements but also improve performance, rehabilitation, and outcomes.[32]

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-anaemia 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 amenorrhoea 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)×[target Hb (13 g dl^{-1})−current 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,