Does Normothermic Regional Perfusion Improve the Results of Donation After Circulatory Death Liver Transplantation?

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ABSTRACT

Background. The so-called grafts or donors with extended criteria are a risk factor for the development of liver transplant activity. One source comes from controlled donation after circulatory death (cDCD). The hypothesis was to verify the improvement in results by comparing DCD liver transplants performed with postmortem normothermic regional perfusion (NRP) vs super-rapid recovery (SRR), the current standard for cDCD. A prospective study comparing both techniques was carried out.

Methods. A total of 42 transplants were performed with cDCD, 22 of which were with SRR and 23 with NRP from April 2014 to September 2019.

Results. Differences were found in early allograft dysfunction (68.1% in the SRR group vs 25% in the NRP group; $P < .01$) and biliary complications (22.7% vs 5%, respectively; $P = .04$). Differences were also found, although not statistically significant, in ischemic cholangiopathy (13.6% in the SRR group vs 5% in the NRP group; $P = .09$), and retransplant rate (9.1% vs 0%, respectively; $P = .3$).

Conclusions. With the use of NRP machines, results are similar to the standard donation with donors in brain death in terms of rate of early allograft dysfunction and survival of the patient and graft attempted, reducing the rate of ischemic cholangiopathy compared with SRR.

THE grafts or donors with extended criteria are a risk factor for the development of liver transplant activity. One of these sources is controlled donation after circulatory death (cDCD). The standard technique for organ recovery in this type of donor was the super-rapid recovery (SRR).

The aim of this study was to verify the improvement in results by comparing DCD liver transplants performed with postmortem normothermic regional perfusion (NRP) vs SRR the current standard for cDCD.

MATERIALS AND METHODS

This was an observational prospective study comparing SRR vs the use of NRP, including all DCD transplants performed in the Hospital Regional Universitario de Málaga between April 2014 and September 2019. We used NRP with premortem vessel cannulation. Postmortem NRP was used for about 90-120 minutes. Five livers were discarded because of technical problems or liver appearance.

Regarding the results of postoperative variable, we defined primary nonfunction as immediate graft failure resulting in either retransplantation or death within the first week. Early allograft dysfunction (EAD) was defined according to Olthoff's definition [1].

RESULTS

During the study period, 45 cDCD transplants were performed, 22 with SRR and 23 with NRP, from April 2014 to July 2019. We did not include transplants in fulminant hepatitis and simultaneous liver-kidney transplants.

A statistical analysis was made of demographics variables of the recipient and the donor. The donor's average age was 53 years in the SRR group and 51 years in the NRP group

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($P = .331$); 77% of the SRR group and 56% of the NRP group were male ($P = .418$), and the body mass index was 26.3 and 26.4, respectively ($P = .834$). The average stay in the ICU before recovery was 7 and 9 days each, respectively ($P = .089$). The cause of death in the SRR group was stroke in 55% of patients, head injury in 9% of patients, and anoxia in 36% of patients. Otherwise, in the NRP group, stroke occurred in 53% of patients and anoxia in 47% of patients. Regarding warm ischemic time, in the SRR group the functional and total warm ischemic times were 15.82 and 23.09 minutes, respectively. In the NRP group, the functional and total warm ischemic times were 14.36 and 21.27 minutes, respectively ($P = .498$ in functional warm ischemic time and $P = .418$ in total warm ischemic time). Table 1 provides donors' characteristics and information about warm ischemic time.

The recipients' average age was 57 years in the SRR group and 60 years in the NRP group ($P = .331$); 81% of the SRR group and 56% of the NRP group were male ($P = .448$), and the IMC was 27.1 and 27.7, respectively ($P = .734$). Model for End-Stage Liver Disease score was 16.3 in the SRR group and 16.1 in the NRP group ($P = .349$). The etiology of the liver disease was associated with alcohol in 32% of patients, with a virus in 18% of patients, and with hepatocellular carcinoma in 36% of patients in the SRR group. In the NRP group, the etiology of the liver disease was associated with alcohol in 19% of patients, with a virus in 6% of patients, and with hepatocellular carcinoma in 50% of patients.

Cold ischemic time in the SRR group was 283 minutes and 280.5 minutes in the NRP group ($P = .331$). Warm ischemic time in transplant surgery was 48 minutes with SRR and 54 minutes with NRP ($P = .418$). Reperfusion syndrome occurred in 27.3% of the SRR group and in 6.3% of the NRP group ($P = .09$). Table 2 shows information about recipient and ischemic time in surgery.

The enzymatic peak of cytolysis was glutamic-oxaloacetic transaminase = 5828 vs 2077 ($P = .01$) and glutamic pyruvate transaminase = 2343 vs 1309 ($P = .05$) in the SRR group and NPR group, respectively.

Differences in EAD were found (68.1% with SRR vs 30.4% with extra-corporeal membrane oxygenation; $P < .01$) and biliary complications (22.7% vs 4.3%; $P = .04$). Rate of ischemic type biliary lesion (ITBL) was 13.6% in the SRR group vs 5% in the NRP group ($P = .09$). Acute rejection occurred in 18.1% of the SRR group vs 15% in the NRP group ($P = .7$), and the retransplant rate was 9.1% in the SRR group vs 0% in the NRP group ($P = .23$). Table 3 details information about postoperative results.

The average follow-up time for the patients was 1052 days in the SRR group and 440 days in the NRP group. Among the SRR group, 85% of patients were alive vs 95% among the NRP group. Four patients in the SRR group died. Two of these patients died immediately after the operation, 1 patient died of a hyperacute rejection and the other because of cardiac failure. The other 2 patients died of chronic rejection in the follow-up period; one of these patients died because of a pancreatitis after an endoscopic retrograde cholangiopancreatography from an ischemic-type lesion. The patient who died in the NRP group was a woman with sepsis and neurologic symptoms, probably from the immunosuppressive therapy. The survival curve appears in Fig 1.

Table 1. Donors Information

	SRR	NRP	*P*
Age	53	51	.331
Male (%)	77	56	.418
BMI	26.3	26.4	.834
ICU stay, d	7	9	.089
Vasoactive drugs (%)	31.80	43.80	.361
Functional warm ischemic time, min	15.82	14.36	.498
Total warm ischemic time, min	23.09	21.27	.418

Abbreviations: BMI, body mass index; ICU, intensive care unit; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

Table 2. Recipient Information

	SRR	NRP	*P*
Age	57	60	.331
Male (%)	81	56.30	.418
BMI	27.1	27.7	.834
MELD	16.3	16.1	.349
Cold ischemic time, min	283	280.5	.331
Warm ischemic time, min	48	54	.418
Reperfusion syndrome (%)	27.30	6.30	.09

Abbreviations: BMI, body mass index; MELD, Model for End-Stage Renal Disease; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

DISCUSSION

The warm ischemia marks important differences with other types of liver donation because biliary cells are exquisitely susceptible to warm ischemia [2]. Initial experiences with DCD liver transplantation described high rates of graft dysfunction and nonfunction and ITBL. Development of ITBL leads to repeat biliary procedures and hospitalizations; up to 70% of patients with ITBL either require retransplant or die [3,4]. This disadvantage is controlled by NRP machines, allowing the evaluation of hepatic grafts prior to their recovery.

There are 4 categories of DCD donor classification: Maastricht type III (ventilated patients with a devastating

Table 3. Postoperative Results

	SRR	NRP	*P*
GOT peak	5828	2077	.01
GPT peak	2343	1309	.05
EAD (%)	68.10	30.40	.01
Acute rejection (%)	18.10	13	.6
Retransplant (%)	9.10	0	.13
Biliary complication (%)	22.70	4.30	.04
ITBL (%)	13.60	0	.09

Abbreviations: EAD, early allograft dysfunction; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic pyruvate transaminase; ITBL, ischemic type biliary lesion; NRP, normothermic regional perfusion; SRR, super-rapid recovery.

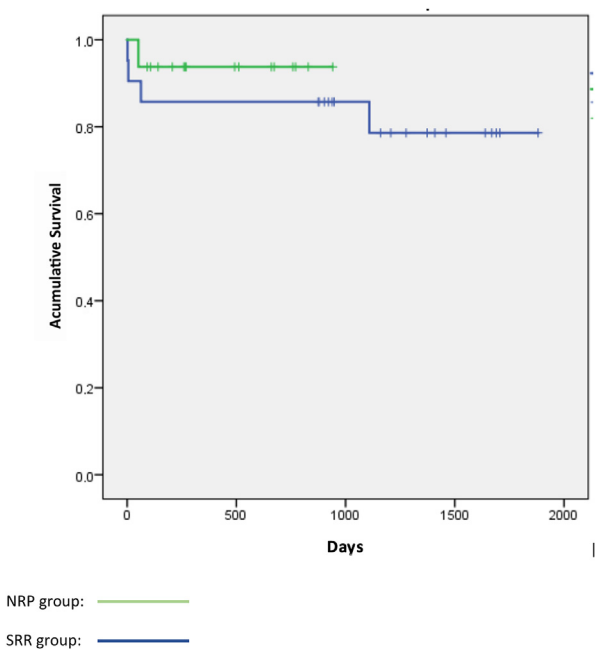

Fig 1. Survival curve.

brain injury that does not meet the criteria for brain death) [5] is the most frequent source of DCD organs and the one that we perform. In 2009, DCD was piloted in Spain, and a legal and ethical framework for its widespread practice was established in 2012.

Our hospital detailed our experience with SRR in DCD against donor brain death [6]. Other research has compared the outcomes of cDCD and donation after brain death [7], also with older patients [8]. Some studies from 2017 have shown the benefit in DCD liver transplantation using NRP [9]. A British study published in 2018 showed improvements in the result of NRP [10]. The researchers compared 43 DCD liver transplants undergoing NRP vs 187 non-NRP DCD liver transplants performed during the same period. Other studies have shown his single experience with NRP as Bilbao group [11].

In 2018, a systematic review about the impact of machine perfusion of the liver on post-transplant biliary complications was published by Boteon et al [12]. In 2019, the first Spanish experience comparing results of DCD liver transplants performed with postmortem NRP vs SRR was published, with the conclusion that the use of postmortem NRP in DCD liver transplantation appears to reduce postoperative biliary complications, ITBLs, and graft loss, and allows for the transplantation of livers even from DCD donors of advanced age [13].

Hessheimer et al [13] conducted the largest study published to date describing the use of postmortem NRP in DCD liver transplantation and the first to suggest that the application of NRP reduces postoperative biliary strictures and ITBL and improves graft survival compared with SRR. In 2019, Hessheimer et al published a review about NRP machines and ex situ normothermic machine perfusion [14].

The results of our study support the use of postmortem NRP in reducing biliary complications, in particular ITBL, and help improve DCD liver graft survival compared with the current standard SRR.

CONCLUSIONS

In conclusion, the use of postmortem NRP in DCD liver transplantation can help achieve improved outcomes compared with the use of SRR.

REFERENCES

[1] Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943–9.

[2] Hessheimer AJ, Cárdenas A, Garcia-Valdecasas JC, Fondevila C. Can we prevent ischemic-type biliary lesions in donation after circulatory determination of death liver transplantation? Liver Transpl 2016;22:1025–33.

[3] Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 2011;253:817–25.

[4] 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. https://doi.org/10.1111/tri.12403.

[5] Thuong M, Ruiz A, Evrard P, Kuiper M, Boffa C, Akhtar MZ, et al. New classification of donation after circulatory death donors definitions and terminology. Transpl Int 2016;29:749–59.

[6] Pitarch Martínez M, Sánchez Pérez B, León Díaz FJ, Fernández Aguilar JL, Pérez Daga JA, Montiel Casado MC, et al. 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. https://doi.org/10.1016/j.transproceed.2018.02.208.

[7] Tang JX, Na N, Li JJ, Fan L, Weng RH, Jiang N. Outcomes of controlled donation after cardiac death compared with donation after brain death in liver transplantation: a systematic review and meta-analysis. Transplant Proc 2018;50:33–41. https://doi.org/10.1016/j.transproceed.2017.11.034.

[8] Croome KP, Mathur AK, Lee DD, Moss AA, Rosen CB, Heimbach JK, et al. Outcomes of donation after cardiac death liver grafts from donors $\geq$ 50 years of age: a multi-center analysis. Transplantation 2018;102:P1108–41. https://doi.org/10.1097/TP.0000000000002120.

[9] Miñambres E, Suberviola B, Dominguez-Gil B, Rodrigo E, Ruiz-San Millan JC, Rodríguez-San Juan JC, et al. Improving the outcomes of organs obtained from controlled donation after circulatory death donors using abdominal normothermic regional perfusion. Am J Transplant 2017;17:2165–72. https://doi.org/10.1111/ajt.14214.

[10] Watson CJE, 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. https://doi.org/10.1111/ajt.15241.

[11] Ruiz P, Gastaca M, Bustamante FJ, Ventoso A, Palomares I, Prieto M, et al. Favorable outcomes after liver transplantation with normothermic regional perfusion from donors after circulatory death: a single-center experience. Transplantation 2019;103:938–43. https://doi.org/10.1097/TP.0000000000002391.

[12] Boteon YL, Boteon AP, Attard J, Wallace L, Bhogal RH, Afford SC. Impact of machine perfusion of the liver on post-transplant biliary complications: a systematic review. World J Transplant 2018;8:220–31. https://doi.org/10.5500/wjt.v8.i6.220.

[13] Hessheimer AJ, Coll E, Torres F, Ruíz P, Gastaca M, Rivas JI, et al. Normothermic regional perfusion vs super-rapid recovery in controlled donation after circulatory death liver transplantation. J Hepatol 2019;70:658–65. https://doi.org/10.1016/j.jhep.2018.12.013.

[14] Hessheimer AJ, Riquelme F, Fundora-Suárez Y, García Pérez R, Fondevila C. Normothermic perfusion and outcomes after liver transplantation. Transplant Rev (Orlando) 2019;33:200–8. https://doi.org/10.1016/j.trre.2019.06.001.