Outcome of Liver Transplants Using Donors After Cardiac Death With Normothermic Regional Perfusion

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ABSTRACT

Background and Aims. The incorporation of normothermic regional perfusion (NRP) to donors after cardiac death (DCD) allows the recovery of liver grafts without the deleterious effects on graft survival the super-rapid technique may cause. The aim of the present report is to determine if the use of NRP in Maastricht type III DCD donors achieves short- and medium-term results comparable to donors after brain death (DBD).

Patients and Methods. This is an observational cohort study including 117 liver transplants executed between November 2016 and April 2021, divided into NRP (n = 39) and DBD (n = 78).

Results. Donors were younger in the NRP group (NRP 52 vs DBD 59.4 years; $P < .005$). Liver recipients in each study group were of similar age and severity of liver disease, although the predominant transplant indication in the NRP group was hepatocellular carcinoma. No differences in ischemia times were found. The incidence of early allograft disfunction and primary nonfunction was balanced between NRP and DBD. Eight patients required retransplant, all of them in the DBD group. No differences were found in biliary complications (NRP 12% vs DBD 5%; $P = .104$). Ischemic cholangiopathy affected a single DBD patient. Graft survival's Kaplan Meier curve shows a better outcome in the NRP group, although the difference did not reach significance ($P = .075$).

Conclusions. The incorporation of perfusion machines, and specifically the NPR in situ, converts suboptimal liver grafts such as DCD into organs comparable to DBDs.

CONTROLLED donation after cardiac death (DCD) in Spain has been rising exponentially since 2012. DCD liver grafts were initially recovered with the super-rapid technique, but the excess of warm ischemia time translated into increased rates of biliary lesions, especially ischemic cholangiopathy (IC), with the consequent deleterious effects on graft survival [1]. This fact led to the use of machine perfusion, which maintains the cellular energy substrates, restoring warm, oxygenated blood to the abdominal organs, mitigating ischemia-reperfusion injury. In Spain, most transplant centers use normothermic regional perfusion (NRP) in situ, which, in addition, involves consideration of the trends of transaminase levels and lactate during perfusion.

The aim of the present report is to determine whether the use of NRP in Maastricht type III DCD donors achieves short- and medium-term results comparable to donors after brain death (DBD).

PATIENTS AND METHODS

This is an observational cohort study including 117 liver transplants executed between November 2016 and April 2021, divided into 2 groups: NRP (n = 39) and DBD (n = 78). Primary sclerosing cholangitis, liver-kidney transplantation, and fulminant hepatitis were excluded.

Cannulation in our hospital is premortem. Life-sustaining treatment is withdrawn in the operating room. Death is confirmed no less than 5

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minutes after asystole and then NRP runs for 90 to 120 minutes. The preservation solution used is histidine-triptophan-ketoglutarate.

Regarding surgical transplant technique, we perform a temporary portocaval shunt, piggyback method, and the biliary reconstruction is end-to-end choledochocholedochostomy, interrupted suture without T tube. There are no differences in immunosuppression according to the type of donor; usually glucocorticoids and anticalcineurinics are used.

RESULTS

Donor

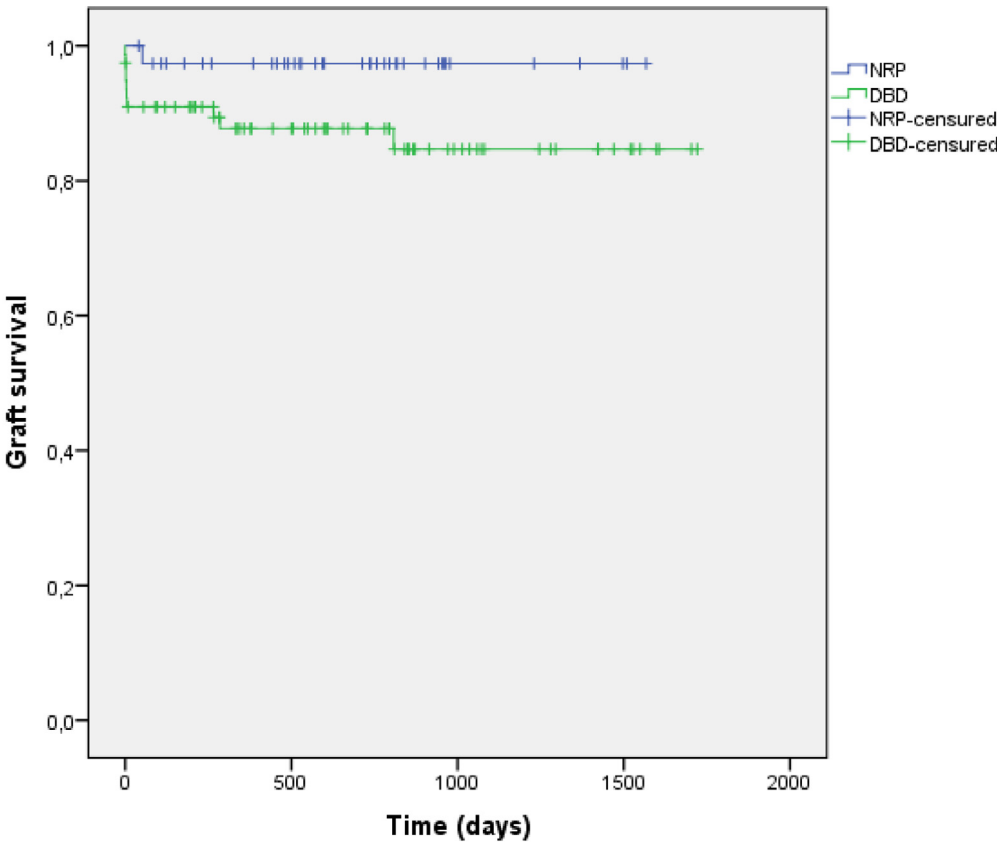
The median donor age in the NRP liver transplants was 52 years, compared to 59.4 years in the comparator group ($P < .005$). There was an increased intensive care unit stay ($P < .000$) and less need for vasoactive agents ($P < .000$) for those undergoing NRP.

Recipients

The liver recipients in each study group were of similar age, sex, and severity of liver disease (Model for End-Stage Liver Disease score = NRP 14.4 vs DBD 16 [$P = .111$]; Child-Pugh C classification = NRP 17.9% vs DBD 18.2% [$P = .975$]). The predominant transplant indication in the NRP group was hepatocellular carcinoma (38.5%) and in DBD alcoholic cirrhosis (31%).

Operative Details

The mean functional and total warm ischemia times were 13.10 minutes and 19.23 minutes, respectively. No significant difference was found between the groups in cold or warm ischemia times. There were also no differences in postreperfusion syndrome, fibrinolysis, or coagulopathy, but a higher consumption of platelets stands out in DBD ($P < .04$).



NRP, normothermic regional perfusion; DBD, donation after brain death.

Comparaciones globales

	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	3,162	1	,075
Breslow (Generalized Wilcoxon)	2,929	1	,087

Fig 1. Graft survival.

Postoperative Details

The incidence of early allograft dysfunction, defined by the Olthoff criteria, and primary nonfunction (PNF) was balanced between NRP and DBD. In DBD recipients, 3.84% (3 patients) developed PNF, and 0 patients in the DCD group. Eight patients required retransplant, all of them in the DBD group. Six of the retransplants were due to arterial thrombosis, 5 were early and 1 late, which developed IC. The other 2 patients who required retransplants were early because of PNF and a high-grade neoplasm in the donor.

Acute kidney injury and hemodialysis were more frequent in DBD, although the difference did not reach significance. All other features were comparable in the 2 groups, including intensive care unit and hospital stay, complications, reoperations, and acute cellular rejection. Regarding postoperative mortality, no differences were found either (NRP 5.1% vs DBD 8.9%; P = .442). The mean follow-up of both groups was similar (NRP 22.66 months vs DBD 22.59 months: P = .827). Patient survival analysis shows comparable 1- and 3-year Kaplan-Meier curves (NRP 94% vs 84% and NRP 71% vs DBD 75%, respectively). Graft survival's Kaplan-Meier curve shows a better outcome in the NRP group, although the difference did not reach significance (P = .075; Fig 1). Donor and recipients demographics and postoperative details are provided in Table 1.

Table 1. Donor and Recipient Demographics and Operative Details

Variable	NRP	DBD	*P*
Number	39	78	
Donor			
Age (years)	52 (15-68)	59.4 (25-81)	.005
Sex (M/F)	26 (66.7%)/ 13 (33.3%)	42 (54.2%)/ 36 (45.7%)	.202
BMI	25.92 (15-34)	26.69 (15.7-39)	.322
ICU stay (days)	7.21 (1-25)	2.62 (1-9)	.000
Vasoactive drugs	35.1%	86.4%	.000
Cause of death			.001
CVA	21 (53.8%)	51 (78.1%)	
Hypoxia	14 (35.9%)	7 (8.9%)	
Head injury	4 (10.35)	10 (13%)	
Recipient			
Age (years)	54.49 (35-70)	56.44 (16-71)	.980
Sex (M/F)	27 (69.2%)/ 12 (30.8%)	50 (64.9%)/ 27 (35.1%)	.644
BMI	26.81 (18.4-35.9)	27.7 (17.9-48.9)	.428
ICU stay (days)	4.54 (1-21)	4.69 (1-23)	
Hepatic function			.975
MELD	14.48 (6-26)	16.14 (6-27)	
Child-Pugh class C	17.9%	18.2%	
Disease group			.392
Viral infections	3 (7.7%)	12 (15.6%)	
Alcohol	9 (15%)	24 (31.2%)	
HCC	15 (38.5%)	22 (28.6%)	
Others	12 (30.8%)	20 (24.7%)	
Procurement			
f-WIT	13.10 (6-26)		
t-WIT	19.23 (10-38)		
Transplant			
CIT	298.21	310	.520
WIT	49.31	49.89	.868
PRS	7 (17.9%)	17 (21.6%)	.489
Fibrinolysis	4 (10.3)	9 (11.5%)	.707
Coagulopathy	1 (2.6%)	6 (7.6%)	.226
Transfusion			
Blood	366.79	419.01	.637
Plasma	111.26	124.16	.813
Platelets	46.79	142.21	.043

NRP, normothermic regional perfusion; DBD, donor after brain death; M, male; F, female; BMI, body mass index; ICU, intensive care unit; CVA, cerebrovascular accident; MELD, Model For End-Stage Liver Disease; HCC, hepatocellular carcinoma, f-WIT, functional warm ischemia time; t-WIT, total warm ischemia time; CIT, cold ischemia time, WIT, warm ischemia time; PRS, post-reperfusion syndrome.

Biliary Complications

No differences were found in biliary complications (NRP 12% vs DBD 5%; P = .104). IC affected a single patient in the DBD group and it was related to an arterial complication requiring retransplant. IC was not found among NRP patients.

Complication details are illustrated in Table 2.

DISCUSSION

Since the approval of the Spanish donation law in 2012, which allows DCD in our country, the trajectory of this kind of donors has changed. Initially, the super-rapid recovery (SRR) was the technique of choice for organ procurement; however, these

Table 2. Postoperative Complications

Variable	NRP	DBD	*P*
Number	39	78	
AST peak	2041.15	2019.50	.968
ALT peak	1289.90	1314.64	.929
EAD	13(34.2%)	15(19.2%)	.126
PNF	0(0%)	3(3.84%)	.210
Complications (Clavien)			.304
Mild (Clavien I-II)	18 (46.2%)	41 (52.5%)	
Severe (Clavien >III)	12 (30.8%)	14 (17.9%	
Reinterventions	4 (10.2%)	12 (15.3%)	.417
ACR	4 (10.2%)	16 (20.5%)	.155
AKI	9 (23.1%)	26 (33.3%)	.203
Hemodialysis	4 (10.2%)	10 (12.8%)	.669
Biliary complications			
Early (<3 months)	2 (5.1%)	3 (3.8%)	.835
Fistula	2	2	
Stenosis	0	1	
Late (>3 months)	3 (7.6%)	1 (12%)	.189
Fistula			
Stenosis			
IC	0 (0%)	1 (1.2%)	.474
Retransplant			.065
Early	0%	7 (8.9%)	
Late	0%	1 (1.2%)	
Hospital stay	14.7 (1-51)	13.7 (7-57)	.419
Postoperative mortality	2 (5.1%)	7 (8.9%)	.448

NRP, normothermic regional perfusion; DBD, donor after brain death; AST, aspartate aminotransferase; ALT, alanine aminotransferase; EAD, early allograft dysfunction; PNF, primary nonfunction; ACR, acute cellular rejection; AKI, acute kidney injury; IC, ischemic cholangiopathy.

organs developed serious rates of biliary complications and graft loss [1]. In 2018, we published a study comparing DCD with SRR vs DBD, and we found DCD recipients had a 10 times higher risk of developing IC [2]. In an attempt to reduce these events, the use of perfusion machines emerged. In 2014, Oniscu et al [3] published the application of NRP in 11 DCD livers and reported 1 PNF and 0% IC. Subsequently, Miñambres et al [4] reported the absence of IC using NRP. In 2020, we published a study comparing 22 SRR vs 23 NRP, obtaining a marked decrease in biliary complications using perfusion machines (22.7% vs 4.3%) [5]. Hessheimer et al [6] presented the first large series of DCD with NRP preservation, comparing 117 SRR vs 95 NRP, where it is stated that NRP reduces biliary complications and improves graft survival. In our study, the results obtained with NRP are superimposable to DBD. No differences were found in early allograft dysfunction or transaminase peak. Nasralla et al [7] demonstrates that NRP achieves a geometric decrease in the transaminase peaks. PNF was 0% in NRP, similar to Watson et al's [8] results. Regarding biliary complications, we also found no differences in the 2 groups. None of them evolved to IC. These results are consistent with the literature [7].

CONCLUSIONS

The incorporation of perfusion machines, and specifically the NPR in situ, converts suboptimal liver grafts such as DCD into organs comparable to DBDs. These results encourage us to use these donors in all clinical scenarios without added risks for patients.

REFERENCES

[1] O'Neill S, Roebuck A, Khoo E, Wigmore SJ, Harrison EM. A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation. Transpl Int 2014;27:1159–74.

[2] Pitarch Martínez M, Sánchez Pérez B, León Díaz FJ, Fernández Aguilar JL, Pérez Daga JA, Santoyo J. Donation after cardiac death in liver transplantation: An additional source of organs with similar results to donation after brain death. Transplant Proc 2019;51:4–8.

[3] Oniscu GC, Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MT, et al. In situ normothermic regional perfusion for controlled donation after circulatory death—the United Kingdom experience. Am J Transplant 2014;14:2846–54.

[4] Miñambres E, Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Ballesteros MA, et al. Improving the outcomes of organs obtained from c-DCD donors using abdominal normothermic regional perfusion. Am J Transplant 2017;17:2165–72.

[5] Muñoz DC, Pérez BS, Martínez MP, León Díaz FJ, Fernández Aguilar JL, Santoyo J. Does NRP improve the results of DCD liver transplantation? Transplant Proc 2020;52:1477–80.

[6] Hessheimer AJ, Coll E, Torres F, Ruíz P, Gastaca M, Fondevila C, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. J Hepatol 2019;70:658–65.

[7] Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Friend PJ, et al. Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. Nature 2018;557:50–6.

[8] Watson C, Hunt F, Messer S, Currie I, Large S, Sutherland A, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. Am J Transplant 2019;19:1745–58.