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Imaging intravenous iron in the body

Submission date
01/09/2022

Recruitment status
Recruiting

Registration date
09/12/2022

Overall study status
Ongoing

Last Edited
16/12/2025

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Iron deficiency (lack of iron) is normally treated with oral iron tablets, which deliver a small amount of iron gradually over a number of weeks. In recent years, an alternative treatment based on intravenous iron (i.e. through a 'drip') has become increasingly common. This can be helpful in patients who are unable to take oral iron, or when there is a need for rapid treatment of iron deficiency e.g. before major surgery. In contrast to oral iron, intravenous iron safely delivers a large amount of iron at once. While it is an efficient way of quickly correcting iron deficiency, it is not known where in the body this large quantity of iron ends up. The aims of the study are to establish the kinetics of iron uptake into the heart, liver, spleen, kidney, skeletal muscle and blood after a single intravenous iron infusion.

Who can participate?
Patients aged 18 years and over with anaemia and/or confirmed iron deficiency who are due to receive intravenous iron infusion (Ferinject) as part of their standard clinical care

What does the study involve?
MRI scans and blood samples are taken at baseline (before infusion), and at 3 hours, 2 weeks and 6 weeks after the infusion.

What are the possible benefits and risks of participating?
Blood sample collection may cause some discomfort, bruising or very minor bleeding. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays).

Where is the study run from?
Oxford University's Centre for Magnetic Resonance Imaging (OCMR), which is located on the John Radcliffe Hospital site (UK)

When is the study starting and how long is it expected to run for?
June 2021 to December 2027

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Prof. Samira Lakhal-Littleton, samira.lakhal-littleton@dpag.ox.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
308355

Central Portfolio Management System (CPMS)
52957

Study information

Scientific Title
Study of tissue iron uptake in iron-deficient patients receiving intravenous iron replacement therapy: a prospective observational study (STUDY)

Acronym
STUDY

Study objectives
Intravenous iron, administered as part of standard clinical care, may increase iron levels within non-erythroid organs such as the heart and kidney.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/06/2022, North West - Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048118, +44 (0)20 7104 8222, +44 (0)2071048016; liverpoolcentral.rec@hra.nhs.uk), ref: 22/NW/0172

Primary study design
Observational

Study design
Observational; Design type: Validation of investigation /therapeutic procedures

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Anaemia and/or confirmed iron deficiency

Interventions
This is a prospective, observational, study exploring the kinetics of tissue iron uptake following intravenous iron infusion (Ferinject), received as part of standard clinical care in a group of iron-deficient patients.

SCREENING, RECRUITMENT AND CONSENT
Participants will be recruited from referrals to the Iron Deficiency Management Service (IDMS), part of Oxford University Hospitals NHS Foundation Trust (OUHFT). This service receives referrals from multiple sources across Oxfordshire. Patient referrals will be screened by members of the NHS Clinical team at IDMS to identify potentially eligible participants. Patients who would require intravenous iron as part of their standard clinical care and who are deemed eligible to participate in the study will be sent an invitation letter and patient information sheet. A few days later, a member of the NHS clinical care team at IDMS will contact the patient by telephone to check they have received the information and are happy to be contacted further about the study by a member of the study team. If so, a member of the study team will telephone the patient to explain the study, answer any questions the patients might have, check their eligibility and register verbal consent in their medical notes. They will then arrange for the participant to be given their intravenous iron, as per standard clinical care, by a member of the NHS clinical care team at the Oxford Centre for Magnetic Resonance (OCMR), which is part of the Oxford University Medical Sciences Division, and is physically located on the John Radcliffe Hospital site. A written version of the Informed Consent form will be presented to the participant when they arrive at OCMR on day 1 of the study. Participants will be grouped into four cohorts of three so that all participants in the same cohorts are scanned on the same days. All MRI scans will also be carried out at OCMR.

DAY 1 - BASELINE ASSESSMENTS
Baseline clinical data for each participant:
1. Confirmation against inclusion and exclusion criteria

Baseline MRI scan (for participant #1 in each cohort; up to 3 hours):
1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2* relaxometry of the heart, liver, spleen, blood and skeletal muscle over 3 hours

Baseline MRI scan (for participants #2 and #3 in each cohort; up to 1 hour)
1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2* relaxometry of the heart, liver, spleen, blood and skeletal muscle over 1 hour

Baseline laboratory data:
1. In addition the research team member will collect the participant's demographic information and medical history from their medical notes
2. Haemoglobin, iron, transferrin saturation and ferritin data available from medical notes

Baseline blood samples:
1. Two collected, one as part of standard clinical care, and the other for study investigations to measure serum iron indices and serum markers of tissue iron damage.

Intravenous iron infusion:
1. Administered by a member of the clinical care team as part of standard clinical care

DAY 1- THREE HOURS POST-I.V. IRON INFUSION
MRI scan (up to 1 hour)
1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:
1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

TWO WEEK FOLLOW-UP VISIT (14 days +/-2 days)
MRI scan (up to 1 hour)
1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:
1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

SIX WEEK FOLLOW-UP VISIT (42 days+/-2 days)
MRI scan (up to 1 hour)
1. Cine imaging for cardiac structure and function
2. Tissue characterisation by R1/R2/R2* relaxometry of the heart, liver, spleen, blood and skeletal muscle

Blood samples:
1. One sample collected for study investigations to measure serum iron indices and serum markers of tissue iron damage

DESCRIPTION OF STUDY PROCEDURES
Magnetic resonance imaging (MRI) will be performed on clinical standard MRI scanners in OCMR (at a conventional field strength of 1.5 Tesla for this study). Participants will be grouped into four cohorts of three, so that all participants in the same cohorts are scanned on the same days. Each scan will consist of MRI scanning techniques to assess cardiac structure and function by

Cine MRI and organ tissue characterisation using R1/R2/R2* relaxometry. The average duration of each MRI scan is envisaged to be around an hour. One participant in each cohort will be chosen to have an extended MRI scan at their first visit, lasting up to 3 hours. This extended MRI scan is needed to optimize the parameters for running of subsequent scans that day. All subsequent scans will be a standard duration of about an hour. This will be communicated to the participants clearly in the patient information sheet and again on day 1 when they attend OCMR for their first scan.

Research sample taking: A total of five venous blood samples will be collected from each participant, one as part of their standard clinical care, and four for study investigations. Each time, a qualified nurse will collect around 5 ml (1 teaspoon) of blood. Serum from the study will be extracted from blood samples at OCMR, then stored in a secure research -80C freezer in OCMR for all participants. At the end of the study, study serum samples will be transported to the Lakhal-Littleton Lab at the Department of Physiology, Anatomy and Genetics (DPAG), Part of the Medical Sciences Division of the University of Oxford for further investigational assays.

Investigational assays: Serum samples derived from all participants and all timepoints will be tested together. Tests include measurements of serum iron indices (iron, ferritin, transferrin and transferrin saturation) using an automated analytical Chemistry instrument (Pentra C400) in the Lakhal-Littleton Lab. Markers of tissue iron damage (including but not limited to HNE and MDA) will also be measured in serum samples using standard commercially available kits (Abcam ab118970 and ab238538 respectively).

STATISTICAL METHODS
The primary outcome is the absolute change from baseline in MR relaxivities R1, R2, R2* at each timepoint post Ferinject infusion, according to the following formulae:
ΔR1 = R1 (at timepoint x) - R1 (at baseline)
ΔR2 = R2 (at timepoint x) - R2 (at baseline)
ΔR2* = R2* (at timepoint x) - R2* (at baseline)
R1, R2, and R2* values are calculated as the inverse of T1,T2, T2* relaxation times obtained by the MR relaxometry or mapping techniques. The results will be reported as time series of average values and standard deviations (median and IQR for nonparametric variables) at each timepoint post Ferinject infusion. The presence of a statistically significant signal will be assessed using ANOVA.

The secondary outcome measure is the change from baseline in serum concentrations of iron indices (including but not limited to iron, transferrin saturation, ferritin and non-transferrin bound iron) and markers of tissue iron toxicity (including but not limited to MDA ad 4-HNE). Results will be expressed both as absolute change from baseline and as percentage change relative to baseline.

Further exploratory analyses will be performed for possible interactions between the observed measures using correlations, crosscorrelations and pharmacodynamic modelling.

SAMPLE SIZE CALCULATIONS
The sample size of 12 participants was not arrived at statistically, due to a lack of information on the magnitude of effects of Ferinject on R1/R2/R2* values at early timepoints. However, an exploratory study of MRI imaging following intravenous infusion with ultrasmall superparamagnetic particles of iron oxide (USPIO) at later timepoints used sample sizes of 5-12 participants per group. Of note, the longitudinal design involving repeated measures will increase the statistical power of the study.

Intervention Type
Other

Primary outcome(s)
Cardiac structure and function (Cine MRI) and multi-organ magnetic resonance relaxometries (delta R1/R2/R2*) measured by magnetic resonance imaging (MRI) at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion

Key secondary outcome(s)
1. Serum iron indices (iron, ferritin, transferrin saturation, non-transferrin bound iron) measured by standard clinical chemistry at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion
2. Serum markers of tissue iron damage, including but not limited to lipid peroxidation markers malondialdehyde (MDA) and 4- Hydroxynonenal (HNE) measured by ELISA at baseline prior to infusion (day 1), 3 h post-infusion (day 1), ~2 weeks post-infusion, and ~6 weeks post-infusion

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Participant is willing and able to give informed consent for participation in the study
2. Aged 18 years or above
3. Anaemia (haemoglobin less than 120 g/l for women and less than 130g/L for men) and/or confirmed iron deficiency (ferritin less than 100 mcg/l and/or transferrin saturation less than 20%)
4. Scheduled to receive intravenous iron for correction of iron deficiency

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
13

Key exclusion criteria
1. Any MRI incompatible implants (e.g. cardiac, neuro, ocular implants, surgical clips, aneurysm clips, shrapnel/bullets)
2. Pregnant or lactating participants
3. Acute decompensated heart failure
4. Unstable clinical status
5. Any other medical conditions which would influence the reliability of the study results determined by the investigators
6. Any other contraindication to MRI to be confirmed by the qualified MRI operator, e.g. tattoos containing traces of metal

Date of first enrolment
01/10/2022

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
Oxford Centre for Clinical Magnetic Resonance Research (OCMR)
Oxford
England
OX3 9DU

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: RE/18/3/34214

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No