ISRCTN82061264 https://doi.org/10.1186/ISRCTN82061264

Elafin Myocardial Protection from Ischaemia RepErfusion injury

Submission date
26/01/2011

Recruitment status
No longer recruiting

Registration date
14/03/2011

Overall study status
Completed

Last Edited
02/06/2017

Condition category
Circulatory System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Heart muscle cells are susceptible to injury and death following interruption of blood flow. A mild form of injury occurs during coronary artery bypass surgery (a surgical procedure used to treat coronary heart disease). Certain white blood cells contribute to this heart injury by releasing enzymes that break down the tissues. Elafin is a naturally occurring protein that can potentially reduce heart injury by blocking these harmful enzymes. We believe that administering elafin to patients undergoing coronary artery bypass surgery will reduce heart injury and potentially improve patient outcome. This study sets out to determine whether elafin can indeed benefit patients in this setting.

Who can participate?
Patients who are 18 years or older undergoing coronary artery bypass graft surgery requiring two or more grafts will be approached to enter the study at Edinburgh Royal Infirmary.

What does the study involve?
If you consent to participating in the trial you will receive the following additional tests over and above your routine clinical care.
1. Cardiovascular magnetic resonance imaging (MRI) heart scan
You will attend for either two or three cardiovascular MRI heart scans on separate days. The first will be conducted within a period of 6 weeks before your operation. The second and third scans will be conducted on consecutive days ideally between day 5 and day 9 after the operation. In order for us to look in more detail at the heart we will administer an agent called gadolinium through a vein in your arm before the scan. Gadolinium is in routine clinical use.
If you are due to get all three MRI scans, we will administer microscopic iron particles, known as ferumoxytol (the trade name is Feraheme) after the second MRI scan. Ferumoxytol is approved for use in the treatment of anaemia and is safely used at the same dose that we propose to give. It has also been used in MRI scanning at this dose but has not been used after bypass surgery in this way. It will be given through a vein in your arm. Your blood pressure will be recorded before the infusion and 30 minutes after the infusion. The infusion itself will take less than a minute. Twenty-four hours after the ferumoxytol infusion, you will undergo the final MRI scan of the heart
2. Blood tests and drug administration

On the day of surgery you will be allocated at random to receive either the study drug (Elafin) or a dummy drug (saline) during the operation. The research team, surgical team and you will not know which of these treatments is given.
During and after surgery blood tests will be taken from a plastic tube (cannula) that is inserted as part of your routine care during the operation. These blood tests will be used to measure heart muscle injury and inflammation. If you participate in the study a small amount of extra blood will be taken for analysis (around 40 ml in total). This will be frozen and stored until we analyse for the different markers of muscle injury and inflammation.
3. Coronary bypass surgery and cardiopulmonary bypass
Patients will have their operation conducted on a cardiopulmonary bypass circuit. This approach is used in over half of coronary bypass operations in Edinburgh. Off-pump surgery is an alternative approach which will not be used in this study. Both techniques are very successful and there is no difference in safety or clinical outcome.

What are the possible benefits and risks of participating?
It is not thought that there are many disadvantages. Previous studies with Elafin in humans including healthy volunteers and surgical patients have suggested that it is a drug with no specific toxicity or side effects. With any drug there is a possible low risk of allergic reaction and you will be monitored for this as part of the trial. There is a similar low risk of reactions to the contrast agents given for the MRI study. The injection of ferumoxytol should not be painful and has not been associated with any significant side effects. However, we will monitor carefully for these at the time of the administration of ferumoxytol and afterwards and would treat you as necessary. People who have a past history of allergies to iron-containing compounds or 'dextran' (a component of ferumoxytol) would be excluded from the final MRI scan. The iron particles will be degraded by your body and removed by your liver. Because we will be giving extra iron, people with a history of conditions associated with abnormally high quantities of iron in the body will be excluded from the final MRI scan. Because MRI scanners use strong magnets, we will complete a detailed safety questionnaire before you enrol in the study to check that there is no reason why it would be unsafe for you to have a scan. People with metal joint replacements, pacemakers or a history of eye injury involving metal (such as from shrapnel or welding) will not be able to take part. Patients who have had brain surgery with the implantation of metalwork will also have to be excluded. MRI scanners do not use x-rays and therefore are not associated with the risks of radiation associated with other imaging methods including CT scans. Other than the risk associated with MRI in people with metal implants, there are no known risks from MRI scanning. The MRI scanner is noisy, so you will wear special headphones to reduce the noise.

Where is the study run from?
Edinburgh Heart Centre (Edinburgh, UK).

When is the study starting and how long is it expected to run for?
The study started in March 2011 and will finish in March 2014. Recruitment ends in September 2013.

Who is funding the study?
The value and importance of this study has been recognised by the Medical Research Council, who have agreed to fund it after rigorous peer-review.

Who is the main contact?
Dr Peter Henriksen
phenrik1@staffmail.ed.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Peter Henriksen

Contact details
Department of Cardiology
Western General Hospital
Crewe Road
Edinburgh
United Kingdom
EH4 2XU
+44 (0)131 5373834
phenrik1@staffmail.ed.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2010-019527-58

Protocol serial number
010506

Study information

Scientific Title
A randomised trial to investigate the effect of Elafin on myocardial injury and inflammation in coronary artery bypass surgery

Acronym
The EMPIRE study

Study objectives
Elafin has cardioprotective effects in myocardial injury.

On 23/07/2013, the target number of participants was changed from 80 to 118 (80 full protocol + 38 extension recruits with no MRI scanning protocol). Other changes are indicated in the corresponding fields.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Research Ethics Committee, 18/02/2011, ref:11/MRE00/5

Primary study design

Interventional

Study design
Single-centre randomised double-blinded placebo-controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Post-ischaemic inflammatory myocardial injury

Interventions
Current interventions as of 23/07/2013:
80 patients will receive an initial magnetic resonance imaging (MRI) scan. They will be randomised to either placebo or Elafin (200 mg) and patients will receive an infusion of this during cardiac bypass surgery. During and after surgery, blood samples will be taken up to 48 hours post-surgery. A second MRI scan will be performed after 7 ± 2 days. After this scan, patients will receive an infusion of Feraheme®. A third MRI scan will be performed 24 hours after the second scan, which will be the end of the trial for patients. Patients in the extension group will be randomised to either placebo or Elafin (200 mg) and will receive an infusion of this during cardiac bypass surgery. During and after surgery, blood samples will be taken up to 48 hours post-surgery, at which point participation in the study will be complete.

Previous interventions:
Patients will receive an initial magnetic resonance imaging (MRI) scan. They will be randomised to either placebo or Elafin (200 mg) and patients will receive an infusion of this during cardiac bypass surgery. During and after surgery blood samples will be taken up to 48 hours post-surgery. A second MRI scan will be performed after 7 ± 2 days. After this scan patients will receive an infusion of Feraheme®. A third MRI scan will be performed 24 hours after the second scan, which will be the end of the trial for patients.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Elafin, Feraheme®

Primary outcome(s)
Area under the curve for plasma troponin I concentration profile over the first 48 hours

Key secondary outcome(s)
1. The effect of Elafin on myocardial injury and inflammation will be further quantified by comparing infarct volume and macrophage infiltration before and after surgery
2. Infarct volume and macrophage infiltration will be quantified using MRI together with late gadolinium enhancement and accumulation of ultra-small superparamagnetic particles of iron oxide (USPIO) respectively. USPIO contrast acts as a cellular marker through the detection of macrophage-mediated inflammation within tissues (added 23/07/2013: not applicable to extension participants)

3. Elafin's effect on inflammatory activation will be assessed by comparing peak and area under the curve of plasma CRP and cytokine (IL-6, TNF-a and IL-8) concentrations
4. Neutrophil activation will be assessed by measuring the white cell and neutrophil differential counts and measuring peak and area under the curve of plasma myeloperoxidase and elastase concentrations
5. Post-operative intensive therapy unit (ITU) stay will be recorded from the end of the operation (as documented on the anaesthetic chart) until the ITU team consider the patient fit for 'step down' either to cardiothoracic high dependency unit (HDU) or general surgical ward. It will be measured in hours.

Completion date
01/03/2014

Eligibility

Key inclusion criteria
Patients (males and females, 18 years or older; no upper age limit) who are referred for coronary artery bypass graft surgery requiring two or more grafts will be approached for consent to enter the study during visits to the cardiothoracic surgery outpatient clinic.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Recent myocardial infarction (a recorded troponin elevation within 1 month of surgery)
2. Emergency surgery
3. Concomitant valve or aortic surgery
4. Re-intervention or re-do surgery
5. Chronic renal failure (estimated glomerular filtration rate less than 40 ml/min)
6. Severe respiratory disease (maintenance corticosteroid therapy or forced expiratory volume in one second [FEV1] less than 50% predicted)
7. Severe left ventricular dysfunction (ejection fraction less than 30%)
8. Contraindication to magnetic resonance imaging (MRI) scanning or a history of chronic inflammatory illness, such as inflammatory joint disease, connective tissue disorder (added 23/07/2013: not applicable to extension participants)
9. Patients unable to give informed consent

Date of first enrolment

01/03/2011

Date of final enrolment
01/09/2013

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Western General Hospital
Edinburgh
United Kingdom
EH4 2XU

Sponsor information

Organisation
NHS Lothian and the University of Edinburgh (UK)

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (MRC) (UK) (ref: 96182)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Funder Name
Chest Heart Stroke Scotland (UK) (ref: r11/A135)

Alternative Name(s)
CHSS

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2015		Yes	No
HRA research summary			28/06/2023	No	No