TRANSPLANT TRIAL WATCH

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THE PETER MORRIS CENTRE FOR EVIDENCE IN TRANSPLANTATION

TRANSPLANT TRIAL WATCH

To keep the transplantation community informed about recently published level 1 evidence in organ transplantation, ESOT (https://esot.org/) and the Centre for Evidence in Transplantation (www.transplantevidence.com) have developed the Transplant Trial Watch. The Transplant Trial Watch is a monthly overview of 10 new randomized controlled trials (RCTs) and systematic reviews. This page of Transplant International offers commentaries on methodological issues and clinical implications on two articles of particular interest from the CET Transplant Trial Watch monthly selection. For all high-quality evidence in solid organ transplantation, visit the Transplant Library: www.transplantlibrary.com

Randomized controlled trial 1

Hypothermic machine perfusion in liver transplantation – a randomized trial. van Rijn, R., et al. *New England Journal of Medicine*. 2021; 384(15): 1391–1401. https://doi.org/10.1056/NEJMoa2031532

Aims

The aim of this study was to compare the effect of hypothermic oxygenated machine perfusion with that of static cold preservation in recipients of liver transplants from donors after circulatory death.

Interventions

Participants were randomized to either the machine-perfusion group or the control group.

Participants

160 liver transplant patients aged ≥18 years.

Outcomes

The primary outcome was the occurrence of nonanastomotic biliary strictures during a period of 6 months following transplantation. The secondary endpoints were graft-related and general complications.

Follow-up

1 year.

CET conclusion

This is a well-conducted, multicentre randomized controlled trial (RCT) that took place across 6 transplant centres in 3 European countries and included 160 patients. Livers from donation after circulatory death were randomized by a centralized, computerized system, with stratification for centre and recipient primary sclerosing cholangitis. The livers were randomized to either static cold storage or static cold storage followed by minimum 2 h of perfusion in the Liver Assist device from Organ Assist, which provides dual oxygenated cold perfusion. Median perfusion time in the study was short (2 h 12 min) but this meant that the overall cold ischaemic time was longer in the perfused group (8 h 44 min versus 6 h 49 min). The study found a significant reduction in symptomatic, nonanastomotic, biliary strictures associated when livers were perfused (6% versus 18%). Importantly, radiologists were blinded to group allocation and scans were reviewed by two radiologists independently, with discrepancies reviewed by a third. There was also a significant reduction in the risk of postreperfusion syndrome with perfused livers. There was one case of primary nonfunction in the control group and none in the study group. There was no significant difference in early allograft dysfunction. This well-conducted study clearly shows that a short period of oxygenated hypothermic perfusion of DCD livers can reduce the incidence of nonanastomotic biliary strictures compared to static cold storage alone, despite a longer overall period of cold storage.

Jadad score 5.

Data analysis Strict intention-to-treat analysis.

Allocation concealment Yes.

Trial registration ClinicalTrials.gov – NCT02584283.

Funding source Non-industry-funded.

Clinical Impact Summary

The period of warm ischaemia experienced by livers from donors after circulatory death (DCD) is associated with increased incidence of nonanastomotic biliary strictures, requiring intervention and in some cases retransplantation. The largest increase in transplantation over recent years has come from the DCD donor pool, and so there is interest in interventions to reduce bile duct injury and improve outcomes. Oxygenated machine preservation may restore mitochondrial

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function and reduce the ischaemia reperfusion injury, with the potential to reduce bile duct injury resulting from the transplant process.

In this multicentre trial, van Rijn et al. randomized livers from controlled DCD donors to conventional static cold storage or hypothermic oxygenated machine perfusion (HOPE) [1]. The primary endpoint was the incidence of symptomatic nonanastomotic biliary strictures up to 6 months post-transplant, which were subsequently confirmed on protocol magnetic resonance cholangiopancreatography (MRCP) by blinded radiologists. The authors demonstrate a significant reduction in the incidence of nonanastomotic strictures, along with reductions in postreperfusion syndrome and early allograft dysfunction.

There are obvious parallels between this study and the recent phase III trial of normothermic machine preservation (NMP) of the liver [2]. The benefits of the two technologies appear similar, with similar magnitude in the effect on reperfusion injury and allograft dysfunction. The NMP study did not demonstrate a statistically significant difference in the incidence of biliary strictures, although the numerical difference was similar to the present study in the smaller DCD cohort.

Perhaps the largest distinction between HOPE and NMP is not clinical outcome, but logistics. HOPE is a much more straightforward technology, not requiring a red cell perfusate and with less monitoring required during perfusion. The potential for liver injury resulting from device malfunction is also lower as the liver is stored cold. However, the maximum perfusion time is shorter – NMP allows for perfusion for up to 24 h, offering obvious logistical advantages in operating theatre management with the potential for daytime operating and multiple transplants.

It will be interesting to see the results of future studies comparing the two technologies head-to-head, in particular exploring the effects on organ utilization from DCD donors.

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2. Nasralla D, Coussios CC, Mergental H, *et al.* Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557** (7703): 50–56.

Randomized controlled trial 2

Every two-month belatacept maintenance therapy in kidney transplant recipients greater than one-year posttransplant: a randomized, noninferiority trial. Badell, I.R., et al. *American Journal of Transplantation* 2021 [record in progress]. https://doi.org/10.1111/ajt.16538

Aims

The aim of this study was to determine whether the administration of belatacept every two months was noninferior to standard monthly dosing in kidney transplant patients with low immunologic risk.

Interventions

Participants were randomly assigned to receive belatacept therapy every month (q1m) or every two months (q2m).

Participants

166 renal transplant patients.

Outcomes

The primary endpoint was the assessment of estimated glomerular filtration rate (eGFR) at 12 months. The secondary endpoints included patient death, graft loss, rejection, the incidence of infections and formation of donor-specific antibodies (DSA).

Follow-up

1 year

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CET conclusions

This well-designed study randomized stable, low-risk renal transplant recipients > 1 year post-transplant to once-monthly or once every 2-month belatacept. The study was conducted on a noninferiority basis, and the authors found that 2-monthly belatacept resulted in non-inferior 12-month eGFR supporting less frequent dosing in these patients. There were numerically more acute rejection episodes in the 2-monthly arm, which the authors ascribe to nonadherent behaviour. There is the possibility of detection bias – for safety reasons, the patients in the 2-monthly arm had more frequent laboratory tests for the 4 months after switching regimens. Nonetheless, this perhaps highlights the importance of careful assessment of patient adherence when considering a regimen such as this, as the potential consequence of missed doses will be greater than more frequent dosing.

Jadad score 3.

Data analysis Strict intention-to-treat analysis.

Allocation concealment Yes.

Trial registration ClinicalTrials.gov – NCT02560558.

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