PROlonged ex-vivo normothermic machine PERfusion for kidney regeneration

Published: 09-04-2021
Last updated: 15-05-2024

Primary Objective: To test clinical safety of PNMP up to 6 hours as a modality to assess viability and evaluate initiation of tissue repair ex-situ in donor kidneys prior to transplantation.Secondary Objective(s): To monitor standard and novel renal...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nephropathies
Study type	Observational invasive

Summary

ID

NL-OMON52366

Source
ToetsingOnline

Brief title
PROPER

Condition

- Nephropathies
- Renal and urinary tract therapeutic procedures

Synonym
kidney transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: kidney, normothermic, perfusion, transplantation

Outcome measures

Primary outcome

The primary clinical outcome will be safety of PNMP of DCD kidneys up to 6 hours, defined as absence of SUSARs and at least similar secondary outcomes at 1 month post transplantation as those expected from kidney transplants with similar donor and recipient characteristics, based on historical matched cohort.

Secondary outcome

Secondary clinical endpoints will include:

1. Glomerular filtration rate (GFR) at 6 months post transplantation.

2. Graft survival and recipient survival up to 6 months post transplantation.

3. Delayed graft function (DGF) defined as the need for postoperative dialysis during the first 7 days after transplantation.

4. Primary non-function (PNF) defined as permanent lack of graft function starting immediately after transplantation.

5. Biopsy-proven rejection.

6. Renal function defined by the estimated glomerular filtration rate (eGFR) according to the 4-variable Modification of Diet in Renal Disease (MDRD) equation at day 7, and 1, 3 and 6 months after transplantation.

7. Adverse events.

8. Postoperative complications graded according to the comprehensive complication index. Special interest will be given to predefined infectious

complications and the total length of use and cumulative doses of antibiotics.

Study description

Background summary

Kidney transplantation is the most effective and cost-efficient treatment for patients with end stage renal disease (ESRD). While outcomes of transplantation have improved, leading to a higher demand in transplantation, the availability of high-quality donor organs has stagnated. In response to this widening disparity between the number of donor organs available for transplantation and number of patients on the waiting list, there has been an increase in the use of kidneys from older and higher risk donors. To date, more and more deceased donor kidneys procured from older donors with co-morbidities i.e. extended criteria donors (ECD) and donors after circulatory death (DCD) are being transplanted. These kidneys are known to have an inferior graft function and survival.

To date, the choice to accept or decline a donor kidney for transplantation is currently based on a number of clinically available criteria, however, the influence of a combination of risk factors is not clear-cut and clinicians are in need of more accurate criteria whether to decline or accept the organ. The discard rate of organs from these higher risk donors is probably unnecessarily high, while other kidneys that are currently deemed suitable may never function in the recipient (primary non-function).

Normothermic machine perfusion (NMP) as ex-situ machine perfusion preservation is a promising graft protective strategy that is increasingly being utilized and is the subject of ongoing research and evolving clinical trials. NMP entails perfusing the kidney with warmed, oxygenated red blood cell (RBC) based perfusate to simulate physiological conditions. Advances in organ preservation have the potential to enable treatment of donor organs with therapeutic interventions that would otherwise be unsuitable for transplantation, thereby increasing organ utilization and the donor pool, reducing the waiting list for transplantation.

In this study, we propose the use of prolonged (>1 hour) NMP (PNMP) which has the added advantage of creating a window for ex-vivo regeneration of marginal donor organs, and to better test graft viability. The most pronounced effect of PNMP can be expected in these marginal kidneys, which will have acquired considerable damage before PNMP is started.

For clinical transplantation, no PNMP preservation method has yet been implemented. In our pre-clinical study using the PROPER protocol in both

participating centers (LUMC and UMCG) we successfully have perfused a total of 24 donor kidneys, deemed untransplantable, for a minimum of 6 hours. In this process we adapted a previously tested protocol of 1-hour NMP to the perfusate that optimally allowed prolonged NMP (dubbed the PROPER protocol). An hourly analysis of standardized parameters of function, damage and repair was performed showing no extra injury.
In conclusion, in the preliminary phase of the PROPER study we have gained expertise in PNMP, optimised the protocol and have established the necessary logistics to proceed to and initiate the clinical phase of PROPER.

The primary aim of this present clinical study is to determine the safety of PNMP for up to 6 hours in kidneys from DCD donors. Moreover, we will investigate whether PNMP allows better assessment and transplantability of DCD kidneys grafts and indeed offers a better platform for reconditioning and regeneration.

Study objective

Primary Objective: To test clinical safety of PNMP up to 6 hours as a modality to assess viability and evaluate initiation of tissue repair ex-situ in donor kidneys prior to transplantation.

Secondary Objective(s): To monitor standard and novel renal function parameters whilst the graft is normothermically perfused in order to help identify a set of markers predictive for organ performance.

Study design

The PROPER study is designed as a clinical safety study. It will be conducted in two transplant centres, LUMC and UMCG, where we developed the optimal conditions for PNMP in discarded human donor kidneys in a pre-clinical setting. The NMP procedures will take place in a dedicated room in the operating theatre, i.e. the Organ Preservation and Regeneration (OPR) room, under sterile conditions performed by a surgeon and the local investigator. Following hypothermic machine perfusion (HMP) during the transportation of the donor kidney, which is standard practice in the Netherlands, a total of n=18 (eighteen) donor kidneys will be subjected to PNMP prior to transplantation.

A cohort of n=6 (six) DCD kidneys will be subjected to 1 (one) hour of NMP and subsequently transplanted. Once this has been successfully achieved, the 1 (one) hour NMP period will be expanded to 3 (three) hours (PNMP3) and an additional n=6 (six) kidneys will be transplanted. Following a successful evaluation of outcomes following PNMP3 an additional n=6 (six) kidneys will be subjected to n=6 (six) hours of PNMP (PNMP6).

From a safety perspective, prior to proceeding from NMP1 to PNMP3, we will

determine that no SUSARs have occurred and at least similar secondary outcomes will be met 1 month post transplantation to those expected from kidney transplants with similar donor and recipient characteristics, based on historical matched cohorts.
Similarly, the step up from PNMP3 to PNMP6 will need to meet at least similar results as the comparable historical cohort.

Intervention

In this study, the use of prolonged (1-6 hours) NMP (PNMP) of donor kidneys will be tested which has the added advantage of creating a timeframe for ex-situ regeneration of marginal donor organs, and allows better assessment of graft viability.

Study burden and risks

In this study, we propose to use prolonged normothermic machine perfusion as a novel technique that entails pumping the kidney with warmed, oxygenated perfusate based on RBCs to closely simulate normal physiological conditions. The potential risks and burden to the patients in this study are minimal.

The minimal potential risks and burden for patients in this trial are related to the procedures which are performed merely for this trial: (prolonged) NMP itself and the additional biopsy that is collected.

For the (P)NMP itself, Hosgood et al. have shown that 1-hour NMP can be performed in a safe manner. We expect similar or better outcomes. However, NMP is performed using a machine, which could display technical failure during perfusion. If a technical failure occurs, an alarm goes off and the kidney can be removed immediately from the machine by the standby surgeon within a sterile environment. It will be immediately flushed with UW cold storage solution to 4ºC as is the case in static cold storage as per standard care. We regard the risk of NMP to be minimal.

Another factor is timing of the transplant. Theoretically, the start of the transplant surgery can be delayed with a minimum of 1 hour and a maximum of 6 hours by participation in this study. However, although we strive to limit cold ischemia time, it is quite common that kidney transplants are delayed for a couple of hours for logistical reasons. We therefore expect that the regular interval needed for logistics (at theatre or when there is a need for dialysis before transplantation) will take place simultaneously with the PNMP, and application of the PROPER protocol will not contribute to significant delay for the transplantation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Adult patients undergoing a kidney transplantation in LUMC (Leiden) or UMCG (Groningen) will be included in this study. Only donor kidneys from Maastricht Type III and V (controlled) donors after circulatory death (DCD, n=18) will be included. Recipient criteria include any single organ first renal transplant at a participating centre.

Exclusion criteria

Recipients of second or subsequent, ABO/HLA incompatible transplants and highly sensitised patients will be excluded. Kidneys with a cold ischaemia time >12 hours at the point of arrival at the transplant centre will be excluded.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2021
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	09-04-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	09-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26491
Source: NTR
Title:

In other registers

Register	ID
ClinicalTrials.gov	NCT04693325
CCMO	NL76344.058.20
OMON	NL-OMON26491