ISRCTN51170824 https://doi.org/10.1186/ISRCTN51170824

Peri-transplant insulin therapy in pancreas transplantation

Submission date
15/01/2019

Recruitment status
No longer recruiting

Registration date
16/01/2019

Overall study status
Completed

Last Edited
13/04/2021

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Pancreas transplantation is the treatment of choice for patients with complex diabetes. Poor blood sugar control during the transplant procedure and for the first five days thereafter is associated with higher rates of failure. It is not known whether this is because the donated pancreas may take a little while to function optimally, or because of the stress that the pancreas experiences during the donation and transplantation process, or because poor blood sugar control compounds both of these effects. Insulin offers a treatment for all of these causes and effects, and good blood sugar control with insulin may improve transplant outcomes. It is standard practice for pancreas transplant recipients to have, when required, an insulin drip before and during transplantation, but this is ceased when the sugar level drops below a certain reading. This study tests a different type of plan for the insulin drip which is continued for the first five days after transplantation, where the dose is specifically tailored to each individual to provide better blood sugar control. A similar approach is routinely used for islet cell transplant recipients, but its safety and feasibility needs to be demonstrated for solid pancreas transplant recipients as well before proceeding to a full trial.

Who can participate?
Patients aged 18 to 65 undergoing simultaneous pancreas and kidney transplantation

What does the study involve?
Participants are randomly allocated to either the intervention group or the control group. Participants in the intervention group receive additional insulin for the first 5 days after pancreas transplantation. This is delivered via a central venous catheter (CVC), and will requires the presence of the CVC for that duration. After 5 days, in the event of ongoing insulin requirement on day 5, insulin is continued for up to two weeks, or until it is no longer required. The control group receive standard treatment. All patients undergo hourly blood glucose monitoring for the first five days, with samples taken from the CVC (not fingerprick). Thereafter, they follow the standard way of measuring glucose levels (fingerprick) at mealtimes, or when clinically indicated. All patients undergo continuous glucose monitoring (CGM) using the Freestyle Libre Pro device from 2 hours before transplant until 14 days after transplant. All patients receive standard follow-up in the Department of Transplantation, which is life-long and involves 2-3 times weekly outpatient appointments for the first month after, and thereafter at a

reducing rate weekly, bi-weekly, monthly at the discretion of the clinical team. In addition, patients are invited to undergo blood tests at 30 days and 90 days after transplantation which are performed at the same time as a routine clinic visit.

What are the possible benefits and risks of participating?
There are no direct benefits of taking part. However, this research may identify better ways of looking after patients with pancreas transplants. Better blood sugar control may have a beneficial effect on how well the transplanted pancreas functions, but this is not certain, which is why the research is required. The researchers have tried their best to limit the disadvantages and risks of taking part in this study, but no study is risk free. The risks include low blood sugar from the additional insulin treatment. However, the researchers have carefully tailored the insulin plan to maximise good blood sugar control and minimise potential episodes of low blood sugar. The protocol includes strict guidance and measures on how to deal with low blood sugar levels and correct the problem rapidly before it has any significant effect. One of the safeguards is that patients receiving the additional insulin will remain in the critical care environment for the duration of the insulin therapy.

Where is the study run from?
Manchester Royal Infirmary (UK)

When is the study starting and how long is it expected to run for?
September 2016 to April 2024 (updated 13/04/2021, previously: October 2020)

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Iestyn Shapey
iestyn.shapey@manchester.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Iestyn Shapey

ORCID ID
http://orcid.org/0000-0003-3300-1053

Contact details
Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester
Department of Renal and Pancreatic Transplantation, Manchester Royal Infirmary
Oxford Road
Manchester
United Kingdom
M13 9WL
+44 (0)1612761234
iestyn.shapey@manchester.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
40497

Study information

Scientific Title
Peri-transplAnt InsuliN Therapy to improve outcomes after pancrEas tRansplantation (PAINTER): an open label randomised clinical trial

Acronym
PAINTER

Study objectives
Peri-transplant insulin therapy in pancreas transplant recipients is safe and feasible.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Health Research Authority, Manchester HRA, 3rd Floor Barlow House, Minshull Street, Manchester, M1 3DZ, Tel: 0207 104 8009, Email: a.ecclestone@nhs.net, 11/12/2018, ref: 18/NW/0778

Study design
Randomised; Interventional; Design type: Treatment, Drug, Surgery

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 to request a patient information sheet

Health condition(s) or problem(s) studied
Pancreas transplantation for treatment of diabetes mellitus

Interventions
Design
The study will be a single centre open label randomised clinical trial

Recruitment
Potential pancreas transplant recipients who are activated on the waiting list will receive a copy of the patient information sheet in advance by post. On the day of transplantation, patients will receive a full verbal explanation and written information concerning the study, it's involvement and associated risks. They will have the opportunity to ask questions and receive as much time as is safely allowable to consider their participation.

Patients may be activated on the transplant waiting list 12-18 months before receiving their transplant, and 30% of the patients listed for transplant will not receive one for various reasons. The most appropriate time to consent patients to be involved with the trial is on the day of admission to the ward before surgery.

Mr Iestyn Shapey will approach patients, accompanied by a research or transplant co-ordinator, once they have attended the ward. In pancreas transplantation, more than one possible recipient is called for each pancreas. On occasions the primary recipient may not be healthy enough or may not be a suitable match for the available organ, in which case the transplant may proceed for a second recipient to prevent wastage of a scarce national resource. Therefore, both the primary recipient and the second choice recipient will be consented for recruitment into the trial. When the second choice recipient is called in the future as a primary recipient, the same consent process will be repeated.
All patients will be consented in compliance with the Helsinki Declaration.

Patients who cannot understand English sufficiently to consent to participate in the trial will be consented with an interpreter, in the same manner as the patient would be consented for non-research clinical procedures.

Sample size
Twenty patients will be recruited with 10 subjects in each of the trial arms. In a previous randomised clinical trial performed by the Department of Transplantation at Manchester Royal Infirmary, a 97% recruitment rate was achieved. Given that around 35 pancreas transplants are performed annually in Manchester, we anticipate that complete recruitment to this trial will take roughly 9 months. This number is sufficient to assess each of the potential outcomes, providing information to power the main trial.

Treatment allocation
The various study designs (cohort study vs clinical trial) and treatment allocation methods (alternative, block, targeted) were discussed in detail within the steering committee, at the public consultation meeting, and in conjunction with the Research and Development departments at the University of Manchester and Manchester University NHS Foundation Trust. An RCT is the preferred design for the study so that we can fully and appropriately assess the feasibility of undertaking a multi-centre RCT. As an open label trial, transplant recipients, treating clinicians and researchers performing the analysis will not be blinded to the treatment arms. Randomisation will be performed by the trial statistician using computer software generated randomisation.

Blinding
As an open label trial, transplant recipients, treating clinicians and researchers performing the analysis will not be blinded to the treatment arms. It will not be practical nor appropriate to blind neither the patients nor the clinicians to the treatment arms. In the future RCT, the individuals who analyse the data will be blinded from the participant's treatment arms.

Summary of Treatments
In this study, patients in the intervention arm will receive additional exogenous insulin delivered by a variable rate insulin infusion (VRII) for the first 5 peri-transplant days after solid pancreas transplantation. The trialists have identified 5 days as the high risk period for peri-transplant dysglycaemia, after which blood sugar levels normalise. This will be delivered via a central venous catheter (CVC), and will therefore require the presence of the CVC for that duration. The study arm will use the validated islet transplantation VRII protocol which is routine practice for all islet transplant recipients at this centre. After 5 days, in the event of ongoing insulin requirement on day 5, insulin therapy will be continued subcutaneously for up to two weeks post-transplantation, or until insulin therapy is no longer required to maintain mean glucose levels <7mmol/L. Prescribing of additional insulin after the first 5 days will be overseen by Dr Martin Rutter, Consultant Diabetologist. The control arm of the study will receive standard treatment as outlined by the solid pancreas transplantation protocol.

Glucose monitoring
All patients will undergo hourly point of capillary blood glucose monitoring for the first five days, with samples taken from the CVC (not fingerprick). Thereafter, they will follow the standard protocol of measuring glucose levels (fingerprick) at mealtimes, or when clinically indicated. All patients will undergo continuous glucose monitoring (CGM) using the Freestyle Libre Pro device from 2-hours pre-transplant until 14 days post-transplant. No CGM data will be available in real time, and only retrospective data will be available to the research team).

Follow up
All patients will receive standard follow-up in the Department of Transplantation, which is life-long and involves 2-3 times weekly outpatient appointments for the first month post-transplantation, and thereafter at a reducing rate weekly, bi-weekly, monthly at the discretion of the clinical team. In addition, patients will be invited to undergo a MMTT at 30-days and 90-days post-transplantation which will be performed at the same time as a routine clinic visit. MMTTs are a routine part of follow-up for all islet transplants and are currently being considered for routine practice in solid pancreas transplantation as well.

Intervention Type
Mixed

Primary outcome measure
The primary outcome for the feasibility study will be patient safety. Safety will primarily be determined by two measures of glycaemic control: a) the number of hypoglycaemic episodes; and, b) time within the target glucose range. Glycaemic control will be measured hourly using two methods, synchronously: capillary blood glucose (as is standard clinical practice), and continuous glucose monitoring (CGM) using the Freestyle Libre Pro device. CGM data will not be available to the clinical team and will only be analysed by the research team retrospectively.
Timepoint(s): Peri-transplant (first five days)

Secondary outcome measures

1. Beta-cell viability, measured using cell death and inflammatory markers pre-transplant and on each of the first 5 days post-transplant
2. Beta-cell function, measured using mixed meal tolerance tests, HbA1c, and c-peptide, at 30 and 90 days
3. Beta-cell survival, measured using return to insulin dependence within 90 days
4. Renal function at 30 and 90 days, measured using:
4.1. Incidence of hyperkalaemia within the first 5 days post-transplant
4.2. Incidence of delayed graft function, defined as dialysis within the first 7 days post-transplant
4.3. eGFR at 30 and 90 days
5. Complications within the first 90 days post-transplantation:
5.1. Surgical complications within the first 90 days post-transplantation
5.2. Medical complications within the first 90 days post-transplantation
6. Acceptability of the study to staff in all relevant clinical areas (Intensive Care, Operating Theatre, General Ward), measured using retrospective questionnaire at the end of the trial
7. Costs associated with undertaking an RCT of peri-transplant insulin therapy will also be determined by calculating the additional days spent in ICU compared with historical cohorts, and costs associated with SUIs and SAEs, assessed at the end of the trial. In the future multi-centre RCT the trialists will also consider the cost of other medical and surgical complications
8. Acceptability of the study to patients: recruitment numbers, invited numbers, assessed using retrospective questionnaire on acceptability (day 90 post-transplant)

Overall study start date
09/09/2016

Completion date
01/04/2024

Eligibility

Key inclusion criteria
All patients undergoing simultaneous pancreas and kidney transplantation will be considered eligible for inclusion in the trial. Eligibility for pancreas transplantation is outlined in the NHSBT Organ Donation and Transplantation Pancreas Selection Policy.

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 20; UK Sample Size: 20

Key exclusion criteria

1. Aged <18 years or >65 years
2. Inability to self-consent
3. Pancreas transplant alone after previous kidney or pancreas transplantation

Date of first enrolment
01/08/2022

Date of final enrolment
01/04/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Manchester Royal Infirmary
Department of Renal and Pancreatic Transplantation
Oxford Road
Manchester
United Kingdom
M13 9WL

Sponsor information

Organisation
The University of Manchester

Sponsor details
c/o Ms Lynne MacRae
Address Faculty of Biology, Medicine and Health
5.012 Carys Bannister Building
Manchester
England
United Kingdom
M13 9PL
+44 (0)161 275 5436
FBMHethics@manchester.ac.uk

Sponsor type
University/education

ROR

https://ror.org/027m9bs27

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/P019250/1

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trialists intend to publish the protocol as soon as possible.

Intention to publish date
01/04/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

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