Normothermic Machine perfusion: an additional value for kidney transplant outcomes?

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON54462

Source
ToetsingOnline

Brief title
APOLLO study

Condition

- Renal disorders (excl nephropathies)
- Renal and urinary tract therapeutic procedures

Synonym
Kidney transplantation, postmortal kidney transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: Kidney transplantation, Machine perfusion, Organ preservation, Quality assessment

Outcome measures

Primary outcome

The incidence of DGF/PNF.

Secondary outcome

Clinical objectives:

To evaluate the impact of NMP on the following graft outcomes:

• The overall incidence of DGF.

• The incidence of DGF, excluding dialysis sessions for hyperkalaemia or volume overload.

• Duration of DGF, which is defined as the time between transplant and the last dialysis session.

• Total number of post-transplant dialysis sessions (measured up to 3 months post-transplantation)

• The incidence of PNF.

• Estimated Glomerular Filtration Rate (eGFR) trajectory in the first year after transplant calculated with the Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) formula.

• eGFR at 1 year, 3 years and 5 years calculated with the CKD-EPI formula.

• Biopsy-proven acute rejection within the first year post-transplant.

• Graft survival up to 5 years.

• Patient survival up to 5 years.

• Length of hospital stay, calculated from transplantation date until the date of discharge.

• The incidence and severity of (serious) adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)

• Postoperative complications, graded according to the Clavien-Dindo classification

Measures of microcirculation and pathophysiological processes:

• To evaluate the association between microcirculation/oxyhaemoglobin concentration during NMP and immediate kidney function (no DGF/PNF).

• To evaluate the association between microcirculation/oxyhaemoglobin concentration during NMP and other important graft outcomes:

• DGF duration

• Biopsy-proven acute rejection within the 1st year post-transplant

• Estimated Glomerular Filtration Rate trajectory in the first year post-transplant

• Graft survival up to 5 years

• To investigate differences in gene expression profile of the donor kidney during the course of NMP (measured in biopsies taken during NMP hourly), and differences in gene expression profile in NMP compared to HMP.

• To investigate the quantity of donor-derived cell-free DNA after transplantation as a marker of ischemia-reperfusion injury (measured in recipient blood on day 1-6 after transplant).

• To evaluate differences in perfusate sodium/urine sodium ratio during the

course of NMP (measured in perfusate and urine produced during NMP)

• To investigate the production of renine, EPO and vitamin D during the course

of NMP (measured in perfusate during NMP).

• To investigate differences in oxygen consumption during the course of NMP

(measured in perfusate during NMP)

• To evaluate differences in renal histology at start and end of NMP (measured

in biopsies taken during NMP), and differences in renal histology in NMP

compared to HMP.

• To evaluate the quantity of extracellular vesicles during the course of NMP

(measured in perfusate)

Study description

Background summary

The major challenge in kidney transplantation is the shortage of suitable donor kidneys. One way to enlarge the kidney donor pool is by using Extended Criteria Donor (ECD) grafts. However, these grafts have a 70% increased chance of graft failure, possibly because these grafts are more sensitive to ischemia-reperfusion injury(2). Because of the increased use of ECD kidneys, therapies to improve quality of these kidneys are of utmost importance. Dynamic preservation techniques have been introduced as being superior to static cold storage (SCS). A randomized controlled trial already showed the benefit of hypothermic machine perfusion (HMP) over SCS, which led to a protocol change in 2016(3). During HMP, the kidney is not metabolically active which means that the injury process persists. For more severely damaged kidneys, such as ECD kidneys, active repair may be needed to optimize the kidney before transplantation. Therefore, normothermic machine perfusion (NMP) has regained interest as a better preservation method for these kidneys.

NMP allows donor organs to be perfused with warm, oxygenated red blood cells in the absence of the immune components normally present in blood, including complement and neutrophils, with the aim of reversing the deleterious effects of warm and cold ischemia.
The first clinical study about NMP of the Cambridge group showed a significant

decrease in DGF/PNF after NMP, which is a surrogate marker for long-term graft survival(4, 5). The second study was carried out in Erasmus Medical Center (POSEIDON study, MEC 2017-503) and also showed a difference in the incidence of DGF and PNF (NMP group: 36%, controls: 63%, manuscript submitted), which was not statistically significant. Currently, an RCT is carried out in the UK to investigate the use of additional NMP against static cold storage only(6). However, it is still unknown whether NMP has additional value to HMP alone.

During NMP, viability and function of the donor kidney can be assessed. So far, clinical assessment of viability is performed through visual inspection, measurement of flow and resistance, urine production, perfusate injury markers and blood gas analysis. However, these methods only provide a general overview of the flow through the kidney without taken into account potential localized, suboptimal perfused areas(7). There is no method of constant real-time feedback on the perfusion of the donor kidney yet. The MoorO2Flo may be a device that can be useful for this purpose. This device is a non-contact, near-infrared-based imaging system with high temporal and spatial resolution, providing an index of blood flow and oxyhaemoglobin concentration over large surface areas. It allows continuous, quantitative assessment of microcirculatory perfusion, perfusion heterogeneity and relative tissue oxyhaemoglobin concentration. It has shown to be feasible to identify ischemic areas on gastric tube reconstructions following esophagectomy(8). However, the MoorO2Flo has not been validated for NMP yet and it is unknown whether differences in microcirculation and oxyhaemoglobin concentration or homogeneity correlate with post-transplant kidney function.

Study objective

The aim of the current study is two-folded. The primary aim is to assess the impact of NMP on the incidence of PNF/DGF. Secondly, we investigate the association between microcirculation and oxyhaemoglobin during NMP as measured with the MoorO2Flo and immediate kidney function (no DGF or primary non function (PNF)).

Study design

Open-label, single-center, prospective randomized clinical trial

Intervention

The intervention for the donor kidney is 2 hours of normothermic, end-ischemic machine perfusion.

Study burden and risks

Because of the normothermic oxygenated nature of the perfusion, failure of the

process leads to warm ischemia. In our pilot study (POSEIDON study, MEC 2017-503), no failures of the NMP procedure were observed and no primary nonfunction occurred. This shows the safety of the NMP procedure. If a failure would occur, a highly trained transplant surgeon is present at all time during the perfusion to switch to cold storage immediately if needed. Therefore, extra risk of the NMP procedure is deemed small. Renal biopsies are obtained during machine perfusion hourly. These biopsies have been shown in previous studies in our institution (INEX study, POSEIDON study) to possess no risk to the patient. Renal biopsies will also be obtained in the control group. One biopsy will be obtained during benching, and one biopsy will be obtained during transplantation after ureter anastomosis. All blood sampling will be combined with routine lab work. The amount of blood samples taken from the patient is 15 ml daily on day 1-6 after transplantation during hospitalization. NB: Blood sampling will only occur in a subset of 45 of the included patients. No extra hospital visits are needed. The most important benefit from participation is the prospect of a better functioning graft post-transplant.

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

Kidney related:
In order to be eligible to participate in this study, the donor kidney must meet the following criteria:
- Donation after Circulatory Death (DCD) type III/IV/V (Maastricht criteria) OR
- Donation after Brain Death (DBD) donor kidney IF the kidney meets ECD criteria:
o Donor >=60, OR
o Donor 50-59 years with 2 of the following risk factors: history of high blood pressure, creatinine greater than or equal to 1.5 mg/dl (133 umol/l), death resulting from stroke.

Recipient related:
- Adult (>=18 years old) recipients.
- Mentally competent recipients.
- Recipients who receive renal replacement therapy at the moment of transplantation.
- Recipients who provided written informed consent.

Exclusion criteria

- Multi-organ transplant recipients (such as combined liver/kidney).
- Receiving a donor kidney preserved on static cold storage.
- Receiving a donor kidney that is explanted after normothermic regional perfusion.
- DCD type I and II (Maastricht criteria).
- Dual kidney transplantation
- The patient receives another immunosuppression regime than standard-of-care (which is induction with basiliximab followed by triple therapy with tacrolimus, mycofenolate mofetil and prednisone)

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-01-2021
Enrollment:	80
Type:	Actual

Medical products/devices used

Generic name:	Kidney Assist
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	12-10-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2023

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL73213.078.20