Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation

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Abstract

Background & Aims:
Although there is increasing interest in its use, definitive evidence demonstrating a benefit for postmortem normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) liver transplantation is lacking. The aim of this study was to compare results of cDCD liver transplants performed with postmortem NRP versus super-rapid recovery (SRR).

Methods:
This was a nationwide observational cohort study including all cDCD liver transplants performed in Spain between June 2012 and December 2016. Outcomes were assessed using propensity score inverse probability of treatment weighting (IPTW) to balance donor, graft, recipient, and center characteristics. Logistic and Cox regression models were used for binary and time-to-event outcomes.

Results:
Ninety-five cDCD liver transplants were performed with postmortem NRP and 117 with SRR. After IPTW adjustment, NRP was associated with significantly lower rates of overall biliary complications (OR 0.14; 95% CI 0.06–0.35), ischemic-type biliary lesions (OR 0.11; 95% CI 0.02–0.57), and graft loss (HR 0.39; 95% CI 0.20–0.78). One- and three-year graft survival rates were higher in the NRP group.

Conclusions:
Postmortem NRP in cDCD liver transplantation reduces biliary complications and graft loss compared with SRR and allows successful transplantation of livers from older donors.

Keywords

Liver transplantation; Donation after circulatory death; Normothermic regional perfusion; Ischemic-type biliary lesions; Graft survival

Introduction

Donation after circulatory death (DCD) donors, who are declared dead following cardiorespiratory arrest, are an increasingly common source of organs for transplantation. The period of donor warm ischemia surrounding circulatory arrest can damage the quality of organs in general and the liver in particular, because biliary epithelial cells are exquisitely susceptible to warm ischemia. As a result, early experiences with DCD liver transplantation were associated with high rates of graft dysfunction, primary non-function, and ischemic-type

biliary lesions (ITBL). Although complication rates have improved with growing experience and refinement of donor and recipient selection, the incidence of post-transplant ITBL remains higher among recipients of DCD grafts compared with those receiving livers from donation after brain death donors, with reported rates of approximately 16% versus 3% according to two meta-analyses.

The development of ITBL is associated with significant morbidity, including repeated biliary interventions and prolonged hospitalizations. Up to 70% of patients who develop ITBL either require retransplantation or die, underscoring the importance of strategies aimed at preventing this complication. Donation after circulatory death donors are typically classified into four categories according to the Maastricht classification system, based on the circumstances surrounding circulatory arrest. Among these, category III controlled DCD (cDCD) donors represent the most frequent source of DCD organs worldwide. These donors are ventilated patients with devastating brain injury who do not meet criteria for brain death, in whom the decision is made to withdraw life-sustaining therapy because it is no longer beneficial.

Experience gained over time has allowed for improved donor selection and perioperative management, leading to outcomes that in some settings approach those achieved with donation after brain death liver transplantation. However, these improvements have often been achieved at the cost of high liver discard rates, particularly among older donors or those with prolonged warm ischemia.

In contrast to many other countries, the initial Spanish experience with DCD focused on donors suffering sudden out-of-hospital cardiac arrest who could not be resuscitated after repeated attempts. These category II uncontrolled DCD (uDCD) donors are declared dead in the hospital, and femoral vessels are cannulated to establish normothermic regional perfusion (NRP), allowing reperfusion and reoxygenation of abdominal organs while donor evaluation and preparation for organ recovery are undertaken. Using NRP, livers exposed to extended periods of warm ischemia, in some cases up to 2.5 hours, have been successfully transplanted, with biliary complication rates and graft survival comparable to those observed with cDCD livers exposed to considerably shorter warm ischemia times.

In 2009, controlled donation after circulatory death was piloted in Spain, and in 2012 a comprehensive legal and ethical framework was established to support its widespread implementation. Unlike most other countries, where reports of NRP use in cDCD have been limited or anecdotal, approximately 25% of all cDCD transplants and 50% of all cDCD liver transplants performed in Spain have incorporated postmortem NRP. This unique national experience provides an opportunity to evaluate the impact of postmortem NRP on graft utilization and post-transplant outcomes in a real-world setting.

Despite increasing interest in NRP, definitive evidence demonstrating a benefit of postmortem NRP in cDCD liver transplantation has been lacking. Most published studies have been limited to single-center experiences or small series, and direct comparisons with the current standard recovery technique, super-rapid recovery (SRR), have been scarce. Therefore, the aim of the present study was to analyze the nationwide Spanish experience with cDCD liver transplantation and to compare outcomes between livers recovered using postmortem NRP and those recovered using SRR, with particular emphasis on biliary complications, graft survival, and overall transplant outcomes.

Patients and Methods

Study design

This was an observational nationwide cohort study including all controlled donation after circulatory death (cDCD) liver transplants performed in Spain between June 2012 and December 2016. Follow-up was completed in December 2017. The study was conducted in accordance with the Spanish National Protocol for Donation after Circulatory Death.

Donor selection and procedure

Potential cDCD donors were ventilated patients with devastating brain injury who did not meet criteria for brain death and in whom the decision was made to withdraw life-sustaining therapy on the grounds of futility. Transplant coordination teams discussed organ donation with the next of kin to determine whether donation was consistent with the patient's wishes and values. Decisions regarding the location and timing of withdrawal of life support were made on a case-by-case basis. When premortem interventions, such as heparin administration or vascular cannulation, were considered, specific authorization was obtained from the legal representatives.

The local liver transplant team was alerted regarding the potential cDCD donor. If the local team declined the offer, the liver was offered to other transplant centers according to geographic proximity. Each donor hospital independently determined the recovery method used for cDCD organs. Recovery options included normothermic regional perfusion (NRP) with premortem vessel cannulation, NRP with postmortem vessel cannulation, and super-rapid recovery (SRR).

Normothermic regional perfusion with premortem vessel cannulation

A bolus of heparin was administered prior to withdrawal of life support. Unilateral femoral artery and vein cannulation was performed. The contralateral femoral artery was cannulated with a deflated aortic occlusion balloon catheter, which was advanced under radiographic guidance into the supraceliac aorta.

Following completion of cannulation, the physicians responsible for patient care withdrew ventilatory support, marking the start of total warm ischemia. A total warm ischemia time exceeding 90 minutes was considered a contraindication to liver recovery. Functional warm ischemia was defined as the time from systolic blood pressure falling below 60 mmHg and/or arterial oxygen saturation below 80%, with a duration exceeding 30 minutes considered a contraindication for liver recovery.

Death was declared after five minutes of complete absence of spontaneous circulation and respiration. The aortic occlusion balloon was then inflated, and the NRP circuit was initiated. Correct balloon positioning, ensuring exclusion of the aortic arch vessels, was confirmed by chest radiography and by absence of arterial flow in the left radial artery catheter.

During NRP, blood samples were obtained at baseline and every 30 minutes to assess biochemical, hematological, and acid–base parameters. Pump flow was maintained above 1.7 L/min/m^2, temperature at 37°C, arterial oxygen tension between 100 and 150 mmHg, and hematocrit above 20%. Hepatic transaminases were monitored throughout the perfusion period; levels exceeding three times the upper limit of normal at baseline and/or more than four times the upper limit of normal at the end of NRP were considered relative

contraindications for liver recovery. In general, NRP was performed for 60 to 120 minutes to allow adequate reconditioning of the abdominal organs.

Normothermic regional perfusion with postmortem vessel cannulation

Following declaration of death, a midline laparotomy was performed. The abdominal aorta and infrarenal inferior vena cava were cannulated proximal and distal to their bifurcations, respectively. The supraceliac aorta was clamped, and the NRP circuit was initiated to restore normothermic perfusion to the abdominal organs.

Super-rapid recovery

After declaration of death, a midline laparotomy was performed. The distal abdominal aorta was cannulated, the supraceliac aorta was clamped, and cold preservation solution was rapidly flushed through the aorta, with venting through the inferior vena cava.

Recipient selection and procedure

Recipient selection policies varied among transplant centers. Some programs allocated cDCD livers to recipients at the top of the waiting list based on the model for end-stage liver disease (MELD) score, while others preferentially selected lower-risk recipients.

Outcomes

Primary non-function was defined as immediate graft failure resulting in either retransplantation or death within the first week following transplantation. Early allograft dysfunction was defined according to Olthoff's criteria. Diagnosis of ischemic-type biliary lesions was considered in recipients presenting with cholestasis and confirmed by cholangiographic imaging, typically magnetic resonance cholangiopancreatography, demonstrating diffuse non-anastomotic biliary strictures with or without prestenotic dilatation in the presence of a patent hepatic artery. All deaths were considered graft loss, regardless of graft function at the time of death.

Legislative, institutional, and recipient approval

The legal basis for the application of NRP in cDCD in Spain was established by Royal Decree 1723/2012 and national consensus protocols. Local protocols were approved by the institutional ethics committees at each participating center. All transplant candidates were informed of the possibility of receiving a DCD liver and provided written informed consent.

Data and statistical analysis

Categorical variables were summarized as frequencies and percentages, and continuous variables as mean and standard deviation or median and interquartile range, as appropriate. Survival analyses were performed using the Kaplan–Meier method.

Propensity score methodology was applied to reduce confounding inherent to the observational design. Inverse probability of treatment weighting (IPTW) was used to create a weighted pseudo-population in which baseline covariates were balanced between the NRP and SRR groups. Covariates included in the propensity model were donor age, sex, cause of death, intensive care unit stay, total and functional warm ischemia times, cold ischemia time, preservation solution, recipient age, sex, laboratory MELD score, transplant indication, and transplant center volume.

Baseline variables were compared using the chi-square test for categorical variables and analysis of variance with rank-transformed data for continuous variables. Logistic regression models were used to estimate odds ratios for binary outcomes, and Cox proportional hazards models were used to estimate hazard ratios for time-to-event outcomes. Covariate balance was assessed using standardized differences, with values below 0.15 considered acceptable. Statistical significance was defined as a p value < 0.05. Statistical analyses were performed using SAS version 9.4.

Results

During the study period, a total of 342 potential cDCD liver donors were evaluated. Among these, postmortem normothermic regional perfusion (NRP) was used in 152 livers (43%), with premortem femoral vessel cannulation performed in 132 cases (87%). Super-rapid recovery (SRR) was used in the remaining 190 livers (57%).

Postmortem NRP was run for a median duration of 120 minutes (interquartile range [IQR] 79–136). Of the livers undergoing NRP, 52 (34%) were discarded for transplantation for reasons detailed in Table 1. Only four livers (3%) were discarded during the NRP procedure itself, all due to significantly altered hepatic transaminases. In six cases (4%), NRP could not be completed due to technical complications; in five of these cases, cold preservation was performed and the livers were ultimately transplanted. These mixed-recovery cases were excluded from further analysis.

Among livers recovered using immediate postmortem SRR, 73 (38%) were discarded for transplantation (Table 1). Ultimately, 95 cDCD liver transplants performed with postmortem NRP and 117 cDCD liver transplants performed with SRR were included in the final analysis.

Donor and graft characteristics

Donor and graft characteristics are shown in Table 2. The median donor age was 56 years (IQR 45–65). Donors in the NRP group had shorter functional and total warm ischemia times compared with the SRR group. Specifically, functional warm ischemia time was reduced by a median of 3 minutes and total warm ischemia time by 4 minutes when premortem cannulation was performed. When cannulation for NRP was performed postmortem, functional and total warm ischemia times were longer compared with premortem cannulation; however, these differences did not translate into worse outcomes.

Cold ischemia times were similar between groups. Significant differences were observed in the type of cold preservation solutions used, with colloid-containing solutions being more frequent in the NRP group prior to IPTW adjustment. After application of inverse probability of treatment weighting, all baseline donor and graft covariates were adequately balanced, with absolute standardized differences below 0.15.

Recipient and transplant characteristics

Recipient and transplant-related characteristics are presented in Table 3. Before IPTW adjustment, differences were observed between groups with regard to recipient age, sex, laboratory MELD score, and transplant indication. Following IPTW adjustment, these imbalances were eliminated.

Median intensive care unit stay was 4 days (IQR 3–6) in the NRP group and 3 days (IQR 2–6) in the SRR group (p = 0.135). Median hospital length of stay was 15 days (IQR 12–23) for NRP recipients and 17 days (IQR 11–21) for SRR recipients (p = 0.818).

Post-transplant outcomes

Postoperative complications and outcomes are summarized in Table 4. In unadjusted analyses, no significant differences were observed between groups for early allograft dysfunction, primary non-function, or hepatic artery thrombosis.

In contrast, significant differences were found for biliary complications. Overall biliary complications occurred in 8% of NRP recipients compared with 31% of SRR recipients. After IPTW adjustment, postmortem NRP was associated with a significantly lower risk of overall biliary complications (odds ratio [OR] 0.14; 95% confidence interval [CI] 0.06–0.35; p < 0.001).

Ischemic-type biliary lesions (ITBL) were diagnosed in 2% of NRP recipients and 13% of SRR recipients. IPTW-adjusted analysis confirmed a significantly lower risk of ITBL in the NRP group (OR 0.11; 95% CI 0.02–0.57; p = 0.008). Among SRR recipients, ITBL was diagnosed at a median of 83 days post-transplant (IQR 47–212), whereas the two ITBL cases in the NRP group were diagnosed at 88 and 212 days, respectively.

Retransplantation rates were lower in the NRP group (5% vs. 9%), reaching statistical significance after IPTW adjustment (OR 0.24; 95% CI 0.07–0.78; p = 0.018). Graft loss occurred in 12% of NRP recipients and 24% of SRR recipients. Postmortem NRP was associated with a significantly reduced risk of graft loss in both raw and IPTW-adjusted analyses (hazard ratio [HR] 0.39; 95% CI 0.20–0.78; p = 0.008).

Patient mortality was lower in the NRP group (7% vs. 17%), although this difference did not reach statistical significance after IPTW adjustment (HR 0.53; 95% CI 0.23–1.22; p = 0.135).

Survival analysis

With a median follow-up of 20 months, one- and three-year patient survival rates were 93% and 93% for NRP recipients, compared with 88% and 84% for SRR recipients. Corresponding graft survival rates were 88% and 88% for NRP grafts and 83% and 76% for SRR grafts, respectively. Kaplan–Meier survival curves for patient and graft survival are shown in Figure 1.

Causes of graft loss

Causes of graft loss are detailed in Table 5. In the NRP group, graft loss was primarily attributable to infections, primary non-function, hepatic artery thrombosis, and ITBL. In the SRR group, ITBL was the most frequent cause of graft loss, followed by primary non-function, vascular complications, recurrent disease, and infections.

Discussion

This is the largest study published to date describing the use of postmortem normothermic regional perfusion (NRP) in controlled donation after circulatory death (cDCD) liver transplantation and the first to suggest that the application of NRP reduces postoperative biliary strictures, ischemic-type biliary lesions (ITBL), and graft loss when compared with super-rapid recovery (SRR).

At one year, rates of overall biliary complications, graft loss, and patient death among recipients of cDCD livers recovered with postmortem NRP were 8%, 12%, and 7%, respectively.

These outcomes were achieved despite a relatively high median donor age of 57 years. Recently published benchmarks for standard donation after brain death liver transplantation in high-volume centers have established acceptable targets of ≤28% biliary complications, ≤11% graft loss, and ≤9% patient death. The fact that outcomes in the present study approached or met these benchmarks, despite being an initial nationwide experience and without differences according to center volume, supports the reproducibility and robustness of these findings.

Several single-center series from North America and the United Kingdom have reported relatively low rates of biliary complications and ITBL following cDCD liver transplantation using SRR. However, in those studies, donor age was considerably lower, with mean or median ages ranging from 28 to 42 years. In contrast, studies evaluating older cDCD donors recovered with SRR have demonstrated biliary complication rates comparable to those observed in the SRR group of the present study, with overall biliary complication rates of approximately 30–33% and ITBL rates of around 12%. These observations suggest that donor age is an important modifier of biliary risk in cDCD liver transplantation and that the use of postmortem NRP may help mitigate this risk.

When NRP is employed, the period of warm ischemia between withdrawal of life support and initiation of perfusion is, at most, slightly longer than the duration of hepatic inflow occlusion commonly used during hepatic surgery. Intermittent hepatic inflow occlusion is generally well tolerated and has even been shown to induce protective effects through ischemic preconditioning in liver transplantation. Experimental and clinical studies have demonstrated that postmortem NRP restores cellular energy substrates, reduces nucleotide degradation products, and improves endogenous antioxidant concentrations prior to graft recovery. The beneficial effects of NRP appear to be mediated, at least in part, through adenosine signaling, as blockade of adenosine A2 receptors abolishes these protective effects.

In addition to restoring metabolic homeostasis, postmortem NRP may reduce the vasoconstrictive effects associated with cold graft washout during static cold storage. This mechanism may be particularly relevant in preventing biliary injury, given the exquisite sensitivity of the peribiliary vascular plexus to ischemia-reperfusion injury.

Over the past decade, there has been increasing interest in ex situ machine perfusion techniques as an alternative to static cold storage, particularly for marginal grafts and those derived from DCD donors. Available evidence suggests that machine perfusion may offer advantages in reducing ischemia-reperfusion injury. However, data demonstrating a consistent reduction in biliary complications or graft loss among cDCD livers remain limited. Moreover, machine perfusion is costly, technically complex, and requires meticulous cannulation and hemostasis to avoid vascular injury, loss of perfusate volume, or inadequate oxygen delivery, all of which may paradoxically exacerbate graft injury.

In contrast, postmortem NRP represents a comparatively economical and logistically simpler approach that can be implemented using existing extracorporeal circulation systems. In the context of cDCD, NRP may reduce or even obviate the need for ex situ machine perfusion, while achieving comparable or superior outcomes.

Ethical considerations surrounding the use of NRP in cDCD remain an important topic of discussion. In cDCD, death is declared based on circulatory criteria under the principle of permanence, meaning that although cardiocirculatory arrest may not be irreversible, it will inevitably lead to irreversible cessation of brain and brainstem function because circulation will not be restored. Concerns have been raised that restoring circulation through NRP could

violate this principle. However, NRP is designed to restore circulation only to the abdominal organs, with strict exclusion of the aortic arch vessels to prevent cerebral reperfusion. In cases of premortem cannulation, correct balloon positioning is confirmed radiographically before withdrawal of life support, and absence of cerebral flow is verified after initiation of NRP using arterial monitoring.

In jurisdictions where premortem interventions such as heparin administration or cannulation are prohibited, postmortem cannulation represents a viable alternative. Although functional and total warm ischemia times are modestly longer with postmortem cannulation, outcomes in the present study were no different from those achieved with premortem cannulation, indicating that the protective effect is attributable to NRP itself rather than minimal differences in ischemia time.

This study has several limitations. Its observational design and the non-random allocation of donors to recovery methods introduce potential selection bias. Differences in warm ischemia times and cold preservation solutions between groups are inherent to the recovery techniques themselves. However, these imbalances were addressed using inverse probability of treatment weighting, resulting in well-balanced covariates and reinforcing the validity of the findings. Cold ischemia times were relatively short across both groups, which may have mitigated the influence of the specific preservation solution used.

In conclusion, the results of this nationwide study provide compelling evidence that postmortem normothermic regional perfusion improves outcomes in cDCD liver transplantation when compared with super-rapid recovery. The use of NRP significantly reduces biliary complications, ischemic-type biliary lesions, and graft loss, while allowing successful transplantation of livers from older donors. These findings support the broader implementation of postmortem NRP as a strategy to improve graft utilization and post-transplant outcomes in cDCD liver transplantation.

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