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A feasibility study of octreotide infusion during liver transplant

Submission date 29/04/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 05/10/2021	**Overall study status** Completed	
Last Edited 17/01/2024	**Condition category** Surgery	

Plain English summary of protocol

Background and study aims
Patients who undergo liver transplantation surgery can suffer complications including kidney failure, major bleeding, and may require blood transfusions. These complications slow down recovery after surgery and increase the chances of death, the liver transplant not working and the need for long-term kidney dialysis.

The drug octreotide is an artificial version of a natural hormone and has been shown to support kidney function in severe liver disease as well as possibly reduce bleeding during liver transplantation. Octreotide has been used in liver disease and liver transplant. However, there are some risks which include changes in heart rate, blood sugar and heart rhythm.

The study team are proposing to run a small scale study (a 'feasibility study') at two transplant centres to investigate the effect of octreotide during liver transplantation surgery. The information we collect will be used to design a larger trial to determine whether octreotide is beneficial to liver transplantation patients and presents value for money.

Who can participate?
Adult patients undergoing primary liver transplantation of a whole or partial liver graft from a cardiac or brain dead donor.

What does the study involve?
30 patients at two hospitals will be invited to participate in the study. The participants will be randomly divided into two groups, 20 participants will receive octreotide during their surgery and 10 will receive an identical-looking treatment with no active medicine. The study team will look for an improvement in kidney function and quality of life of participants as well as a reduction in bleeding and the need for blood transfusion as reported by patients three months after their surgery.

The study team will closely monitor patient's blood sugar levels, heart rate and rhythm during the study to make sure they are normal. If there are any concerns they will stop giving the octreotide medication. This will allow the study team to assess the risks posed by octreotide during surgery.

What are the possible benefits and risks of participating?
Octreotide is an artificial version of a hormone that the body produces constantly to help regulate the gut and digestion. Octreotide is used routinely in the NHS for treatment of kidney failure and bleeding in liver disease. Some hospitals use octreotide routinely during liver transplant surgery and feel it provides benefits. Octreotide is used quite commonly in patients who have liver disease. It is generally regarded as a very safe medication.

There is no direct benefit from participating in this trial. The information from this study will help improve the treatment of people who are receiving future liver transplants

However, there are risks with all medical treatments. Effects that have been found from the use of octreotide are:
1. Changes in blood sugar levels (very common, 1 in 10 or higher)
2. A slowing down in the heart rate (common, between 1 in 10 and 1 in 100)
3. Changes in heart rhythm (uncommon, less than 1 in 100)
During and after liver transplant surgery participants' heart rate and rhythm will be monitored constantly and if there are any concerns this can be treated. Their blood sugar levels will be checked approximately hourly throughout surgery and at a similar frequency after surgery on the intensive care unit. If there are concerns regarding blood sugar levels these are treated routinely.

If at any point during the surgery, there is a concern that the medication is causing any problems that cannot be easily treated then the trial medication will be stopped.

There are no risks associated with the placebo infusion.

Where is the study run from?
Surgical & Interventional Trials Unit (SITU) (UK)

When is the study starting and how long is it expected to run for?
From September 2018 to October 2023

Who is funding the study?
The National Institute for Health Research (UK), Research for Patient Benefit (RfPB)

Who is the main contact?
1. situ.octreotide@ucl.ac.uk (Public)
2. Dr Mike Spiro (Scientific)
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
278918

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 48821, IRAS 278918

Study information

Scientific Title
A double-blind randomised placebo-controlled feasibility study to assess the impact of octreotide infusion during liver transplantation on post-operative renal failure.

Study objectives
Is it feasible to recruit and retain patients in this study of continuous infusion of octreotide during liver transplantation surgery?

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 21/04/2021, East Midlands, Leicester South (**Currently being held remotely via Teleconference/ZOOM** Best Western Three Swans Hotel, 21 High Street, Market Harborough, Leicestershire, LE16 7NJ; +44 (0)207 104 8115, +44 (0)207 104 8310, +44 (0)207 104 8372; leicestersouth.rec@hra.nhs.uk) ref: 21/EM/0076

Study design
Multi-centre randomized controlled feasibility study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Perioperative bleeding, liver transplant

Interventions
This feasibility study is designed to demonstrate that we can perform the trial safely and effectively before expanding the study to a larger number of hospitals and recruiting the number of patients needed to show whether octreotide provides a benefit or not. As such, there are no formal primary outcomes on which this study is based. However, our hypotheses regarding octreotide infusions during liver transplant surgery are that:
1. There will be an increase in kidney function and urine production during surgery
2. The kidneys will function better after surgery
3. Fewer patients will require kidney support after surgery, such as dialysis
4. Patients' blood pressure will be better during surgery and fewer medications will be required to support blood pressure
5. There will be less bleeding during surgery
6. Patients will require fewer blood transfusions during and after surgery
7. As a consequence of these improvements in outcomes after surgery, patients will experience a greater improvement in their quality of life after liver transplant surgery

In order to find out whether or not octreotide provides a benefit to patients, we need to compare patient outcomes between those who have and have not had octreotide. To make the study as effective as possible we will compare the octreotide drug to a placebo. A placebo is a dummy treatment that looks like the real thing but is not. It contains no active ingredient. Patients who agree to be part of this study will receive either an infusion of octreotide or an infusion of an inactive drug (a saline solution). In order to find out whether or not octreotide

provides a benefit to patients, we need to compare patient outcomes between those who have and have not had octreotide. Additionally, in order to find out whether octreotide is safe to use we need to check whether patients who have octreotide show a greater rate of complications or other concerns around their surgery when compared to patients who did not have octreotide. While octreotide is used safely in a range of liver disease conditions and treatment areas and has also been used in liver transplant for some time, there is no robust proof that it can be used safely in liver transplant surgery and we need to show this is the case in order to recommend its use in the NHS if we find improvements in patient outcomes.

To make the study as high a quality of research as is possible it will be performed in a blinded fashion. Therefore patients will not know which treatment group they are in. Furthermore, the doctors and research team involved in the study and clinical care of patients will also not know in which treatment group a patient is in (although, if a doctor needs to find out he/she can do so).

The timetable for this feasibility study is as follows:
Set-up: 4 months
Recruitment: 11 months
Follow-up: 4 months
Data cleaning, analysis, presentation, focus group meeting, preparation of substantive trial: 4 months
Total: 22 Months
There will be no interim analyses or reports.

All patient recruitment, consenting, study assessments, and interventions, including the octreotide infusion during liver transplant surgery will be performed at either the Royal Free NHS Foundation Trust or the University Hospitals Birmingham NHS Foundation Trust. Patients listed for liver transplantation and eligible for the study will be identified by a member of the research team at regular pre-operative anaesthetic clinics. Patients will be approached by a member of the research team to discuss the study, answer questions, and at a later timepoint to obtain written, informed consent. The intended recruitment of thirty patients for this feasibility study, twenty in the octreotide arm and ten in the control arm, will provide useful information regarding the safety profile of octreotide. This sample size will allow us to demonstrate the feasibility of conducting a full-scale randomised trial in the future. This phase of the study is not formally powered to detect differences in patient outcomes. Rather, the sample size will permit us to demonstrate we can perform the study safely and effectively as well as gain important information required to predict the number of patients we will require for the main follow-on study. We have obtained advice from a senior statistician and the National Institute for Health Research in choosing the sample size for this study.

The octreotide or placebo medication will be given to patients as an infusion while they are asleep for liver transplant surgery and there are no further doses of the medication before or after surgery. There are no lifestyle or dietary restrictions required for patients taking part in this study, other than those that are routinely advised on for liver transplant surgery. Patients in this study will experience no differences in their surgery and their care both before and after the transplant procedure will be identical to patients who are not taking part in the study. Other than the infusion of octreotide or control medication the only difference to normal care that patients will experience is we will ask them to complete two questionnaires in the weeks prior to surgery and the same questionnaires three months after surgery. The study will not require patients to attend any additional clinics or hospital appointments or receive phone calls at home.

The extra parts of the study include:
1. The completion of a written informed consent form

2. The infusion of the study medication, performed while under general anaesthesia for liver transplant surgery
3. The completion of two quality of life questionnaires (taking roughly 30 min) during the pre-operative assessment
4. The completion of two quality of life questionnaires around three months after surgery.
5. These will be done at a routine follow-up appointment and take roughly 30 min.

Patients and their families have been actively involved in the development of this study, the research questions, and the design. Our patient expert, who is a member of the Trial Management Group and a co-applicant on our research grant, has also been involved in the development of our patient materials and this ethics application.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Octreotide

Primary outcome measure
Feasibility of conducting a randomised controlled trial of octreotide versus placebo infusion during liver transplantation measured using:
1. The recruitment rate, calculated from the number of patients consented to participate in the study and the number of patients approached, during the recruitment period
2. Rate of completion of the study intervention, calculated from the number of patients receiving full study intervention at 4 months and the number of patients enrolled during the recruitment period
3. Incidence of drug-related serious unexpected adverse events (SUSARs), calculated from the number of SUSARs between baseline and 4 months and the number of patients enrolled during the recruitment period
4. Follow-up data collection rate, calculated from the number of complete PROM questionnaires at 3 months and the number of patients enrolled during the recruitment period
5. Patient refusal to enrol, calculated from the number of patients enrolled and the number of eligible patients admitted for transplantation during the recruitment period
6. Clinician refusal rate, calculated from the number of clinician refusals and the number of patients enrolled during the recruitment period

Secondary outcome measures
1. Blood loss measured using intra-operative cell salvage volume during each surgical phase
2. Intra-operative urine output measured during each surgical phase
3. Mean arterial blood pressure measured during each surgical phase
4. Requirement for and mean vasopressor and/or inotrope infusion rate measured during each surgical phase,
5. Transfusion requirements measured from the de novo packed red blood cells and all clotting products required during surgery and on the ICU within the first 24 h, within the first 72 h, and within the first week
6. Incidence of Acute Kidney Injury (AKI) measured using the Acute Kidney Injury Network stage 1 criteria within the first 24 h, within the first 72 h, and within the first week
7. Incidence of postoperative renal replacement therapy (RRT) measured at 24 h, 72 h, 1, and 2

weeks
8. Incidence of new or worsened chronic kidney disease (CKD) measured using eGFR and KDIGO status at 30 and 90 days. New or worsened CKD is defined as a new persistent estimated glomerular filtration rate <60 ml/min/1.73m² or a decline in pre-existing glomular function to a more severe KDIGO chronic kidney disease status.
9. Patient mortality measured at 30 and 90 days
10. Early allograft dysfunction measured using INR, bilirubin, AST and ALT at 7 days. Early allograft dysfunction is defined as the presence of one or more of the following:
10.1. Total bilirubin ≥10 mg/dl (171 µmol/l)
10.2. INR ≥1.6
10.3. ALT/AST >2000 IU/l within the first 7 days post-operatively
12. Incidence of liver graft loss (primary non function) measured at 30 and 90 days
13. Liver graft function measured using INR, bilirubin, AST, ALT, and ALP at 30 and 90 days
14. Patient recorded outcome measures (PROM) measured using the Liver Disease Quality of Life questionnaire and the EuroQOL-5D-5L questionnaire preoperatively and at 90 days
15. The incidence of major safety outcomes be measured throughout the study and will include:
15.1. Unexpected or resistant bradycardia
15.2. New or worsening QTc interval or associated arrhythmia
15.3. Unexpected or resistant hypoglycaemia
15.4. Potential allergic or anaphylactic reaction to any medication
15.5. Any report of an abnormal response to codeine or morphine
15.6. Development of venous or arterial thrombosis
15.7. Cardiac events including acute coronary syndrome, new heart failure, arrhythmia, or resuscitated cardiac arrest

Overall study start date
12/09/2018

Completion date
31/10/2023

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Undergoing primary liver transplantation of a whole or partial liver graft from a cardiac or brain dead donor
3. Provision of written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 30; UK Sample Size: 30

Total final enrolment
30

Key exclusion criteria
1. Previous solid organ transplant
2. Acute liver failure
3. Fulminant hepatic failure
4. Patients receiving a living donor liver graft
5. Patients currently admitted to ICU prior to transplantation
6. Requirement of haemodialysis or Continuous Veno-Venous Hemofiltration (CVVHF) pre-operatively
7. Known allergy or adverse reaction to octreotide
8. Pre-operative decision to use intra-operative CVVHF
9. A positive pregnancy test

Date of first enrolment
10/10/2021

Date of final enrolment
01/05/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Surgical & Interventional Trials Unit (SITU)
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Study participating centre
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Sponsor type
University/education

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ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
We intend to publish the data from this study in a high-impact peer-reviewed journal within one year of the trial completion date.

Intention to publish date
30/04/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the scientific contact for the study (situ.octreotide@ucl.ac.uk). Third party data access will be assessed on a case-by-case basis by the Trial Management Group, approved by the Trial Steering Committee and limited specific anonymised digitalised data will be released, as appropriate. Patients will be consented for further analysis of anonymised data. Data will not be shared prior to study publication. There is no limitation regarding the timescale of the request, it's nature or the type of proposed analysis.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	For patients awaiting assessment for liver transplant (In person) version v1.2	07/05/2021	21/07/2021	No	Yes
Participant information sheet	For patients on the transplant waiting list (Phone) version v1.2	07/05/2021	21/07/2021	No	Yes
HRA research summary			20/09/2023	No	No