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Evaluation of Results in Liver Transplantation with Ultrafast Technic Harvesting in Non-Heart-Beating Donors (Maastricht II and III): An Analysis of a Large Single-Center Experience

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Abstract

Objective: To determine the viability of liver graft obtained from NHBD Maastricht II and III and long-term recipients survival.

Material and Methods: Retrospective study of LT performed with en bloc technique for abdominal organ harvesting in NHBD in our hospital from December 1995 to January 2015.

Results: 25 cases were performed: 17 Maastricht category II and 8 cases category III. Maastricht II. With a mean follow-up of 91.36 months (0,5-211m) one year recipient survival was 82.35% and 70.6% at 5 years. Liver graft survival was 70.6% and 64.7% at one year and five years, respectively. None of deaths during follow-up was secondary to graft failure. 3 patients were retransplanted: 2 were urgently for PAF and one at 3 years for HBV. Maastricht III. With a mean follow up of 14.67 months one year recipient survival was 100% and 88,9% of the graft survival. Two retransplantation were performed: one urgent for "small for size" and another at 18 months because of ischemic cholangitis. Conclusions: Grafts from NHBD allows acceptable results in terms of patient and graft survival.

Keywords: Liver transplantation; Non-heart-beating donors; Ischemic cholangitis; Primary allograft failure, Early allograft dysfunction

Abbreviations:

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CPS: Cardiopulmonary Support; DBD: Donation/Donor After Brain Death; ECMO: Extracorporeal Membrane Oxygenation; EAD: Early Allograft Dysfunction; GS: Graft Survival; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; INR: International Normalized Ratio; IC: Ischemic Cholangitys; LT: Liver Transplantation; MELD: Model End Stage Liver Disease; NHBD: Non-Heart-Beating Donors; PAF: Primary Allograft Failure; RS: Recipients Survival

Introduction

Liver transplantation (LT) is the treatment of choice in patients with end-stage liver disease. However, about 10% of transplant candidates patients die waiting for an organ, being a chronic shortage of organs the main factor limiting organ transplantation. According to the latest data from UNOS less than 50% of patients on waiting list in the US of 2012 were conducted. The scenario is similar in Spain. Currently, the transplant team have the challenge to develop strategies to increase the number of donors [1,2]; one alternative available to increase the number of grafts is the use of organs from non-heart-beating donors (NHBD). Although this donors appears to have promising results in terms of graft survival, it raises several medical, ethical, legal, economic, and logistic challenges at the intersection of cardiac arrest, resuscitation, organ donation, and organ preservation after declaring death [3].

Cardiac death donors were initially classified into four groups in the first International Workshop of NHBD on Maastricht in 1995 [4]. However, this classification does not fit exactly to cardiac death donation in our country; therefore we currently use Maastricht classification amended in 2011 in Madrid [5]. In clinical practice donors are classified into controlled and uncontrolled deaths, depending on where cardiac arrest occurs. Although uDCD appears to have promising results in terms of graft survival, it raises several medical, ethical, legal, economic, and logistic challenges at the intersection of cardiac arrest, resuscitation, organ donation, and organ preservation after declaring death

Due to the warm ischemia times (WIT) commonly associated with NHBD, the use of this type of organ is related to higher rates of graft loss and other complications compared to Donation after Brain Death (DBD). Some multicenter trials have shown worse long-term outcomes of LT from NHBD, including increase of primary allograft failure (PAF) and shorter overall survival [6].

The aim of this study is to determine the feasibility of liver graft obtained from donors after cardiac death Maastricht category II and III, and recipients long-term survival at "Complejo Hospitalario Universitario de A Coruña" (CHUAC).

Material and Methods

Retrospective study of LT from NHBD Maastricht amended, category II and III, made in our hospital from December 1995 to January 2015. Cases of category III have been performed from June 2012.

The selection criteria of NHBD were those reflected in the national protocol of donor LT and donation after cardiac death in force in each period [5,7]. Recipients of LT were included on the waiting list under agreement of the Liver Transplantation Department of our hospital, and initially classified according to Child-Pugh score [8] as a prognostic marker of severity of liver disease in stage cirrhosis and, from 2003, the "Model for End-stage Liver Disease" (MELD) score [9] was associated.

Organ preservation

Maastricht II: The donor remained in the emergency room and 5 minutes after declaration of death, cardiopulmonary support (CPS) was initiated to preserve organ viability. CPS included simultaneous application of chest (mechanical) and abdominal (manual) compression.

If family and legal authorities consented to donation, the patient was transferred to the operating room for organ harvest. The en bloc technique for abdominal organ harvesting was used [9]. The organ was prefunded by University of Wisconsin solution at 4°C until reperfusion of the liver in the recipient.

Maastricht III: The Critical Care team identifies patients who meet criteria for organ donation. If there is consensus between the family and the relevant legal authorities, the donor is transferred to the operating room and is withdrawal from life support.

Five minutes after asystole, death is declared and the aorta is cannulated and the in bloc technique for abdominal organ harvesting is initiated [10]. Normothermic extracorporeal membrane oxygenation (ECMO) was used in the last two donors (MAQUET CARDIOHELP ® device), performing cannulation of aorta and abdominal cava vein and then clamping thoracic aorta above the diaphragm. The infusion was continued for 45-60 minutes, until arterial pH normalization and improvement in lactate levels.

Definitions

Warm ischemia time: Time ranging from start of cardiac arrest to aortic perfusion. This period of time is only considered in Maastricht II NHBD and includes time of cardiac/abdominal massage, reporting and observation of death and beginning of surgery (Figure 1).

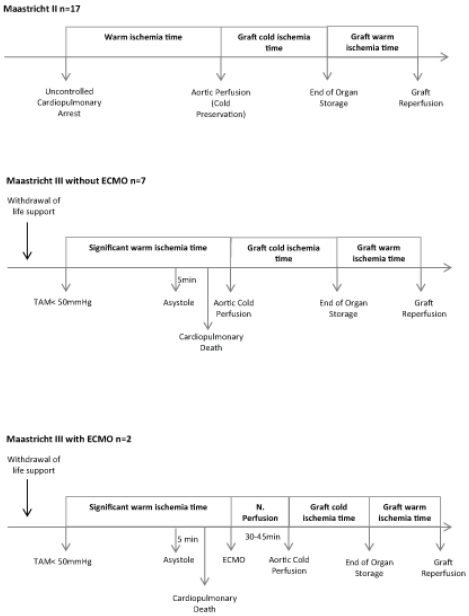

Figure 1: Ischemia times in Maastricht category II and III.

Significant warm ischemia time: Time from the decline of donor mean arterial pressure below 50 mmHg to start of arterial perfusion. This time period includes only Maastricht III NHBD (Figure 1).

Graft warm ischemia time: Elapsed time from the beginning of in situ graft implant to reperfusion via portal vein.

Graft cold ischemia time: From aortic perfusion at harvest to start of graft warm ischemia time.

Reperfusion síndrome: Decrease of 20% or higher in blood pressure after reperfusion organ. It may be hypotension or asystole.

Early allograft dysfunction (EAD): Presence of one or more of the following postoperative laboratory analyses reflective of liver injury and function: bilirrubin >10mg/dL on day 7; international normalized ratio (INR) >1,6 on day 7; and alanine or aspartate aminotransferases >2000 IU/L within the first 7 days [11,12].

Results

In the study period a total of 934 LT were performed at our institution 26 grafts were from NHBD; 17 Maastricht category II and 9 category III. Table 1 shows characteristics of each group. The average age of donors and recipients was 46.48 and 55.85 years respectively.

	Maastricht II	Maastricht III	Total
Media age of recipient (years)	54.71 (44-67)	58 (52-66)	55.85 (44-67)
Media age of donor (years)	43.9 (18-72)	51.67 (6-71)	46.48 (6-72)
LT indications			
Alcohol	11 (64.7%)	3 (33,3%)	14 (53,8%)
Hepatocellular carcinoma	1 (5.9%)	5 (55.6%)	6 (23.1%)

HCV	1 (5.9%)	0 (0%)	1 (3.8%)
HBV	1 (5.9%)	0 (0%)	1 (3.8%)
BPC	0 (0%)	1 (11.1%)	1 (3.8%)
PSC	1 (5.9%)	0 (0%)	1 (3.8%)
Cryptogenic	1 (5.9%)	0 (0%)	1 (3,8%)
Caroli D.	1 (5.9%)	0 (0%)	1 (3,8%)
Follow up (month)	91.36 (0.5-211)	14,77 (1-30)	64.85 (0,5-211)
Graft Survival (1 year)	70,5%	88.9%	80.8%
Recipient Survival (1 year)	82.35%	100%	88.5%

Table 1: Features per group. LT: Liver transplant; HCV: Hepatitis C Virus; HCB: Hepatitis B Virus; BPC: Billiary Primary Cirrhosis; PSC: Primary Sclerosing Cholangitis.

The most common indication of LT was alcoholic cirrhosis (52%), followed by hepatocellular carcinoma. With a mean follow up of 64.85 months, one year GS was 80,8% and RS was 88,5% (Table 1).

Maastricht II: The mean age of donors in this group was 43.9 years in the range of 18-72 years and a mean age of recipients was 55.5 years (44-67a). The mean warm ischemia time was 103.4 minutes (30-175minutos). In this group, the most frequent cause of LT was alcoholic cirrhosis (64,7%).

Surgical times: As evidenced in Table 2, the mean graft warm ischemia time was 40.59 minutes and graft cold ischemia 599.12 minutes, with a range between 330 to 815 minutes. The average time of surgery was 328.24 minutes.

	Maastricht II	Maastricht III
Warm and Significant Warm ischemia time	103.41 (30-175)	19.22 (13-25)
Graft warm ischemia time	40.59 (15-125)	32.5 (20-45)
Graft cold Ischemia time	599.12 (330-815)	328.33 (225-365)
Surgery time	328.24 (200-495)	235.83 (170-265)

Table 2: Ischemia times.

With a mean follow-up of 91.36 months (0.5-211 m) one year RS was 82.35% and 70.6% at 5 years. One year and five years GS was 70.6% and 64.7%, respectively. None of deaths during follow-up was secondary to graft failure.

Complications: Table 3 shows complications during follow-up. Four grafts (23.5%) had ischemic cholangitis (IC).

Two of these patients had PAF requiring urgent retransplantation and in the other two cases hepatojejunostomy was performed with good evolution during follow-up. A third patient was retransplanted three years later for Hepatitis B Virus (HBV) cirrhosis.

	Maastricht ii	Maastricht iii	Total
Ischemic Cholangitis	4 (23.5%)	1 (11.1%)	5 (19.23%)
Small for Size	0	1 (11.1%)	1 (4%)
Primary allograft failure	2 (11.8%)	0	2 (8%)
Retrasplantation	3 (17.6%)	2 (22.2%)	5 (19.23%)

Table 3: Complications.

Maastricht III: In this group, recipients mean age was 58 years (52-66) and 51.67 years of donors. The average time of significant warm ischemia was 19.22 minutes with a range of 13-25 minutes. The most common cause of LT was hepatocellular carcinoma (55.6%) followed by alcoholic cirrhosis (33.3%).

Surgical times: Mean graft warm ischemia time was 32.5 minutes; the graft cold ischemia was 328.33 minutes and the average operating time was 304 minutes. With a mean follow up of 16.5 months, one year recipient survival was 100% and 87.5% for graft survival.

Complications: Two retransplantation were performed, one was urgent after diagnosis of small for size syndrome and the other 18 months later, secondary to IC. One patient developed hepatic artery and bile duct stenosis performing artery angioplasty and hepatojejunostomy (Table 3).

Causes of Complications: Table 4 shows the cross between IC and reperfusion syndrome, showing that most patients with reperfusion syndrome will not develop IC.

	Ischemic Cholangitis	NO Ischemic Cholangitis
Reperfusion syndrome	3 (25%)	9 (75%)
NO Reperfusion syndrome	2 (14.3%)	12 (85.7%)

Table 4: Relationship between ischemic cholangitis and reperfusion syndrome.

In our series the mean highest value of alanine aminotransferase (ALT/GPT) recorded in the first week was 1443.46 IU/L (28-20000), and 2366.58 IU/L (150-3800) for aspartate aminotransferase (AST/GOT), 34.6 % of patients presenting values over 2000 IU/L. INR at day 7 was 3.4, more than 50% of recipients had levels below 1.5. The maximum value of bilirubin in the 7th postoperative day was 19 mg/dL. However only 20% of patients had values over 10 mg/dL, and most of them had significant hyperbilirubinemia prior to LT.

Based on these data, a total of 12 patients (46.15%) fulfilled EAD criteria. Only 1 patient (3.84%) developed a PAF, and this patient did not meet EAD criteria.

Discussion

The obvious need to increase organ donors to reduce mortality of patients with terminal liver disease on the waiting list for a transplant, have forced to seek alternative sources to increase the number of liver grafts. Among these alternatives is living donor transplantation, domino LT, bipartition and organs from donors after cardiac death. The NHBD was described from the beginning of transplantation

history, recovering special interest from the first international conference transplant held in Maastricht in 1995 [4]. In Spain uncontrolled NHBD are more frequent. However, since the legislation change in 2012 controlled NHBD have been a new interest group.

There is great concern about the possible complications arising from the use of these organs subjected to a warm ischemia period, particularly complications related to billiary tract, like IC. About this topic, O'Neill et al. [5] in their meta-analysis show a significant increase of biliary complications in category III NHBD against donors from brain death (DBD), demonstrating a 16% (3-39%) of IC in NHBD versus 3% in conventional donations. Similar figures about all NHBD are described Jay CL et al. [12] in another meta-analysis. This generates that recipients who develop IC present progressive deterioration, reducing the time between the transplant and the first ERCP and retransplantation, implying an increase in the number of interventions and medical costs, with impact on patient survival [2].

Early allograft dysfunction (EAD) is a clinical definition that tries to determine specific risk factors in the immediate postoperative period (1 week) after transplantation for PAF. The PAF is multifactorial, describing various risk factors associated, including donor older than 50 years or weight higher than 100kg; warm ischemia time greater than 35 minutes and cold ischemia greater than 6-8 hours; recipient older than 55 years; history of previous transplant; MELD higher than 30, tested positive for Hepatitis C Virus (HCV) and others [2]. According to these factors, there are low risk receptors and grafts, and their association could result in comparable survival to livers from DBD [2]. According to Olthof et al. [10] patients with EAD have 10 times risk of die in the first 6 months post-transplant. Other groups, like Croome et al. [12] argue that the definition of EAD, based on transaminases levels, is inappropriate for recipients of NHBD organs, as these organs are subjected to a warm ischemia period, justifying AST and ALT elevation in most patients without a relationship to possible primary failure. In our review, we obtain similar results since a significant percentage of patients (34.6%) had transaminases levels higher than 2000 IU/L without a graft failure and the two patients with PAF showed no data of EAD.

About billiary complications, our series show a 19% IC. However, only 11% of patients required retransplantation: 2 of 4 recipients that developed IC in category II NHBD and one in Maastricht III NHBD group. These percentages are similar, or slightly lower than those referred in literature for NHBD (7.6 to 31%), and at maximum range of the percentage of retransplantation if DBD (2.5-12%) [2].

Initially, trials about uncontrolled NHBD described alarming numbers of GS. However, in our country, including our center, rates between 50-80% have been achieved [13-16], similar to the 80.8% one year graft survival year demonstrated in our series. In this study, one year survival patients are 88.5%. In the meta-analysis of O'Neill et al. [5] similar figures are described, with 88% of one year RS with liver from NHBD, with no significant differences in RS of grafts from DBD. Despite the incidence of IC evidenced in our series, we show no decrease in patient survival secondary to this cause.

Recent studies show promising results in improving outcomes in liver transplant from NHBD using ECMO [17,18]. However, clinical studies are needed to validate the good results obtained in the experimental field.

Conclusions

In conclusion, graft survival from NHBD is less than those organs from DBD. However, it is clear the benefits that provide faster access to a LT through grafting NHBD, beating risks from probable death while waiting for a standard graft. Further studies are needed to determine the risk factors for IC and EAD organs from NHBD to improve survival of these grafts and their recipients.

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