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Study protocol for a multicentre, 2×2 factorial, randomised, controlled trial evaluating the interest of intravenous iron and tranexamic acid to reduce blood transfusion in hip fracture patients (the HiFIT study)

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ABSTRACT

Introduction Blood transfusion and anaemia are frequent and are associated with poor outcomes in patients with hip fracture (HF). We hypothesised that preoperative intravenous iron and tranexamic acid (TXA) may reduce the transfusion rate in these patients.

Methods and analysis The HiFIT study is a multicentre, 2×2 factorial, randomised, double-blinded, controlled trial evaluating the effect of iron isomaltoside (IIM) (20 mg/kg) vs placebo and of TXA (intravenously at inclusion and topically during surgery) versus placebo on transfusion rate during hospitalisation, in patients undergoing emergency surgery for HF and having a preoperative haemoglobin between 95 and 130 g/L. 780 patients are expected. The primary endpoint is the proportion of patients receiving an allogenic blood transfusion of packed red blood cells from the day of surgery until hospital discharge (or until D30 if patient is still hospitalised). Enrolment started on March 2017 in 11 French hospitals. The study was stopped between July 2017 and August 2018 (because of investigation of serious AEs with IIM in Spain) and slowed down since March 2020 (COVID-19 crisis). The expected date of final follow-up is May 2022. Analyses of the intent-to-treat and per-protocol populations are planned.

Ethics and dissemination The HiFIT trial protocol has been approved by the Ethics Committee of Comité de Protection des Personnes Ouest II and the French authorities (ANSM). It will be carried out according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The results will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals. The HiFIT trial will be the largest study evaluating iron and TXA in patients with HF.

Strengths and limitations of this study

- The HiFIT study will be the largest randomised controlled trial to evaluate both intravenous iron and tranexamic acid (TXA) in patients with hip fracture (two to four times the number of patients of previous studies); it should have sufficient power to detect serious adverse events (AEs).
- The administration of TXA will be performed through both intravenous and topic routes, which may improve efficacy and tolerance.
- HiFIT study will evaluate the benefit of iron and of TXA on rehabilitation at 3 months.
- All serious AEs are reported using standardised forms and adjudicated by an independent expert committee.
- Recruitment in the study has been hampered by external events (the study was suspended for 1 year because of serious AEs declared in Spain with iron isomaltoside and slowed down since March 2020 because of the COVID-19 crisis).

Trial registration number clinicalTrials.gov identifier: NCT02972294; EudraCT Number 2016-003087-40.

INTRODUCTION

Hip fractures (HFs) are very common, with an incidence of approximately 1.6 million cases per year worldwide.[1] This high incidence is anticipated to grow rapidly in the next decades, driven by population ageing. By the year 2040, the estimated annual healthcare costs will reach $9.8 billion in the USA.[2] Currently, HFs are responsible for

79 000 hospitalisations per year in France, with an average length of hospital stay of 12.7 days. It is estimated that more than 16% of the French population will be over 85 years old in 2020 and 24% in 2050. Moreover, age is a major risk factor for perioperative mortality, particularly after HF.[3] Hospital mortality rate after HF is 3.6% in a recent French cohort of more than 319 000 patients,[4] and the mortality rate within 1 year is as high as 36% despite aggressive management including early surgery and rehabilitation. Among modifying factors associated with poorer outcome following HF, anaemia is the most prevalent.[5] Indeed, anaemia is very frequent on admission for HF, affecting up to 45% of patients, with a mean haemoglobin (Hb) level of 125±2 g/L.[6] This high prevalence of preoperative anaemia together with blood losses, secondary to the fracture itself and to the surgery, are responsible for a high blood transfusion rate (approximately 40%–50% of patients).[5 6] Both anaemia and blood transfusion are associated with poor outcomes, including increased mortality. In a recent systematic review, preoperative anaemia was associated with a risk ratio (RR) for mortality of 1.64, 95% CI (1.47 to 1.82), p<0.00001 and blood transfusion with a RR of 1.53 (1.35 to 1.75), p<0.00001.[5] In addition, blood is a scarce and expensive resource and its use should be limited as much as possible.[7] There is therefore a need to treat this anaemia and/or to prevent the decrease in postoperative haemoglobin. For this purpose, intravenous iron may be proposed as in patient blood management programmes,[8–10] even using short-term perioperative treatment.[11] Some non-randomised, mainly retrospective, studies have shown that perioperative intravenous iron was able to reduce blood transfusion (ie, the number of patients transfused and the number of units per patient) in patients with HF (from 48.8% to 32.4%, p=0.001, in a pooled analysis of 5 studies including 1361 patients).[12] A small (n=200 patients), single-centre, randomised trial comparing intravenous iron (600 mg of iron sucrose) to standard of care showed no difference in transfusion rate.[13] Another randomised controlled trial (RCT), evaluating the same dose (600 mg), given preoperatively and postoperatively, showed a significant increase in reticulocyte count (the primary endpoint) without significant reduction in transfusion rate.[14] At last, in a study of 306 patients with HF, 1 g of ferric carboxymaltose with or without erythropoietin did not reduce the need for transfusion, but improved recovery from postoperative anaemia.[15] There is thus no definitive data showing a benefit of giving intravenous iron preoperatively in patients with HF. New iron formulations allowing to deliver high doses of iron in one short intravenous injection (as much as 20 mg/kg, maximum 2000 mg, over 30 min for iron isomaltoside (IIM)) are efficient to reduce postoperative anaemia when given on the day of surgery,[16] when smaller iron doses (ie, 600 mg) were ineffective in patients with HF.[17] In addition, iron deficiency is responsible for fatigue and muscular weakness, which may be corrected by intravenous iron.[18–22] This could be particularly important for this older population, for whom postoperative rehabilitation is of crucial importance.

Another way to reduce blood transfusion would be to reduce perioperative bleeding. Tranexamic acid (TXA) is efficient for this purpose both in trauma[23] and in elective surgery patients.[24 25] However, when we designed this study, there were only two randomised trials investigating the interest of TXA in HFs, and they were not conclusive probably because of a lack of power.[26] To date, eight new RCTs evaluate the interest of intravenous TXA, the largest one included only 138 patients and was negative.[27] Two recent meta-analyses report a significant reduction in blood transfusion using intravenous TXA in patients with HF; however, the heterogeneity is important (I^2=60%) and the sample size is too small to evaluate the tolerance of this treatment.[28 29] In addition, use of intravenous TXA could be limited in this population of frail patients and topical use of TXA appears to be an effective and safe alternative, at least in major orthopaedic surgery patients.[30–32] It has also been reported that the combined use of intravenous and topical TXA may be superior to intravenous alone in orthopaedic surgery patients.[33 34]

Although HF is a very frequent pathology, with a high burden of care, few data are available that focus on the management of perioperative anaemia in this context. The interest for perioperative blood management[8 35] has recently increased, thanks to better recognition of the adverse effects of blood transfusion, better understanding of iron metabolism, new intravenous iron drugs and a renewed interest in former medications (ie, TXA).[8 36] We therefore propose to evaluate the interest of intravenous iron and TXA to reduce blood transfusion in patients with HF, through a 2×2 factorial design study.

METHODS AND DESIGN

Hypothesis and study objectives

We made three hypotheses for this 2×2 factorial randomised trial in patients undergoing emergency surgery for HF with a preoperative Hb between 95 and 130 g/L:

1. That a preoperative infusion of 20 mg/kg of IIM will reduce the need for red blood cell transfusion during the hospital stay after surgery (or until D30 if the patient is still hospitalised).
2. That the administration of TXA (intravenously preoperatively and topically during surgery) will reduce the need for red blood cell transfusion during the hospital stay after surgery (or until D30 if the patient is still hospitalised).
3. That there will be no interaction between the two treatments.

Trial design

This is a multicentre, 2×2 factorial, randomised, double-blinded, controlled study of parallel groups. Two arms will be compared: IIM versus its placebo (P_{IIM}) and TXA versus its placebo (P_{TXA}). Patients will be included in four

groups (see figure 1). This study protocol is composed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. The SPIRIT checklist is provided in the supplementary files as well as the full study protocol (see online supplemental file 1).

Study population

Patients hospitalised for a HF and scheduled for HF surgery will be approached by the study investigators as soon as possible. Eligibility criteria are presented in table 1. Very dependent patients are not eligible (corresponding to a GIR 1 or 2 class). The GIR classification[37] (from the French 'autonomy gerontology groups iso-resources') classifies patients' dependency from 1 (very dependent) to 6 (autonomous).

Setting

The study involves 13 French public, university and private hospitals.

Treatment allocation

Randomisation will be performed using a web-based system (Clinsight software). Patients will be randomly assigned in a 1:1:1:1 ratio to one of the four groups (figure 1) using a minimisation algorithm based on four determinants:

- HF type (extracapsular or intracapsular).
- Chronic use of anticoagulant/antiaggregant therapy (excluding salicylic acid).
- Time to hospital admission (<48 hours or ≥48 hours from HF).
- Centre.

Intervention

Study medications will be infused as soon as possible after randomisation as follows:

- IMM (iron isomaltoside, MONOFER, Pharmacosmos, Denmark) or P_{IIM} (placebo IIM) will be infused as a 30-minute bolus infusion, after dilution of 20 mg/kg or placebo in NaCl 0.9%. An 'open' nurse will dilute 20 mL of IMM/P_{IIM} in 40 mL of saline, in 60 mL syringe. The volume to be administered will be calculated according to the patient's weight (automatically calculated in the eCRF). This volume is calculated using the following formula: Administered volume (mL)=patient weight (kg)/2. The infusion rate (mL/h) corresponds to patient's weight (in order to infuse the solution over a 30-minute period).
- One gram of TXA (tranexamic acid, EXACYL, Sanofi-Aventis, France) or an identical volume of P_{TXA} will be infused as a slow bolus infusion after dilution in 50 mL of NaCl 0.9% followed by a continuous infusion using an automated syringe (1 g or placebo in 48 mL of NaCl 0.9%) over 8 hours (infusion speed: 6 mL/hour).
- Three grams of TXA or P_{TXA} will be administered topically during surgery using two 60 mL syringes. During surgery, the anaesthetic nurse will dilute 30 mL of TXA or placebo in a saline bag of 100 mL (NaCl 0.9%). The surgeon will draw, through the saline bag in sterile conditions, two syringes of 60 mL of the solution for topical administration.
  - The first syringe will be topically administered just before implantation of the orthopaedic device by the surgeon who will wait at least 5 min before continuing the surgery.
  - The second syringe will be used at the end of surgery, just before skin closure. The study medication (60 mL) will be spread over the wound; the suction drains, if present, will not be open during the first 5 min following application.

Nurses at each participating centre will learn to identify hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions following iron injection, and resuscitation material as well as medical teams are available at any time with no delay in case of emergency at all the study centres.

Blinding

Because IIM is a dark brown solution easily distinguishable from placebo, 'open' nurses are required for study medication preparation and infusion, they will not be involved in data collection, in study assessments or in patient care. Preparation of study medication (open-label) will be performed in a different room so that the physician or nurses in charge cannot observe it. In addition, a curtain will be used to cover the syringe and a jersey will cover the injection site and the intravenous line from the patient's view. At the end of infusion, the intravenous line will be flushed using 10 mL of saline before removing the curtain so that no dark solution remains in the intravenous line.

TXA and P_{TXA} look the same, so that no blinding material is needed. During surgery, an anaesthetic nurse, not involved in patient's care, will prepare the solution, so that the surgeon and the anaesthetist cannot see the treatment vials. Thus, all physicians and personnel involved in patient's care will remain blind to the treatment received and the patient too.

Procedures

Patients hospitalised for a HF and scheduled for hip surgery will be approached by the study investigators as soon as possible. After having verified the presence of all inclusion criteria and the absence of exclusion criteria, complete oral and written information about the study will be given to each patient (the patient's consent form is presented in online supplemental file 2). Inclusion will be effective as soon as the patient has signed the consent form after a sufficient reflection period. In case of inability for the patient to consent, the study investigator will inform the patient's next of kin in order to obtain his/her consent, as soon as able, the patient will have to be informed and to sign a consent himself to continue his study participation. If patient cannot consent and patient's relatives cannot be contacted in time, the study investigators may enrol the patient through an emergency procedure. In the latter two cases, investigators inform

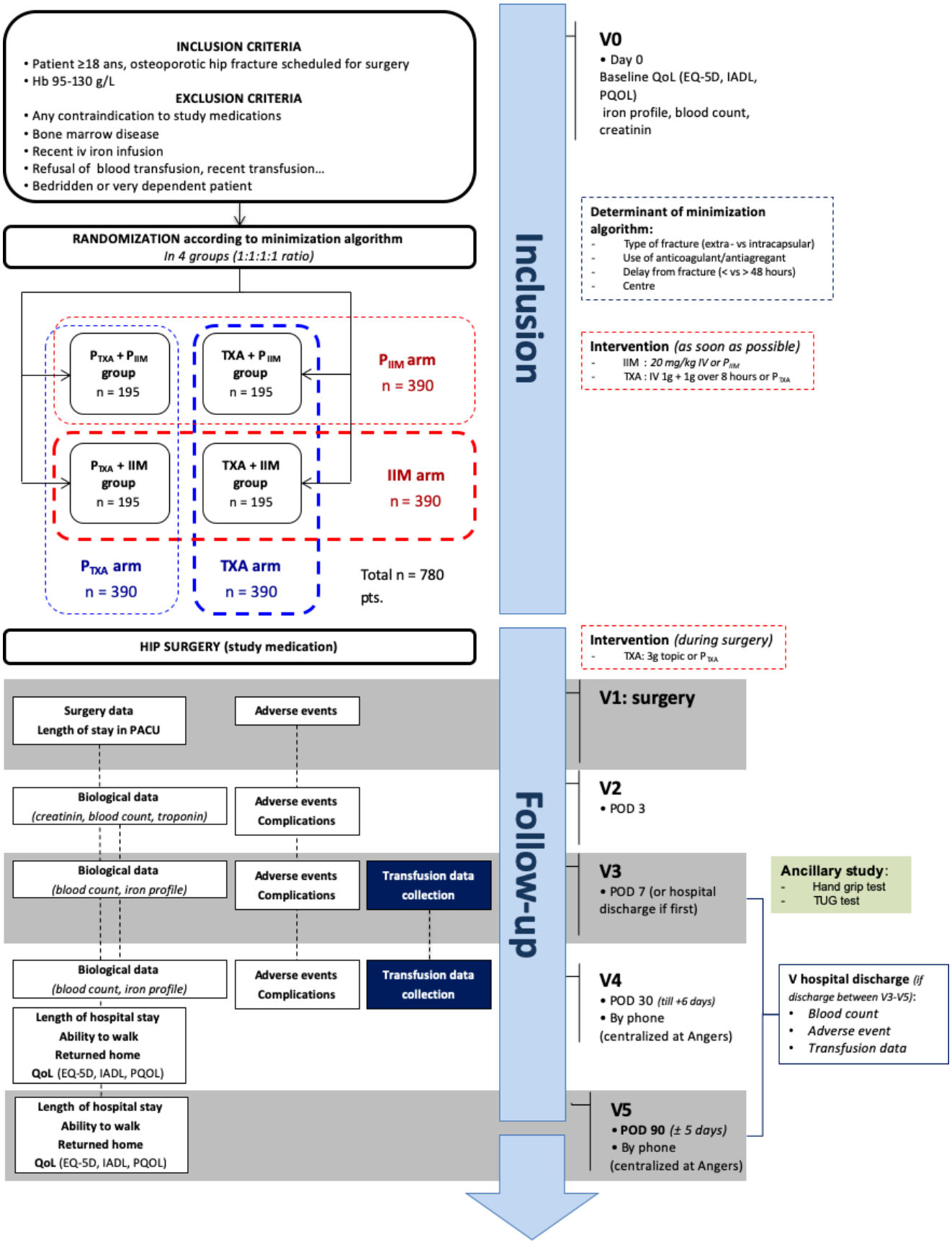

Figure 1 HiFIT study overview. Iron profile includes blood tests for ferritin, transferrin saturation and C reactive protein. EQ-5D, EuroQol 5 Dimensions; IADL, Instrumental Activities of Daily Living; IIM, iron isomaltoside; PQoL, perceived QoL; P_{IIM}, placebo for IIM (=saline); P_{TXA}, placebo of TXA (=saline); POD, postoperative day; pts, patients; QoL, quality of life; TUG, timed up and go test; TXA, tranexamic acid; V, visit.

Table 1 Patient's eligibility criteria for the HiFIT study

Inclusion criteria	Patient ≥18 years old, hospitalised for an osteoporotic HF (eg, femoral neck fracture, subtrochanteric or intertrochanteric fracture) scheduled for a HF surgery.
	Preoperative haemoglobin between 95 and 130 g/L (95≤Hb≤130 g/L).
	Signed informed consent of the patient or his/her next of kin or emergency procedure for inclusion.
Exclusion criteria	Bone marrow disease or ongoing treatment (such as chemotherapy, etc), which could interfere with bone marrow erythropoiesis.
	Known allergy or contraindication to study drug.
	Uncontrolled hypertension.
	Recent intravenous infusion of iron (within 1 week). (Use of oral iron is not an exclusion criteria.)
	Blood transfusion within 1 week before inclusion or preoperative blood transfusion already scheduled, any patient who cannot be transfused or has refused consent for a blood transfusion.
	Bedridden or very dependent patient (equivalent to GIR 1 or 2 class).
	Non-affiliation to French healthcare coverage. Adult patient protected under the law (guardianship).
	Pregnancy.

The GIR classification[37] (from the French 'autonomy gerontology groups iso-resources') is used to classify patients' dependency from 1 (very dependent) to 6 (autonomous).
Hb, haemoglobin; HF, hip fracture.

patient and research the patient's consent (as soon as the health status allows).

The choice of anaesthesia type (general and/or loco regional) will be left to the discretion of the attending physician. Management of perioperative anticoagulation therapy, antiplatelet agent, antibioprophylaxis and thromboprophylaxis will follow the recommendations of the French Society of Anaesthesiology (SFAR, Société Française d'Anesthésie Réanimation).[38] The use of low molecular weight heparin preoperatively for thromboprophylaxis is recommended (eg, enoxaparin 40 mg, in the absence of renal insufficiency).

Attending physicians and research personnel will remain blind to the treatment administered.

Seven visits are scheduled for all patients enrolled in the study (see figure 1). All data, anonymised, will be collected in an electronic clinical research form (eCRF). A detailed description of the procedures is available in online supplemental files 1.

Outcome measures

Primary endpoint

The primary endpoint will be the proportion of patients receiving an allogenic blood transfusion of packed red blood cells from the day of surgery until hospital discharge (or until D30 if the patient remains hospitalised).

Recommendations for red blood cells transfusion will be made in each centre based on the FOCUS study[39] and the 'Haute Autorité de Santé' (HAS) recommendations on transfusion.[40] The recommended transfusion trigger will be a Hb level below 80 g/L or symptoms of anaemia (chest pain thought to be cardiac in origin; congestive heart failure; unexplained tachycardia or hypotension; signs of volume depletion unresponsive to fluid replacement).

The occurrence of any transfusion of packed red blood cells, fresh frozen plasma or platelets as well as the number of units and the date of transfusion will be recorded in the transfusion file of the patient. The recording of transfusions on a patient's chart is a legal obligation. Therefore, no missing data are anticipated.

Secondary endpoints and ancillary study

- The proportion of transfused patients and the number of transfused units per patient (including red blood cells, fresh frozen plasma and platelets) on postoperative day (POD) 3, POD7, hospital discharge and POD30.
- Postoperative Hb levels and anaemia rate (WHO definition: Hb<130 g/L for men and <120 g/L for women) on POD3, POD7, hospital discharge and POD30.
- Perioperative blood loss will be estimated according to the following published formula[41]: (HtD0–HtD3)*TBV+number of RPBC transfused unit×200 mL. Ht=haematocrit, TBV=total blood volume (70 mL/kg in men and 65 mL/kg in women).
- Postoperative iron deficiency (defined as a ferritin <100 µg/L or <300 µg/L together with transferrin saturation <20%, according to the FAIR-HF study definition[42]); on D0, POD7 (or hospital discharge if it happens first) and POD30.
- Postoperative rehabilitation on POD30 and POD90, as follows:
  - Number of hospitalisation days after surgery.
  - Proportion of patients returned at home (or at their previous place of living).
  - Proportion of patients able to walk a distance of 10 feet without assistance (the same criteria used in the FOCUS study).[39]

- Quality of life (QoL) using the variation of EQ-5D score[43] from admission to POD30 and POD90 and on perceived QoL with a single overall item from PQoL scale[44] from admission to POD7 and POD90.
- Dependencies of patients for daily life activities using the variation of IADL test (Instrumental Activities of Daily Living)[45] from inclusion to POD90.
- Safety will be evaluated according to:
  - Death rate from all causes until POD90.
  - Rate of adverse events (AEs) until POD90 including the following clinical complications: vascular events (all kinds of cerebrovascular accidents, acute coronary syndrome (defined by an increase in troponin with or without EKG modifications), new venous thrombosis, arterial embolism), heart failure, renal failure (assessed by a creatinine level according to RIFLE criteria),[46] infectious complications (pneumonia, urinary tract infection, surgical site infection, bloodstream infection and so on), any anaphylactic reaction and severe anaemia defined as a Hb<80 g/L. Troponin and creatinine concentrations will be measured on POD3.

An ancillary study will be performed in selected centres to assess if IIM and/or the correction of iron deficiency will improve postoperative functional rehabilitation of patients on POD 7 or hospital discharge whichever happens first, by measuring:

- Maximum strength of the hand and forearm muscles assessed by the Hand Grip Strength test.
- Muscular fatigability assessed as the variation of strength measured at the first and the third attempt of the Hand Grip Strength test.
- Level of locomotion and balance assessed by the Timed 'Up and Go' test.[47]

Monitoring

A clinical research associate mandated by the study sponsor will ensure the successful completion of the study, the collection of data, documentation, recording and report, in accordance with the Standard Operating Procedures implemented in the Angers Hospital and in accordance with Good Clinical Practice and the laws and regulations.

The following items will be reviewed:

- Signed informed consent.
- Compliance with the study protocol and procedures that are defined.
- Quality of data collected in the case report form: accuracy, missing data, data consistency with the documents 'source' (medical records, appointment books, original lab results and so on).
- Study drug boxes stored at the pharmacy.

After monitoring data on site, an automated check of the data entered will be made by the data management team based on the data validation plan signed by the coordinating investigator. Detected errors will lead to the issuance of requests for information and electronic correction.

Study oversight

Study sponsor is the Centre Hospitalier Universitaire d'Angers. Experienced research staff monitor the study for quality and the integrity of data in all the participating centres. Serious AEs and unexpected related or possibly related serious events are to be reported to the sponsor within 7 days.

An independent data and safety monitoring board (DSMB) is appointed by the sponsor at the beginning of the study. The DSMB reviews safety issues as the study progresses, with a meeting every 200 patients included. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research.

In addition, an independent adjudication committee of three experts (in anaphylaxis, thrombosis and infectious disease) has been named at the beginning of the study. It will be assembled to review any expected as well as unexpected AEs related to study medication (mainly anaphylaxis and infection for iron; thrombosis and renal failure for TXA). Their report will be available for the DSMB before each meeting. Specific report forms for anaphylaxis, septic and thrombosis AEs are available in the eCRF.

Sample size calculation

We have reviewed the charts of 402 patients operated in 2013 at the CHU Angers. Among them, the transfusion rate was 41%. Considering only the 261 (65%) patients meeting our inclusion criteria, this transfusion rate was 50%. Based on these data and the literature,[5 6 15 39] we expect a transfusion rate of 50% in each placebo arm (P_{IIM} and P_{TXA} arms). We expect an absolute reduction of transfusion rate of 10% for the IIM arm and of 15% for the TXA arm, which were the lowest magnitude of the effects observed for the two drugs in previous studies.[12 26] We hypothesise an absence of interaction between the two drugs. According to these hypotheses, with an alpha risk of 0.05 and a power of 0.8, a bilateral test, the total number of patients needed is 390 per arm (195 per group), representing a total of 780 patients. Because our primary endpoint is short term and easy to obtain (blood transfusion traceability in patient files is required by law), we do not expect any missing data for the primary endpoint. In addition, in case of interaction between the two treatment arms, the study will still have a 0.82 power to detect a difference in transfusion rate from 50% to 35% for TXA versus P_{TXA}.

Statistical analysis

A flow chart of the patients (included or not) and descriptive statistics will be used to describe baseline characteristics as well as the outcome measures of patients in each arm.

All comparisons will be performed first in intention-to-treat analysis (all patients fulfilling the inclusion criteria/exclusion criteria and randomised) and then per-protocol analysis (all patients treated according to their treatment allocation, excluding protocol violations).

Comparability of each arm will be checked, with regard to factors known to influence the transfusion rate (mainly preoperative Hb, history of coronary artery disease, body weight, gender, use of anticoagulation therapy, delay of surgery, type of HF, type of surgery, surgeon experience, preoperative iron deficiency). A site effect will also be checked.

Primary endpoint analysis

The absence of statistically significant interaction between the two study drugs on the transfusion rate will be tested before any further analysis using a fixed-effect logistic regression model. The proportion of transfused patients during their hospital stay will then be compared respectively in IIM versus P_{IIM} and in TXA versus P_{TXA} patients, using a χ^2 test (Fisher's exact test). In case of imbalance between groups (IIM vs P_{IIM} and TXA vs P_{TXA}), an adjusted analysis will be performed.

Secondary endpoints

The absence of statistically significant interaction between the two study drugs will then be tested for secondary endpoints before each comparison. The following parameters will be compared between TXA versus P_{TXA} and IIM versus P_{IIM} groups, respectively, using a χ^2 or a Mann-Whitney test, as appropriate.

* Prespecified subgroup analysis will be performed for the same comparisons with regard to

- Presence or not of anticoagulation/antiaggregant therapy.
- Type of HF (extracapsular or intracapsular) and type of HF surgery.
- Presence or not of iron deficiency at baseline (defined as a ferritin <100 µg/L or <300 µg/L together with transferrin saturation <20%).
- Delay between trauma and surgery (<48 hours or ≥48 hours).

One interim analysis will be scheduled after recruitment of 390 patients; if a significant effect is found at p<0.001, for IIM versus P_{IIM} or TXA versus P_{TXA} comparisons, the study (or one of its arm) will be stopped. In the absence of significant differences, the study will continue, with statistical significance set at p<0.05 (Haybittle-Peto method to keep the alpha risk at 5%).

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

The HiFIT trial protocol has been approved by the Ethics Committee of The Comité de Protection des Personnes Ouest II (number 2016/42, approval date 15 November 2016), by the Agence Nationale de Sécurité du Médicament (ANSM, Number 160 828A-21, approval date 27 December 2016), by the 'Commission Nationale Informatique et Liberté' (CNIL, decision DR-2017-390, approval date 14 December 2017) and by the 'Comité Consultatif sur le Traitement de l'Information en matière de Recherche sans le domaine de la Santé' (CCTIRS, Number 16-716, approval date 29 September 2016). The actual version of the protocol is No. 10.

The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Data sharing

The coordinating investigator will have access to the final study dataset. Data sharing: patient level data and/or full dataset and/or statistical code will be available on request to the corresponding author. Consent was not obtained but the data presented are anonymised and the risk of identification is low and the potential benefits of sharing these data outweigh the potential harm.

Trial status

The trial has already achieved many milestones. After approval by the ethics committee and the authorities, the trial has been registered on clinicaltrial.gov (NCT02972294) on 23 November 2016 and inclusions started on 31 March 2017. The trial has been suspended between 24 July 2017 and 18 July 2018 because of new information about safety regarding the IIM, reported by Spanish System of Pharmacovigilance on 5 July 2017 to the European Medicines Agency. Among 108 reported cases of serious anaphylactic reactions or serious clinical situations related to anaphylaxis/anaphylactic shock, associated with the intravenous administration of any of the iron preparations, 44 were related to administration of IIM. Because this signal was not confirmed elsewhere in Europe, the agencies' recommendations regarding intravenous iron treatments, including IIM, were not modified (neither by the European nor the by the French Medicine Agencies) and the study was authorised to restart. Since mid-March 2020, due to the pandemic of COVID-19 pneumonia, the study recruitment has slowed down dramatically after the inclusion of 245 patients. Two centres remain open for inclusions. End of recruitment is expected in early 2022, with the last follow-up in May 2022 (depending on the evolution of the COVID-19 crisis).

DISCUSSION

Anaemia and blood transfusion are both frequent and are associated with poorer outcome in surgical patients, justifying the concept of patient blood management.[8 35] However, management of perioperative anaemia requires time,[9] which is not available in case of emergency surgery, such as HF surgery. Furthermore, in elderly patients, anaemia (and iron deficiency) is even more frequent.[6] The benefit of giving iron preoperatively to reduce blood transfusion is not proven yet in large randomised controlled study,[48] but may be of great interest in this population of frail patients.[11–13]

TXA has proven its efficacy in many surgeries, including orthopaedic surgery,[24 25] but data are still scarce in

patients with HF, without any definitive data regarding safety.[26 29] In addition, the association of intravenous and topical TXA may be superior, without increase in side effects.[34] The HiFIT trial will be the largest study in patients with HF to evaluate (1) the interest of a preoperative high-dose intravenous iron and (2) the interest of TXA (administered intravenously and topically) on rate of blood transfusion.

The HiFIT study, in its ancillary part, will also investigate the impact of iron deficiency on postoperative strength and recovery, as well as the benefit of treating it. Indeed, iron deficiency is frequent in the elderly, is associated with fatigue and its treatment may be beneficial.[20–22 42] It will also evaluate the impact of these treatments on patients' quality of life after surgery.

The trial encountered difficulties because of numerous external events: 'new events' with IIM requiring 1 year of study suspension and recently the COVID-19 crisis. However, this study should provide definitive information on the interest of two main pillars of patient blood management programmes: high-dose intravenous iron and TXA, in a specific patients' population: the patients with HF.

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