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Controlled oxygenated rewarming of liver grafts by ex-situ machine perfusion prior to transplantation

Submission date	Recruitment status	[ ] Prospectively registered
03/08/2017	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
08/08/2017	Stopped	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
02/11/2018	Surgery	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Patients with end-stage liver disease can be treated with a liver transplant. A marginal graft is a donated organ with an increased risk for poor function or failure. The quality of marginal donor grafts can be improved by using different methods of organ preservation or techniques to revitalise the tissue before transplantation. The side effects of extended storage times, for instance, can be reduced with a short period of hypothermic (low temperature) oxygenated machine perfusion. The protective effect of this procedure can be improved with a limited and slow proceeding increasing of the temperature during oxygenated machine perfusion (controlled oxygenated rewarming). This results in a slower and more gentle activation of cell metabolism and reduces the risk of rewarming injury affecting cold stored tissue upon abrupt warming up during reperfusion. A series of individual treatments have been recently performed on marginal livers without complications and resulted in apparently good graft recovery after transplantation. The aim of this study is to test whether controlled oxygenated rewarming by machine perfusion improves the graft quality of donor livers.

Who can participate?

Patients aged over 18 with end-stage liver disease who are listed for liver transplantation

What does the study involve?

Donor livers are randomly allocated to the control group or the treatment group. The control group donor livers do not receive any experimental treatment before implantation. The treatment group donor livers are subjected to 2 hours of temperature controlled oxygenated machine perfusion before implantation, starting with a perfusion temperature of 10°C which is slowly increased up to 20°C. All patients are observed for 7 days following transplantation on a daily basis. Follow up includes additional observations on the day of discharge and 3 months after transplantation. Patients are followed until 3 months after the last patient joins the study and are asked to attend clinical routine follow up after the end of the study.

What are the possible benefits and risks of participating?

Possible benefits are an expected reduction of reperfusion injury of the graft and an improved

early recovery of liver function after transplantation. The planned treatment has been tested in animals as well as in an earlier study and is considered to be a safe procedure.

Where is the study run from?
University of Duisburg-Essen (Germany)

When is the study starting and how long is it expected to run for?
October 2016 to October 2019

Who is funding the study?
German Research Foundation (Germany)

Who is the main contact?
Prof. Andreas Paul

Contact information

Type(s)
Public

Contact name
Prof Andreas Paul

Contact details
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Hufelandstr. 55
Essen
Germany
45147

Additional identifiers

Protocol serial number
-

Study information

Scientific Title
Controlled Oxygenated Rewarming as Adjunct in Liver transplantation (CORAL) of human allografts from extended criteria donors (ECD): a prospective randomized controlled trial

Acronym
CORAL

Study objectives
Study hypothesis:
1. Controlled oxygenated rewarming of the cold preserved liver graft prior to warm repefusion will mitigate rewarming/reperfusion injury upon liver transplantation
2. Functional data obtained during ex-situ machine perfusion will help to evaluate graft integrity prior to transplantation

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee, Medical Faculty, University of Duisburg-Essen (Ethik Kommission der Medizinischen Fakultät der Universität Duisburg-Essen), 29/11/2016, ref: 16-7110 BO

Primary study design
Interventional

Study design
Single-center randomized controlled clinical pilot study with two parallel arms

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Preservation and implantation of liver grafts

Interventions
Randomisation: 1:1 block randomisation. The donor liver is randomized. Only patients who had given informed consent to participate in the study will be included in the randomization and the study.

Control study arm: everything will be left according to clinical standards without any experimental treatment.

Experimental study arm: Livers will be put on a CE-certified organ perfusion machine (Liver Assist®, Fa. Organ Assist, The Netherlands) and machine perfusion is started via hepatic artery and portal vein in a closed circuit with Belzer machine perfusion solution. Perfusate will be oxygenated to a pO2 > 500mmHg via two oxygenators included in arterial and portal circuits and temperature of the perfusate will be increased slowly over time to reach a steady state of 20°C afte 60 min. Total perfusion time will be 90 min or slightly longer, if the recipient preparation time will exceed the minimal perfusion time of 90 min (for further details see: Hoyer DP et al. Controlled Oxygenated Rewarming of Cold Stored Livers Prior to Transplantation: First Clinical Application of a New Concept. Transplantation. 2016;100:147-52).

All patients are observed for 7 days following transplantation on a daily basis. Follow up includes additional observations on the day of discharge and 3 months after transplantation. Patients are followed until 3 months after the last patient is randomised for this trial and are asked to attend clinical routine follow up subsequent to termination of the study.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Serum peak value of aspartate aminotransferase-AST during the first 3 days after transplantation

Key secondary outcome(s)

1. Death/6 month graft survival
2. Re-transplantation within 6 months after implantation
3. Time of stay in intensive care unit
4. Early Allograft Dysfunction (EAD) according to Olthoff (bilirubin>10mg/dl or INR >1.6 at POD 7, or peak-AST > 2000 U/L during first week after transplantation
5. Hepatic tissue perfusion measured 1h after revascularisation

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Completion date
01/10/2019

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
Enhanced criteria donor according to recommendations of the German Medical Chamber:
1. Donor age > 65 years
2. Intensive therapy including assisted ventilation > 7 days
3. Obesity of donor (BMI > 30)
4. Serum Na > 165 Mol/l
5. GOT GPT > 3 x of normal
6. S-Bilirubin > 3 mg/dl
7. Liver steatosis (histologically proven) > 40%

Patient:
1. Patient suffering from end-stage liver disease
2. Listed for liver transplantation
3. Signed informed consent
4. Age >18 years
5. Living in Germany

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex

All

Key exclusion criteria
1. HU-listed
2. Re-transplantation
3. Simultaneous participation in other preservation trial
4. HIV-positive
5. MELD score >25

Date of first enrolment
31/07/2017

Date of final enrolment
31/07/2017

Locations

Countries of recruitment
Germany

Study participating centre
University of Duisburg-Essen
Essen
Germany
45122

Sponsor information

Organisation
University Hospital Duisburg-Essen

ROR
https://ror.org/04mz5ra38

Funder(s)

Funder type
Government

Funder Name
Deutsche Forschungsgemeinschaft

Alternative Name(s)
German Research Association, German Research Foundation, Deutsche Forschungsgemeinschaft (DFG), DFG

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Germany

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date