Intravenous ferric carboxymaltose versus oral ferrous sulfate replacement in elderly patients after acute non-variceal gastrointestinal bleeding (FIERCE): protocol of a multicentre, open-label, randomised controlled trial

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ABSTRACT

Introduction Acute gastrointestinal bleeding (GIB) is a life-threatening emergency with a critical economic burden. As a result of bleeding, anaemia often requires intravenous or oral iron supplementation. Elderly patients are even more prone to untoward outcomes after hospital discharge if iron supplementation is inefficient. There is a gap in current guidelines on which supplementation route clinicians should choose. We aim to investigate the effect of one dose of intravenous iron therapy versus 3-month oral iron administration on anaemia in an elderly population.

Methods and analysis The FIERCE study is an open-label, randomised controlled, two-armed trial. At least 48 hours after the acute non-variceal GIB treatment, patients will be recruited in participating centres. A random sequence generator will allocate the participants to group A (intravenous ferric carboxymaltose, 1000 mg) or group B (oral ferrous sulfate (FS), ca. 200 mg every day) with an allocation ratio of 1:1 on the day of the planned discharge from the hospital. Randomisation will be stratified for participating centres and the need for transfusion within the same hospitalisation before recruitment to the trial.

Quality of life assessment, functional measurement and iron repletion. 4

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study with a randomised controlled, open-label, two-armed design will provide type A evidence concerning the route of iron supplementation in elderly patients with acute non-variceal gastrointestinal bleeding.

⇒ Patients will be continuously monitored during hospitalisation and the 3 months follow-up period.

⇒ Data will be handled by an Independent Data Management Board.

⇒ Providing intravenous iron to study participants requires substantial financial and human resources.

⇒ The estimated sample size of 570 participants may extend the study period by years.

INTRODUCTION

Acute gastrointestinal bleeding (GIB) is a life-threatening emergency with a critical economic burden that requires frontline medical care. 1 Anaemia affects 25% of the population, and iron-deficient anaemia (IDA) is its most common form, accounting for half of all cases. 2 Recent evidence suggests that the so-called restrictive transfusion strategy (starting red blood cell transfusion at a lower haemoglobin (Hb) threshold, eg, 70–80 g/dL) is the safest and most effective in GIB to treat anaemia. 3 However, most patients with significant gastrointestinal blood loss will develop a degree of IDA regardless of the blood transfusion, which needs post-transfusion reassessment and iron repletion. 4

Patients with IDA either have one to six intravenous iron infusions or receive 3 months of oral iron supplementation.
Oral supplementation is simple, with a recommended dose of 100–200 mg of elemental iron once a day. Nevertheless, 70% of patients report oral iron’s gastrointestinal side effects, leading to poor compliance and adherence. Intravenous iron needs trained medical staff and close monitoring, available on the GIB index admission. Intravenous iron replacement may be expensive, but fewer doses are needed, and its gastrointestinal side effects are less frequent than oral iron. Besides, it results in quick restoration (3–6 weeks) of iron stores, a faster improvement of QoL, and can guarantee adequate iron replacement in the least compliant patients. Based on the current guideline, oral iron should be used as first-line treatment; however, intravenous iron should be considered in case of significant bleeding and lack of compliance. There is no information on which approach clinicians should choose in the elderly (>65 years), potentially multimorbid patients.

Based on our systematic search conducted on 15 January 2021, we identified two randomised controlled trials (RCTs) comparing intravenous to oral iron administration after acute GIB. In the article of Bager et al, the baseline anaemia was not that marked in either group (10.1 g/dL in oral and 9.7 g/dL in the intravenous group), the dose of intravenous ferric carboxymaltose (FCM) was not the recommended (1500–2000 mg). Participants had very few comorbidities with a median Charlson comorbidity index of 1 (range 0–4). In the open-label RCT of Ferrer-Barcelo et al, patients with significant comorbidities were excluded, and controls received only 6 weeks of oral FS. Unsurprisingly, 40% of the oral group did not reach the normal Hb levels (≥12 g/dL in women and ≥13 g/dL in men) at the end of the study.

From the reported outcomes of these two RCTs, we can conclude that intravenous supplementation is helpful in the quick replenishment of iron stores. In the Bager et al RCT, it was even shown that with a lower dose of oral (200 mg/day, given for 3 months) and intravenous (1000 mg) iron, the Hb level can reach its normal value. However, because of the slow Hb level increase with oral iron, elderly patients are more likely to suffer from the complications of anaemia. A large prospective cohort study, with patients having a mean age of almost 60 years in the moderate anaemic (Hb between 11 and 9 g/dL) group, showed a threefold increase in 30-day hospital readmission rate compared with patients who were not anaemic. In a multicentric, retrospective study, the hospital readmission was 22.6%, while the mortality was 4.6% within the first month from discharge, with a Hb level between 10 and 7 g/dL. Markedly anaemic elderly patients may have an even higher chance of mortality and readmission if their iron stores are not refilled quickly. Currently available RCTs are not shedding light on this important clinical question. We hypothesise that intravenous iron is superior in efficacy and safety compared with oral iron regarding all of our outcomes.

Objective
Our trial’s primary objective (Aim I) is to compare the effect of intravenous iron supplementation and oral iron replacement on mortality, anaemia-associated unplanned emergency visits and anaemia-associated hospital readmissions in elderly patients with acute non-variceal GIB. The secondary aim (Aim II) is to assess FCM’s and FS’s effect on the quality of life and patients’ physical well-being. We will compare (Aim III) the side effects of these two drugs and measure (Aim IV) the repletion of iron stores and H levels. At the end of the trial, a cost-effectiveness analysis (Aim V) will also be carried out.

METHODS AND ANALYSIS
Study design and setting
Our study will be a multicentric, parallel-group RCT with a superiority framework. Haemodynamically stable patients with anaemia will be recruited 48 hours after the acute non-variceal GIB treatment in participating centres. A random sequence generator will allocate the participants to group A (intravenous FCM) or group B (oral FS) with an allocation ratio of 1:1. Randomisation will be stratified for participating centres and the need for transfusion during hospitalisation. Allocation concealment will be maintained. Data analysts will be blinded in the study. The primary endpoint will be the composite outcome of all-cause mortality, anaemia-associated unplanned emergency visit and hospital readmission within 3 months after enrolment.

Initially, the trial will be launched in two academic hospitals (Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary; Fejér County Szent György University Teaching Hospital, Székesfehérvár, Hungary). The leading study site will be the Division of Gastroenterology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary. Other hospitals with internal medicine departments with available endoscopic imaging will also be invited to join our study.

Trial organisation, committee, and boards
This trial’s guarantor is the Hungarian Gastrointestinal Bleeding Study Group from the Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary.

The steering committee (SC) will be led by BE (internal medicine specialist, gastroenterologist). The members will be BT (medical doctor, PhD student), HA (internal medicine specialist, haematologist), IS (internal medicine specialist, gastroenterologist), RH (internal medicine and intensive care specialist, gastroenterologist), EB (gastroenterologist, PhD student), ZS (medical doctor), SV (clinical research specialist) and NF (biostatistical specialist). SC will make the relevant decisions during the study according to participation and dropouts.

The International Advisory Board (ITAB) will include DK and KS, who will provide recommendations to the SC and guidance on strategic matters.
Proper data handling will be ensured by an Independent Data Management Board (IDMB).

**Study protocol development**

The SC and ITAB members created the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.13

The study will be financially sponsored by the Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary. IS (KA-2020-32) and RH (KA-2021-10) received the Grant of the University of Pécs (PTE ÁOK; KA-2020-32 to IS). There was no sponsor involvement in the study design. Sponsors will have no access to the randomisation code and the database generated during the trial.

**Study population**

On each study site, all eligible patients will be offered the opportunity to participate in the trial. After the physician delineates the study design and intervention and provides the patient leaflet, patients should confirm their intention to participate by signing the written informed consent (see online supplemental files 1-2). The flowchart of participants is shown in figure 1.

The inclusion criteria for our trial are:

1. age ≥ 65 years.
2. endoscopically proven acute non-variceal GIB source.
3. 48 hours after the endoscopic diagnosis and/or treatment.

**Figure 1** Flow chart of participants according to the Standard Protocol Items: Recommendations for Interventional Trials 2013 Statement. ECOG, Eastern Cooperative Oncology Group.
4. haemodynamically stable (systolic blood pressure ≥100 mm Hg or/and heart rate <100/min).
5. the discharge of the patient is planned.
6. Hb level <10 g/dL on the day of randomisation.
7. 24 hours after the last transfusion and no need for further transfusion.
8. signed informed consent and patient leaflet.

We will exclude patients with:
1. known hypersensitivity to iron products (mild side effects excluded).
2. previous diagnosis of iron overload (eg, transferrin receptor saturation >50%, ferritin >160 ng/mL for women or >270 ng/mL for men) or disorders of iron utilisation.
3. pregnancy or breastfeeding.
4. diagnosis of iron malabsorption (at the discretion of the attending clinician; eg, severe inflammatory bowel disease, active coeliac disease).
5. chronic end-stage diseases (eg, chronic heart failure—New York Heart Association Classification class 4, liver cirrhosis with Child-Pugh C score, chronic kidney disease (eGFR <30 mL/min/1.73 m²) with or without dialysis, chronic obstructive pulmonary disease (COPD) stage 4, chronic inflammatory disease, malignancies, AIDS).
6. active malignant disease or malignancies under treatment affecting anaemia.
7. liver cirrhosis with known varices at high risk of bleeding (endoscopic features of high risk of variceal bleeding or liver stiffness measured by transient elastography >20 kiloPascal and platelet count <150×10⁹ cells/L).
8. gastrointestinal tract malignancies with high risk of GIB.
9. high risk of poor compliance or no fixed abode.
11. myeloproliferative or lymphoproliferative diseases.
12. anaemia not attributable to iron deficiency (eg, sideroblastic anaemia, aplastic anaemia, haemolytic anaemia, thalassaemia, B₁₂ vitamin or folic acid deficiency or combination of these with IDA).
13. primary coagulation disorders (eg, Glanzmann thrombasthenia, Von Willebrand disease, Haemophilia A, Haemophilia B).
14. the patient will be transferred to another institute after discharge (eg, hospital, senior care centre).

Baseline and follow-up assessments
Each study site will perform baseline and follow-up assessments of participants at baseline, 1 and 3 months±7 days after enrolment to the trial (see figure 2). The medical history, details of the acute non-variceal GIB episode treatment, and the need for transfusion will be recorded. Physical examination of patients, status evaluation, quality of life assessment, functional tests, and laboratory measurements will be completed at baseline and during each follow-up.

Quality of life will be measured with 36-Item Short-Form Health Survey (SF-36) and the FACT-T-fatigue scale. While SF-36 consists of 36 questions arranged in eight domains and focuses mainly on physical and emotional health in the past 4 weeks, FACT-T-fatigue collects specific information about anaemia-associated symptoms in the past week. Both scales correlate with the Hb level and provide reliable information regarding the quality of life.

We will measure 3 essential health indicators for functional tests: the gait speed, the 6-Minute Walk Test (6MWT), and handgrip strength tests to assess and follow-up patients’ functional status. Gait speed will be evaluated on a 4-metre flat walking path. The floor will be marked with tape at 0, 1.5, 5.5 and 7 m. The patient will be asked to start walking, and the investigator will start the stopwatch when the 1.5-m mark is reached. The stopwatch will be stopped when the patient arrives at the 5.5-m sign. Measurement will be performed twice, with 1 min rest between the two tests. We will use the scale published by Middleton et al to interpret the gait speed. The 6MWT will be performed on a 30-m flat walking path. Distance covered over 6 min, the oxygen saturation and heart rate will be measured to evaluate patients’ endurance changes. Handgrip strength will be assessed for both hands, then analysed related to age and anthropometric variables.

The following laboratory parameters will be measured: Hb level, haematocrit, serum iron, serum transferrin, transferrin saturation, soluble transferrin receptor (sTfR) concentration, ferritin level, reticulocyte count, red blood cell count, total iron-binding capacity (TIBC), erythropoietin level, C reactive protein (CRP) level, phosphate level and hepcidin level. Laboratory analysis will be carried out at each study site. The same reference ranges
will be used for the acquired laboratory data to prevent measurement bias.

Experienced side effects of treatment will be noted at baseline and during the 1, and 3-month±7 days visits.

Randomisation
Randomisation will be on the day of the planned discharge from the hospital (if the discharge would be on the weekend, then on the last working day). An IDMB will allocate the participants to group A (IV FCM) or group B (oral FS) with an allocation ratio of 1:1 by using a random sequence generator and randomly varying block sizes between 2 to 6. Randomisation will be stratified for participating centres and the need for transfusion within the same hospitalisation before recruitment to the trial. The allocation sequence will be ensured using sealed envelopes.

Blinding
The FIERCE trial will be an open-label RCT. Masking of physicians carrying out the intervention would decrease the feasibility of the trial since it would require extra personnel monitoring patients after the intravenous interventions. Also, since oral iron leads to stool discoloration, it will not be possible to blind participants on the control arm. However, allocation sequences will be concealed until enrolment to reduce performance bias, and physicians examining participants during the follow-up period will not be aware of the received intervention. Concerning the components of the primary endpoint, detection bias will be minimised, since data will be retrieved from specific authorities besides asking the participants and their relatives. Data analysts comparing the primary and secondary outcomes will also be blinded.

Intervention
The interventions will be initiated after randomisation. Group A will receive one dose, 1000mg of intravenous FCM, on the day of randomisation. In group B, oral iron supplementation will be performed with one FS tablet every day (200mg) for 3 months. Patients receiving antibacterial, quinolones, chloramphenicol, antacids and mineral supplements, bisphosphonates, cholestyramine, dimercaprol, dopaminergic, methyldopa, mycophenolate mofetil, penicillamine, thyroid hormone, trientine, zinc or other drugs that can interact with the orally administered iron, should take the iron 2 hours before the administration of the other drug.

Endpoints
Primary outcome
The primary outcome will be a composite endpoint including all-cause mortality, anaemia-associated unplanned emergency visit and anaemia-associated unplanned hospital admission for any reason assessed within 3 months after the enrolment to the trial. The following reasons will be accepted for emergency visits and hospital readmissions:

Symptoms of anaemia: lethargy, weakness, tiredness, syncope, shortness of breath, reduced exercise tolerance, palpitations, dizziness, angina, chills, difficulty concentrating, bruises, pica and restless leg syndrome. Ishaemic events: acute myocardial infarction, acute stroke, acute kidney injury stage III, acute mesenteric ischaemia and acute peripheral vascular ischaemia. Other complications: acute exacerbation of COPD, acute heart failure and falls.

Before each follow-up period, the participants or their relatives will be contacted via email, letter or phone to check if the primary endpoint was reached. If one of the outcome components is reached, the trial will be closed for that patient. Data regarding mortality will be cross-referenced in the Civil Registration Database. The National Health Insurance Fund Administration and Central Administration of National Pension Insurance will be interrogated for unplanned emergency visits and hospital readmission.

Secondary outcomes
The secondary endpoints will be the following: after 1 and 3 months to enrolment, we will assess the absolute value and the causes of (1) all-cause mortality; (2) anaemia-associated unplanned emergency visits; and (3) anaemia-associated unplanned hospital readmission. 1 and 3 months±7 days after receiving the treatment, we will evaluate the (4) changes in quality of life measured with the SF-36 and EuroQol five-dimensions-5 levels (EQ-5D-5L) questionnaire from baseline; (5) changes in gait speed from baseline; (6) changes in 6MW from baseline; (7) changes in handgrip strength from baseline; (8) normalisation of the Hb level (percentage of participants with Hb levels ≥12 g/dL in women and ≥13 g/dL); (9) absolute changes in Hb level, haematocrit, serum iron, serum transferrin, transferrin saturation, sTfR concentration, ferritin level, number of reticulocytes, number of erythrocytes, TIBC, erythropoietin level, CRP level, phosphate level and hepcidin level; (10) discontinuation of the treatment due to adverse events; (11) adherence to the oral treatment measured by the Medication Adherence Rating Scale (MARS) scale; and (12) cost-effectiveness.

Data collection and management
Participants will be provided consecutively with an identification number. Data collection will be carried out continuously on predefined forms (see online supplemental files 3-5). Questionnaire A will be completed on the day of randomisation. Questionnaire B will be filled out during each follow-up visit. The completion of Questionnaire C has to be carried out at baseline and also during each follow-up visit. Participants’ identification numbers and personal information can only be available for those involved directly in the research and stored and locked separately from other data. Deidentified information after data collection will be entered in Electronic Case Report Forms (eCRF). The principal investigator will ensure the accuracy, legibility, and completeness of


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the data in the eCRF. Information from the completed eCRF will be validated in four steps under the coordination of the IDMB. Any missing data will be referred back to the principal investigator and documented for each participant.

Safety and adverse events
Participants receiving the intravenous iron will be supervised during and 30 min after the treatment to manage potential allergic reactions. If hypersensitivity reactions, intolerance or paravenous leakage are observed, the infusion must be interrupted immediately. The most commonly anticipated adverse events due to FCM are hypophosphataemia, headache, dizziness, flushing, hypertension, nausea and infusion site reaction. Phosphate levels will be measured during the follow-up period. If the phosphate level is <1.5 mg/dL and the patient is experiencing increased fatigue, we will provide intravenous phosphate infusions. Oral iron administration is most associated with gastrointestinal side effects, which can be the following: constipation, diarrhoea, nausea, abdominal pain, dark stools, vomiting and heartburn.

Patients showing a less than 1 g/dL increase in the Hb level on the first-month visit will receive a rescue iron infusion with 1000 mg of FCM on both study arms.

After detailing the intervention-related adverse events on a separate form, investigators (medical doctors) will refer it to the SC. After the SC confirms the adverse events’ realness, those will be reported to the relevant institutional and national ethics committee (http://www.ett.hu/tukeb.htm).

Withdrawal from the study
Additional treatments will be accepted during the trial.

Study participants, investigators and IDMB can submit a recommendation for dropouts from the per-protocol analysis. All requests will be filed. Based on the received information, the SC can decide to exclude the patient from the per-protocol analysis if the deviation from the protocol is related to the intervention or if it influences the outcome. Automatic dropout of the study participants shall be ordered if: (1) severe adverse reactions are observed; (2) the dose of administered intravenous iron is less than 80% of the planned total; (3) rescue intravenous iron is needed; (4) rebleeding occurred or transfusion was needed; (5) the participant took extra oral iron supplementation (besides multivitamins); and (6) withdrawal of consent at any point.

Sample size calculation
Available data in the literature regarding the differences in the investigated endpoints and elderly patients are scarce. Therefore, we performed a sample size calculation using data from the Hungarian Gastrointestinal Bleeding Registry collected between 2020 December and 2022 August. Post-hoc analysis of all patients who fit our current inclusion criteria and received oral iron at discharge (20 patients) resulted in a 20% occurrence for our primary outcome within 3 months. Reasons for mortality (20/3) and readmission (20/1) were related to ischaemic events. The assessed effect size is similar to already published data. A cohort analysis with elderly patients (>65 years) showed a 4.5% mortality rate for the whole population and a 32% 30-day readmission rate with anaemia. Considering that 28% of that cohort had malignancy and authors assessed all causes of readmission, a 15%–20% lower rate for unplanned rehospitalisation due to anaemia could be imagined if the iron stores are not replenished fast enough. Also, another study showed that when elderly patients are discharged with moderate or severe microcytic anaemia, the 3-month mortality rate can reach 8% (without excluding patients with cancer—22% of the cases).

Based on the RCT of Bager et al., participants receiving intravenous iron had normalised Hb levels after 1 month. Data are lacking about the effect of intravenous iron on the investigated outcomes. However, results from other study populations found a 5% rate of anaemia-related events leading to hospitalisation only with intravenous iron and 0% mortality (two studies with small sample sizes). Due to unlimited data, we assumed that intravenous iron could result in at least a 50% risk decrease (to 10%) after non-variceal GIB since it could result in a quicker haematopoeisis, preventing ischaemic events.

With a 30% dropout rate, using a power of 80% and a significance level of 5% (two-sided $\chi^2$ test) to measure the treatment effect, we calculated a sample size of 570.

Statistical analysis
For all outcomes, we will carry out a per-protocol analysis (regarding the participants that finished the study as the protocol requires) and an intention-to-treat analysis (for all the patients that received the intervention, excluding study withdrawals). In the final analysis, we will favour intention-to-treat analysis over per-protocol. For the primary endpoint, we expect no missing values. The Last-Observation-Carried-Forward method will be implemented to handle missing data regarding the secondary outcomes.

Descriptive statistics with count and percentage will summarise the patient’s baseline and disease characteristics. Continuous variables (as a central tendency with a measure of dispersion) with the changes from baseline to follow-up periods and end-of-trial visits and dichotomous variables (with absolute and relative frequencies) will also be reported. To compare continuous variables, we will use the $t$-test or Mann-Whitney test. The $\chi^2$ or Fisher’s exact test will be applied for dichotomous outcomes. Survival analysis (with Kaplan-Meier and Cox regression) is also planned to be carried out. Results will be considered statistically significant if the p value is <0.05.

We will compare subgroups of patients based on the related cause for the following secondary outcomes: all-cause mortality, unplanned emergency visits and unplanned hospital admission.
The R programming language (R Core Team, 2019, Vienna, Austria, R V.4.1 or later version) will be used for statistical analysis.

Cost-Effectiveness analysis
A cost-effectiveness analysis will be performed to evaluate the impact of FCM on our primary outcome and QoL (measured with EQ-5D-5L). For this, we will calculate the incremental cost-effectiveness ratio (ICER): incremental costs (all healthcare sector-related costs—e.g., interventions, resources, consumables—collected from financial records) divided by incremental effectiveness (number of events for the primary outcome, quality-adjusted life years). We will compare the ICER to the Hungarian threshold value.36

Patient and public involvement
Two patients (JF, RA) from the Division of Gastroenterology, University of Pécs, Pécs, Hungary were included in the protocol development phase. Both of them would have been eligible for the study. After introducing them to the aim of our trial, primary outcome and protocol, we asked them to read the informed consent and patient leaflet. They found the written documents understandable and informative. Both patients found our clinical question highly relevant. If possible, both of them would choose intravenous iron therapy, as they were already familiar with oral iron therapy’s gastrointestinal side effects. They were not against the functional tests, QoL questionnaires and laboratory measurements; they highlighted the importance of the follow-up visits.

Trial duration
We plan to start patient enrolment on 1 September 2023, and the expected completion date (including the 3-month follow-up) is 31 December 2027.

Protocol amendments
This is the first version of the protocol, completed on the 3 of November 2021. If protocol modifications are needed, we will update the online version on clinicaltrials.gov. Major modifications have to be approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council. Deviations from the original protocol will be mentioned in all future publications.

ETHICS AND DISSEMINATION
The study will follow the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines. The protocol has been approved by the Scientific and Research Ethics Committee of the Medical Research Council (46395-5/2021/EÚIG).

Hungarian and foreign centres can participate in patient enrolment. We will provide authorships based on the criteria set by the International Committee of Medical Journal Editors. One member from each centre after every 25 patients will be nominated as a coauthor.

After the trial is completed, we will present its results at international and national conferences and publish them in peer-reviewed journals. On reasonable request, we will provide the data generated and/or analysed during the trial. Supplementary materials will report all results supporting the trial’s findings.

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