Digestive and Liver Disease 49 (2017) 676–682

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Octogenarian donors in liver transplantation grant an equivalent perioperative course to ideal young donors

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ARTICLE INFO

Article history:
Received 5 September 2016
Accepted 10 January 2017
Available online 21 January 2017

Keywords:
Organ donation
Organ transplantation
Perioperative care

ABSTRACT

Background: Use of grafts from very old donors for liver transplantation is controversial.
Aim: To compare the perioperative course of patients receiving liver grafts from young ideal vs octogenarian donors.
Methods: Analysis of the perioperative course of patients receiving liver grafts from young, ideal (18–39 years) vs octogenarian (≥80 years) deceased donors between 2001 and 2014.
Results: 346 patients were studied: 179 (51.7%) received grafts aged 18–39 years whereas 167 (48.3%) received a graft from a donor aged ≥80 years. Intra-operative cardiovascular ($p = 0.2$), coagulopathy ($p = 0.5$) and respiratory ($p = 1.0$) complications and incidence of reperfusion syndrome ($p = 0.3$) were similar. Patients receiving a young graft required more fresh frozen plasma units ($p \leq 0.03$) but did not differ for the need of packed red cells ($p = 0.2$) and platelet ($p = 0.3$) transfusions. Median ICU stay was identical ($p = 0.4$). Patients receiving octogenarian vs young grafts did not differ in terms of death or re-transplant ($p = 1.0$) during the ICU stay. Similar cardiovascular, respiratory, renal, infectious and neurological postoperative complication rates were observed in the two groups.
Conclusions: Octogenarian donors in liver transplantation grant an equivalent perioperative course to ideal young donors.

1. Introduction

Various strategies have been developed to expand the donors pool with the specific aim of matching the ever increasing demand for liver transplantation (LT). As a result, programs of living donation, domino transplantation, donation after cardiac death and split LT have been considered with a growing interest. However, these options are limited by constrains in organ availability, technical problems or ethical issues [1–3]. Therefore, maximizing the utilization of the potential donor pool by extending the original criteria for donor acceptance remains the key strategy to increase the number of LTs [4]. Accordingly, donors with an elevated body mass index (BMI), high serum sodium levels, altered liver function tests, positive hepatitis B virus and hepatitis C virus (HCV) serology, prolonged ischemia time and intensive care unit (ICU) stay, altered hemodynamics, liver trauma, graft's steatosis, active bacterial infections and older age have been increasingly and extensively used [1,4–7]. With regard to age, although the young adult donor is universally recognized to be ideal, the utilization of liver grafts from older donors is on the rise [8–13]. In fact, in the non-transplant setting, the liver's physiologic function can remain preserved throughout life likely due to its unique regenerative capacity [8]. Accordingly, despite the lack of a consensus on which should be considered the upper age limit for liver donors, seniority is no longer considered a contraindication for liver allograft acceptance [7–13]. However, older donor age is also universally recognized as a significant risk factor that may negatively affect the outcome of a LT because of the higher risk of graft failure, complications and mortality [1,6,14–17]. As the vast majority of the studies assessing the outcomes of patients receiving a graft from elderly donors report mainly mid and long-term results, with this study we focus on the perioperative LT period. Aiming at stressing any possible difference, we speculated that, with appropriate selection and management, the perioperative period after LT of patients transplanted with octogenarian donors could be not inferior in terms

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http://dx.doi.org/10.1016/j.dld.2017.01.149
1590-8658/

of graft survival, complications and resources utilization to that of patients receiving a graft from a young, ideal, donor.

2. Methods

Ethical approval for this study (Study no. 807/2015) was provided by the Comitato Etico Sperimentazione Area Vasta Nord-Ovest, Pisa, Italy. This is a retrospective analysis using our prospectively-obtained database including the entire series of all the LT procedures from deceased donors performed at our centre between January 1st, 2001 and December 31st, 2014. The study focuses on deceased donor LTs performed using grafts from octogenarian (80 years or more) vs ideal young donors (18–39 years).

2.1. Recipients

All liver transplantations were performed using conventional technique with vena cava replacement and veno-venous bypass, according to our institutional guideline. A T-tube was routinely used for duct-to-duct biliary anastomosis. Intraoperative and ICU management were based on our institutional standard protocol and all cases were treated according to a fast-track LT protocol and admitted to the ICU [18]. Data included in the current analysis were: demographics, BMI, indication to LT, clinical status at transplantation as per MELD score. Other variables we analyzed were: duration of surgery, perioperative blood transfusions, ICU length of stay (LoS), postoperative duration of mechanical ventilation, intraoperative and ICU complications, postoperative liver function test sampled immediately on the day of LT and on postoperative days (POD) 1, 2, 3. Time-dependent data were censored at time of event, latest available follow-up, or as of 30 June, 2015. Patients who received a LT due to a fulminant hepatic failure, those undergoing re-transplantation or receiving a graft from an AB0 incompatible donor or a split liver (the division of a donor liver into parts in order to transplant the tissue into a child or small recipient) were excluded from analysis. Also patients receiving a graft from donation after cardiac death were excluded.

Before implementation of a consensus-based allocation model in June 2015 [19], Italy had a region-based donation and transplantation network whereby no national liver graft algorithm existed except for United Network for Organ Sharing (UNOS) status 1 patients, pediatric transplantations, and patients with MELD scores ≥30 who were granted national priority. Beyond these indications, grafts were allocated within the region(s) of origin based on center-based algorithms. In 2005 we implemented a MELD-based allocation algorithm for adult transplantation whereby, in the absence of national priorities, allocation of liver grafts <80 years was as follows: re-transplants > combined liver-kidney transplantation > MELD scores 30-25 > T3-HCC > MELD 24-23 > T2-HCC > MELD scores 22-10. Exceptions to MELD scores were graded according to international guidelines published elsewhere [20]. Donor grafts ≥80 years were deliberately not assigned to recipients with biochemical MELD score >24, except for UNOS status 1 patients.

2.2. Donors

Donor data were obtained from the clinical charts at our regional donation coordination bureau. Eligibility to liver donation was evaluated as per our institutional policy and according to the Italian National Transplant Agency guidelines [21]. The variables included in our investigation were: age, gender, BMI, cause of death, liver function tests at procurement, comorbidities (with focus on diabetes mellitus, cardiovascular disease, renal disease and dyslipidemia), use of vasopressor drugs, ICU length of stay. Based on national guidelines, reasons for discarding a reported deceased liver graft were donor HIV-positivity, history of melanoma or lymphoproliferative disease, or any intractable systemic infection [21]. History of malignancy within 5 years (10 years for breast cancer), HCV-positivity and hepatitis B surface antigen (HBsAg)-positivity required donor–recipient matching and evaluation of urgency and benefit of transplantation [21]. Liver graft biopsy was performed on demand based on surgical evaluation at procurement and histology was reviewed at the Pathology Institute of our hospital. At our center, a liver graft was discarded in the presence of macrovescicular steatosis ≥30%, necrosis ≥5%, fibrosis ≥2 as per Ishak's score, severe micro-angiopathy (with arteriolar thickening >60%) and macro-angiopathy precluding arterial anastomosis, unless otherwise indicated as per the recipient's clinical status. All grafts were routinely evaluated on the back table before LT for vessel patency and anatomical variants.

2.3. Definitions

According to the data reported in the study, (a) cold ischemia time was defined as the time passed from the donor aortic clamp-time to the moment in which the graft was put out of cold storage; (b) warm ischemia time was the time passed from the moment in which the graft was put out of cold storage to the recipient arterial de-clamping (at our center portal and arterial clamps are contemporary released); (c) donor major hemodynamic instability was defined as any episode of cardiac arrest and/or severe hypotension (pulse arterial pressure <60 mmHg) for at least 5 min; (d) recipient reperfusion syndrome was defined accordingly to Paugam-Burtz et al. [22]; (e) early graft function (EGF) was defined according to Olhoff's criteria as bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7 and alanine or aspartate aminotransferases > 2000 IU/L within the first 7 days [23]. Post-LT complications were categorized accordingly to the Clavien-Dindo Classification [24].

2.4. Statistical analysis

Categorical variables were reported as number of cases and percentages; continuous variables as medians and inter-quartile ranges (IQR). Categorical variables were analyzed using the chi-square and the Fisher exact test, where appropriate. All continuous variables were tested using the Mann–Whitney U test. A multivariable regression logistic model was constructed using as covariates 12 different variables: recipient age and gender, recipient HCC or HCV positivity, donor age and gender, recipient MELD, donor cause of death, donor hemodynamic instability, donor history of arterial hypertension or diabetes mellitus, and cold ischemia time. All these variables were evaluated as risk factors for early recipient death (within 90 days), recipient hospital stay > 30 days, delayed graft function and any complication 3b-5 according to the Clavien-Dindo classification. A stepwise conditional methods was done. Odds ratios and 95% confidence intervals were reported.

Patient and graft survival were plotted using Kaplan–Meier curves. Cost analysis was performed actualizing the costs at the 2015 prices. A Propensity Score Match (PSM) was performed aiming at compensating for the non-randomized design of this retrospective study: a multivariate logistic regression model was performed using donors age (18–39 vs ≥80 years) as the independent variable and seven different possible confounders for graft's loss (donor age, recipient age, recipient gender, MELD, HCV-positive status, presence of HCC and cold ischemia time) as covariates. PSM was performed using a "nearest neighbor matching" algorithm, preferably selecting identical scores. Each pair was used once. Unpaired patients were discarded from analysis. A final 1:1 match was generated. For all the performed analyses, a p value <0.05 was considered