A Multicenter Randomized Controlled Trial to Compare the Efficacy of End-ischemic Dual Hypothermic Oxygenated Perfusion with Standard Static Cold Storage of Liver Grafts Donated after Circulatory Death in Preventing Non-anastomotic Biliary Strictures after Transplantation

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To study the efficacy of end-ischemic DHOPE in reducing the incidence of NAS within six months after controlled DCD (Maastricht category III) liver transplantation.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON47263

Source
ToetsingOnline

Brief title
DHOPE-DCD Trial

Condition

- Gastrointestinal conditions NEC
- Hepatic and hepatobiliary disorders
- Hepatobiliary therapeutic procedures

Synonym
End-stage liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,fonds NutsOhra,Bridge to Life

Intervention

Keyword: donation after circulatory death, hypothermic oxygenated perfusion, liver transplantation, non-anastomotic biliary strictures

Outcome measures

Primary outcome

The incidence and severity of NAS as diagnosed by an Adjudication committee

(who are blinded for the group assignment) by means of magnetic resonance

cholangiopancreatography (MRCP) at six months after DCD liver transplantation.

Secondary outcome

To study the effect of the intervention (end-ischemic DHOPE after SCS), in

comparison to the control group (SCS only), concerning:

1. The severity and time interval of NAS after transplantation

2. The graft and recipient survival

3. The incidence of primary non-function (PNF)

4. The incidence of initial poor function (IPF)

5. The biochemical analysis of graft function and ischemia-reperfusion injury

6. The hemodynamic status of the recipient after graft reperfusion

7. Length of stay in the ICU and hospital

8. The incidence of postoperative complications, including infections and use

of antibiotics

9. The renal function

10. The perfusion characteristics during DHOPE (in the intervention group only)

11. The perfusate analysis during DHOPE (in the intervention group only)

12. Prognostication of NAS, based on micro ribonucleic acid (miRNA) profiles

(in the intervention group only)

13. Pathobiology of liver parenchyma and bile duct samples

14. Metabolic function, including new onset diabetes after transplantation

(NODAT)

15. Overall cost of treatment within 6 months (in/excluding return to work)

16. Health related quality of life

Study description

Background summary

Recent publications report good results of controlled donation after circulatory death (DCD) Maastricht category III liver transplantation when strict donor-recipient matching is applied and ischemia times are kept to a minimum. However a major concern remains the high rate of biliary complications after transplantation of DCD livers. Non-anastomotic biliary strictures (NAS) occur in 29% of patients receiving a DCD graft whereas the incidence of NAS in recipients of donation after brain death (DBD) liver grafts is 11%. NAS are associated with higher morbidity and increased cost of liver transplantation. Injury to the biliary epithelium and the peribiliary vascular plexus occurring during donor warm ischemia and static cold storage (SCS) has been identified as a major risk factor for development of NAS. Machine perfusion has been proposed as an alternative strategy for organ preservation, offering the opportunity to improve the quality of the organ by providing oxygen to the graft. Experimental studies have shown that end-ischemic hypothermic oxygenated machine perfusion (DHOPE) helps liver grafts to recover from ischemia by restoring mitochondrial function. Moreover, DHOPE has been shown to provide better preservation of

peribiliary vascular plexus of the bile ducts, which could be an important step forward in reducing the incidence of NAS after transplantation.

Study objective

To study the efficacy of end-ischemic DHOPE in reducing the incidence of NAS within six months after controlled DCD (Maastricht category III) liver transplantation.

Study design

An international, multicenter, prospective, randomized, controlled, interventional, clinical trial with a two parallel arm approach (treatment/control).

Intervention

In the intervention group liver grafts will be subjected to two hours of hypothermic, oxygenated perfusion at the end of SCS and before implantation. In the control group donor liver grafts will be preserved in accordance to standard practice by SCS only, without any further intervention.

Study burden and risks

Patients participating in this trial will experience minimal burden. There are only three differences compared with the routine practice: livers undergo DHOPE and patients undergo a MRCP at six months after transplantation and fill in a questionnaire. The intervention, DHOPE, is associated with a non-significant risk of injury of the isolated liver due to perfusion pressure or perfusion failure. The perfusion pressures in this protocol are very low and are reported to cause no harm to the organ. In case of perfusion failure, the liver can easily and quickly (within minutes) be brought to the same conditions as in the control group. In these bridging minutes the organ has a metabolism of 19% instead of the 11%. This is non-significant especially because the organ is saturated with oxygen before the possible event. There is a burden but there are no risks related to MRCP, which is planned during a routine hospital visit. When the intervention is effective in reducing the incidence of NAS, the patients participating in this trial benefit substantially when they are randomized to the intervention group. This study can only be performed in these patients because they undergo a DCD liver transplantation. The questionnaire is on health related quality of life and consists of six questions which take about 5 minutes to fill in. The questionnaire is obtained before transplantation and six months after transplantation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adult patients (>= 18 years old) with end-stage liver disease
- Signed informed consent
- Willing and able to attend follow-up examinations
- Donor liver graft from a controlled donation after circulatory death (Maastricht category III)
- Donors with a body weight >=40 kg

Exclusion criteria

- Simultaneous participation in another clinical trial that might possibly influence this trial
- Mental conditions rendering the subject incapable to understand the nature, scope and consequences of the trial

- Listed for liver transplantation due to fulminant liver failure or retransplantation because of PNF
- Recipient positive test for HIV
- Donor positive for HIV, Hepatitis B or C
- Patients with contra-indications for MRCP (i.e. pacemaker)
- Patients with simultaneous transplantation of another organ

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-01-2016
Enrollment:	100
Type:	Actual

Medical products/devices used

Generic name:	Liver Machine Perfusion with Liver Assist
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	07-10-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL52011.042.15

Study results

Date completed: 11-01-2020

Actual enrolment: 120

Summary results
Trial is onging in other countries