ISRCTN94278797 https://doi.org/10.1186/ISRCTN94278797

Heme Oxygenase-1 in Liver Surgery

Submission date 02/10/2008	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 04/12/2008	**Overall study status** Completed	
Last Edited 07/06/2017	**Condition category** Surgery	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mr Stephen McNally

Contact details
Room W2.13
Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
United Kingdom
EH16 4TJ

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
1.4 October 2008

Study information

Scientific Title

Induction of heme oxygenase-1: a therapeutic approach to reduce hepatic ischaemia-reperfusion injury in liver surgery

Acronym
HOLS study

Study objectives
There is a growing clinical need for hepatic surgery for malignant disease, where liver resection offers the only chance of cure. The most common indication for liver resection in Scotland is for metastatic colorectal cancer. Scotland has the highest incidence of colorectal cancer in the United Kingdom and one of the highest rates of colorectal cancer in Europe. Approximately 50% of all patients diagnosed with colorectal cancer will develop liver metastases, and surgical resection offers these patients their only chance of a cure. However, hepatic resection has significant risks, with a peri-operative mortality rate of 5%, and a major morbidity rate of 20%. The greatest contributor to post-operative liver failure is inadequate function in the residual liver tissue. Hence, any treatment which improves the tolerance of the liver to such insults would have clinical potential.

The hepatic insult in elective liver surgery is predominantly due to ischaemia-reperfusion injury (IRI) which occurs as a result of the surgical process when hepatic inflow clamping is used (the Pringle manoeuvre). The Pringle manoeuvre is performed to minimise blood loss during liver transection. It is commonly used for patients undergoing extended right or left hepatectomy, and in some centres it is used routinely for standard hemi-hepatectomy. Development of a treatment which can reduce the IRI associated with the Pringle manoeuvre would be important in preserving post-operative hepatic function in these patients and reducing post-operative complications.

Heme oxygenase 1 (HO-1) has the potential to modulate and reduce the severity of IRI. HO-1 is an intrinsic part of the cellular defence machinery and is critical for cellular protection from injury. Upregulation of HO-1 protects human liver cells from IRI in vitro. It also reduces the severity of ischaemia reperfusion injury in animal models, and is effective in multiple different organs. Induction of HO-1 reduces the severity of injury in experimental rat and mouse liver IRI and HO-1 protects against transplantation-associated ischaemia reperfusion injury in liver, kidney and cardiac grafts. Furthermore, HO-1 mediated protection is effective in reducing IRI in livers which have poorer tolerance of injury, such as fatty liver, aged liver and cirrhotic liver. HO-1 therefore has the potential to be used as a treatment to reduce ischaemia-reperfusion injury in human liver surgery. At present there is no specific therapy for reducing IRI in hepatic resection.

There is a need for treatments to minimise hepatic damage following liver surgery, in order to reduce the risks of liver resection. The drug heme arginate strongly induces HO-1 in human liver cells in vitro and in in-vivo models. This study will investigate the hypothesis that heme arginate can be used to induce HO-1 in human liver, and whether this can protect patients undergoing hepatic surgery from ischaemia-reperfusion injury.

Please note, as of 14/02/2012 the following changes have been made to the record.
Anticipated start date: amended from 01/03/2009 to 01/10/2010.
Anticipated end date : amended from 01/06/2010 to 01/02/2012.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland A Ethics Committee, pending as of October 2008

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Liver surgery/pharmacological preconditioning

Interventions
There will be three arms to the study. Participants will be randomised to:
Arm A: this is the control group, which will receive an infusion of saline over one hour into a peripheral vein
Arm B: this group will receive an infusion of 3 mg/kg heme arginate over one hour into a peripheral vein
Arm C: this group will receive an infusion of 6 mg/kg heme arginate over one hour into a peripheral vein

The infusion will be given one the day prior to surgery. Follow-up will continue until the patient has been discharged from hospital (usually 7 - 10 days post-operatively).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Heme arginate

Primary outcome measure
Heme oxygenase-1 induction will be measured in the resected liver specimen, and also in peripheral blood cells. HO-1 levels will be assessed by laboratory mesasurement of HO-1 messenger ribonucleic acid (mRNA) and protein level (real-time polymerase chain reaction [PCR] and Western blotting respectively) and HO enzymatic activity. HO-1 will be localised in the liver

by immunohistochemistry of the liver tissue. Total body production of carbon monoxide (CO, a product of HO-1 activity) will be measured by CO levels in exhaled air and by blood levels of carboxy-haemoglobin.

Secondary outcome measures
Liver function on each day during the hospital stay will be assessed by clinical and biochemical means. Clnical evidence of encephalopathy and clinical progress will be measured. Serum levels of alanin aminotransferase (ALT), prothrombin time (PT), lactate and bilirubin will be measured biochemically. Hepatic clearance of indocyanine green will be measured.

Overall study start date
01/10/2010

Completion date
01/02/2012

Eligibility

Key inclusion criteria
1. Patients scheduled to undergo major hepatic resection (three or more segments)
2. Aged between 18 and 80 years, either sex

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
42

Key exclusion criteria
1. Patients undergoing minor resections (less than three segments)
2. Jaundiced patients (bilirubin greater than 100 µmol/l)
3. Patients with established cirrhosis
4. Patients who have had a previous liver resection
5. Patients who are unable to give informed consent
6. Patients who are pregnant or breastfeeding

Date of first enrolment
01/10/2010

Date of final enrolment
01/02/2012

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Queen's Medical Research Institute
Edinburgh
United Kingdom
EH16 4TJ

Sponsor information

Organisation
University of Edinburgh (UK)

Sponsor details
Edinburgh Clinical Trials Unit
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ
+44 (0)131 242 9446
ECTU@ed.ac.uk

Sponsor type
University/education

Website
http://www.clinicaltrials.ed.ac.uk

ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office of the Scottish Executive Health Department (UK) (ref: CZB/4/442)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration