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Work Package 2 (WP2) - Normothermic Liver Perfusion Vs Cold Storage in Liver Transplants

Submission date
05/02/2014

Recruitment status
No longer recruiting

Registration date
27/03/2014

Overall study status
Completed

Last Edited
25/10/2018

Condition category
Surgery

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

Plain English summary of protocol

Background and study aims
There is a nationwide shortage of livers for transplantation. The OrganOx Metra machine has been developed and investigated to maintain a liver at normal body temperature prior to transplantation. It is hoped that using normothermic preservation will help to improve the quality of livers when they are transplanted and may mean that more organs become suitable for use in liver transplantation. The safety of this device has been demonstrated, but any benefit in humans when compared to conventional storage on ice still remains to be seen. The purpose of this study is to compare normothermic machine perfusion (NMP) and cold storage (SCS).

Who can participate?
There are four liver transplant centres in England participating in this study, as well as three others in the EU. All patients meeting the inclusion / exclusion criteria currently on the waiting list for a liver transplant at any of these hospitals will be invited to participate in this study. Detailed information will be given both verbally and in the form of a Patient Information Leaflet. Patients will be given a minimum of 24 hours (if required) to consider the information before deciding whether to give written consent to participation. A list of consenting patients will be maintained by the study coordinator and the liver transplant coordinators.

What does the study involve?
All organs which fulfil the entry criteria and are accepted for transplantation using the criteria used by the participating transplant units will be included. When a suitable donor organ becomes available and this is allocated to a recipient patient who has provided consent, then the recipient will be asked to affirm the consent that has already been provided by signing and dating the Informed Consent Form for a second time. This process may also be done with a documented phone call. If the patient is not willing to proceed in the study at this stage, then the patient will not be included in the trial and the organ retrieval and preservation will be carried out using conventional procedures.
If the patient is willing to proceed with the study and, if the OrganOx metra machine and team are available, then the recipient transplant coordinator will enter the required baseline details about the donor and recipient into the secure online electronic database, which will then randomise (allocate in a random fashion like tossing a coin) the liver to either machine perfusion (NMP) or cold storage (SCS). A total of 260 donor livers will be included in this study, 130 in each

group.
If the liver is allocated to the SCS group then the organ retrieval, preservation, transport and implantation will proceed in the conventional manner, with the liver stored in an ice box.
If the liver is allocated to the NMP group then the OrganOx metra machine and team will travel to the retrieval hospital at the same time as the organ retrieval team. The organ retrieval will proceed in the conventional manner until the liver has been removed from the donor. No aspect of the donor management will be altered by involvement in this study. The only change in management occurs in the preservation of the liver once it has been removed from the donor. After removal from the donor, the liver will be flushed with a cold preservation solution, prepared on the backtable, cannulated and then attached to the machine where it is perfused with blood, oxygen and nutrients, as well as some medications, at normal body temperature. It will remain on this machine during transport to the recipient transplant centre and during the transplant operation itself until the transplant surgeon is ready to transfer the liver from the machine into the recipient. At this point the liver is removed from the device, flushed with a cold solution and then transplanted in the conventional manner.
After the transplant, the patient will be treated according to the standard clinical protocols of the respective transplant unit. Data will be collected at the timepoints identified in the Study Schedule below. The only study-specific investigations (requiring an intervention not otherwise stipulated for clinical reasons) will be a quality of life (EQ5D5L) and health economic questionnaire and an MRCP (magnetic resonance cholangiopancreatogram) scan. In some of the participating transplant centres this scan is standard clinical practice whilst in others this will be done specifically for the trial.
Study Schedule for all participants:
- Demographic donor data.
- 2 liver biopsies will be taken during the preservation process, and 1 after implantation.
- Intraoperative blood pressure changes will be recorded at the time of organ implantation (post-reperfusion syndrome).
- Liver function tests (bilirubin, AST, gammaGT, INR and lactate) will be measured on days 1-7 post-operatively. These will not involve any additional study-specific samples. These tests will be measured and recorded again at day 30 and 6, 12 and 24 months postoperatively.
Throughout the study period we will record graft and patient survival.
A baseline quality of life questionnaire (EQ5d5L) will be recorded preoperatively. This will be repeated, along with a resource use questionnaire, at day 30 and 6 months postoperatively.
An MRCP will be performed 6 months postoperatively looking for ischaemic cholangiopathy.
Additional samples will be taken from NMP livers whilst they are on the OrganOx metra:
- Perfusion blood samples (approximately 5mls) from the machine at 15mins, 1hour and the end of preservation.
- A sample of the bile produced by the liver whilst on the machine
An additional tick box is included on the consent form for samples to be taken for the Oxford Radcliffe Bioresource. If participants have consented to this, additional blood and urine samples will be taken from the recipient during the transplant. If participants have not consented to this, they will still be included in the trial but these specific samples will not be taken.

What are the possible benefits and risks of participating?
Participation in this trial will not affect a patients position on the liver transplant waiting list or their likelihood of receiving a liver transplant. Similarly, withdrawal of a participant from the trial at any point and for any reason will not affect their position on the liver transplant waiting list or their likelihood or receiving a liver transplant.

Where is the study run from?
Four liver transplant centres in England participating in this study (King's College Hospital, London; Royal Free Hospital, London; Queen Elizabeth Hospital, Birmingham; and

Addenbrooke's Hospital, Cambridge), as well as three others in the EU (Belgium, Germany and Spain).

When is the study starting and how long is it expected to run for?
April 2014 to January 2019 (as of 25/10/2018)

Who is funding the study?
European Commission Seventh Framework Programme (FP7)

Who is the main contact?
Prof Peter Friend
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Study website
http://www.cope-eu.org/work-packages/wp2

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title

A multicentre randomised controlled trial to compare the efficacy of ex-vivo normothermic machine perfusion with static cold storage in human liver transplantation

Study objectives
Normothermic machine perfusion (NMP) is superior to static cold storage (SCS) of human liver allografts for reduction of preservation injury in liver transplantation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. London - Dulwich Research Ethics Committee, 11/4/2014, ref: 14/LO/0182
2. MHRA, 26/2/2014, ref: CI/2014/007

Study design
Multicentre non-blinded randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Other

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
We are studying the effect of using normothermic liver perfusion to preserve the donor liver on the outcomes of liver transplantation. The disease common to all the recipients is end-stage liver failure.

Interventions
The intervention is 'Normothermic liver perfusion'.

The current standard method of storing and preserving a liver for transplant after it has been removed from the donor is by flushing it with a cold preservation solution e.g. University of Wisconsin solution, and then placing it in an ice box. Although cold preservation slows metabolism by 1.5- to 2-fold for every 10°C drop in temperature, considerable metabolic activity still occurs at 1°C. This leads to accumulation of metabolic products which act as substrates for metabolism that takes place when the organ is re-perfused with oxygenated blood the basis of the ischaemia-reperfusion phenomenon. Livers which are cold stored prior to transplant undergo injury at several consecutive stages: 1) warm ischaemia prior to preservation, 2) cold preservation injury, 3) ischaemic rewarming during surgical implantation and 4) reperfusion

injury. These consecutive events lead to a cumulative cellular injury that may not be compatible with recovery after transplantation.

Normothermic preservation promises to improve the quality of livers used in transplantation by providing the liver with oxygenated blood, nutrients and some medications at normal body temperature during the preservation process. The donor procedure is not changed in any way but, after the liver has been removed from the donor it is prepared and cannulated on the back-table before being attached to the normothermic machine where it is remains perfused throughout the transport and storage process. The recipient operation is also carried out in the conventional manner until the transplant surgeon is ready to implant the donor liver. At this point the liver is removed from the preservation device, flushed with cold preservation solution e.g. University of Wisconsin solution, and then transplanted in the conventional way.

Added 16/06/2016:
Participants will be followed up for a total of 2 years. The first official analysis of outcomes will be performed using 30 day follow up data and then, again, at 6 months

Intervention Type
Procedure/Surgery

Phase
Not Applicable

Primary outcome measure
The difference in peak serum aspartate transaminase level (AST) within 7 days post-transplant between the two treatment arms.

Secondary outcome measures
To compare graft and patient survival between NMP and SCS livers.
1. Primary non-function: irreversible graft dysfunction requiring emergency liver replacement during the first 10 days after liver transplantation, in the absence of technical or immunological causes.
2. Graft survival at 30 days and 6, 12 and 24 months following transplantation.
3. Patient survival at 30 days and 6, 12 and 24 months following transplantation.
To compare biochemical liver function between NMP and SCS livers.
1. Daily serum bilirubin, GGT, AST and INR at days 1-7 following transplantation.
2. Daily serum lactate at days 1-7 whilst in high level (ITU/HDU) care
3. Serum bilirubin, GGT, AST and INR at day 30 and months 6, 12 and 24 following transplantation.
4. Early allograft dysfunction (EAD) [41]; defined by any one of:
4.1. Bilirubin >170 ìmol/l (10mg/dL) on day 7 post-transplant
4.2. INR >1.6 on day 7 post-transplant.
4.3. Peak aspartate transaminase (AST) >2000 IU/L within the first 7 days post-transplant

To compare the physiological response to reperfusion between NMP and SCS livers
1. Post-reperfusion syndrome, defined as a decrease in mean arterial pressure (MAP) of more than 30% from the baseline value for more than one minute during the first five minutes after reperfusion. This will be assessed in the context of vasopressor use
2. Length of stay in high level (HDU/ITU) care
3. Length of hospital stay
4. Need for renal replacement therapy (haemodialysis, haemofiltration, haemodiafiltration)

To compare evidence of reperfusion injury between NMP and SCS livers.
1. Histological evidence of reperfusion injury in post-reperfusion biopsies (taken immediately prior to abdominal closure). These will be compared to baseline pre-reperfusion biopsies (on removal of the liver from SCS/NMP) and graded using standard histological criteria

To compare evidence of ischaemic cholangiopathy between NMP and SCS livers.
1. Evidence of biliary stricturing on magnetic resonance cholangiography (MRCP) at 6 months post-transplant.

To assess the ability of perfusion parameters and biomarkers in perfusion fluids to predict clinical outcomes following transplantation.
1. Perfusion parameters (logged automatically by the device):
1.1. Arterial and caval pressures (in mmHg)
1.2. Arterial, portal and caval flow rates (in mmHg)
1.3. pO2, pCO2 and pH
1.4. Blood temperature (oC), Glucose (mmol/L) and bile production (ml/h)
2. Perfusate ALT and AST at 15 minutes, 1 hour and the end of NMP
3. Perfusate IL6, TNF, vWF at 15 minutes, 1 hour and the end of NMP
4. In addition to these pre-specified outcomes, additional biological samples will be taken for the COPE WP7 bioresource.

To assess the feasibility and safety of NMP as a method of organ storage and transportation.
1. Organ discard rate
2. Perfusate culture. At the end of preservation a sample will be taken for microbiological culture (cold preservation or warm perfusate).
3. Adverse event rates and severity, graded according to the Clavien-Dindo classification [45] as described in Appendix A4.
3.1. Recipient infection
3.2. Biopsy proven acute rejection
3.3. Biliary complications (biliary strictures - anastomotic and non-anastomotic, bile duct leaks)
3.4. Vascular complications (bleeding, hepatic artery stenosis, hepatic artery thrombosis, portal vein thrombosis)
3.5. Reoperation rate
3.6. Technical complications/device failures

To assess the health economic implications of normothermic liver perfusion.
Full health economic analysis utilising:
1. Logistical costs, measured using national unit costs where available.
2. Healthcare resource use; measured by a combination of hospital episode records and a patient-completed resource use log.
3. Quality of life by delivery of the EQ-5D-5L questionnaire at baseline, day 30 and month 6 post-transplant.

Overall study start date
01/04/2014

Completion date
31/01/2019

Eligibility

Key inclusion criteria
Donor Inclusion Criteria:
1. Donors over the age of 16 years.
2. Liver allografts from donation after brain death (DBD), standard and extended criteria donors (SCD, ECD) and donation after circulatory death (DCD) donors.

Recipient Inclusion Criteria:
1. Adult patients (18 years or more)
2. Active on the waiting list for liver transplantation
3. Able to give informed consent.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
260

Key exclusion criteria
Donor Exclusion Criteria:
1. Living donors
2. Liver intended for split transplant
3. Donor age <16 years
4. Liver in which investigator is unwilling to randomise to either arm

Recipient Exclusion Criteria:
1. Age less than 18 years
2. Acute/fulminant liver failure
3. Transplantation of more than one organ (e.g. liver and kidney)
4. Refusal of informed consent
5. Unable to give informed consent.

Date of first enrolment
01/04/2014

Date of final enrolment
08/03/2016

Locations

Countries of recruitment
Belgium

England

Germany

Spain

United Kingdom

Study participating centre
Director of Oxford Transplant Centre
Oxford
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
European Commission Seventh Framework Programme (FP7)

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2018		Yes	No
HRA research summary			28/06/2023	No	No