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Is the use of marginal donors justified in liver transplantation? Analysis of results and proposal of modern criteria

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Abstract A discrepancy exists worldwide between the number of suitable liver donors and the increasing demand for transplantation. Thus many centers have considered widening their liver donor acceptance criteria and this may increase the incidence of primary dysfunction (PD) with negative effect on the results of transplantation. In order to reduce the incidence of PD and improve patient and graft survival it becomes important to identify those risk factors associated with its occurrence. In a retrospective univariate and multivariate analysis we evaluated several donor, preservation and recipient parameters and their correlation with PD. In our Department 282 orthotopic liver transplantations (OLT) were performed on 256 adult patients over a 10-year period. Excluded were 15 cases with early vascular problems and 4 intraoperative deaths. A complete series of donor, recipient and procedure-related data were analyzed. About 30 % of donors showed abnormal values. In 70 cases of PD (26 %) there was a 61.4 % graft failure rate compared with 15 % in the group with immediate function ($P < 0.05$). Univariate analysis showed donor age, steatosis, ischemia time, amines, oliguria, hypotension and ICU stay to be significantly associated with PD. Multivariate analysis showed steatosis, ischemia time and amine dosage to be independent risk factors for the development of primary non function. In conclusion, the acceptance of marginal donors worsened the results of transplantation, but the rejection of these donors would reduce by about 30 % our transplant activity resulting in increased mortality in the waiting list. Combinations of risk factors when possible should be avoided, and ischemia time, as the only variable that can be controlled, should be kept as short as possible.

Key words Liver transplantation · Liver donor selection · Donor criteria

Introduction

The current selection criteria for liver donation are the subject of great controversy at different centers as they are considered of little value in the prediction of transplant outcome. The discrepancy between the increasing number of candidates for liver transplantation (OLT) and the number of available organs is largely attributed to the fact that many potential suitable donors are not harvested because they do not fulfil predefined criteria. To remedy this deficit, many centers have considered widening their liver donor acceptance criteria. Thus abnormal liver tests, hemodynamic instability, older age and steatosis are no longer absolute contraindications to organ retrieval [5, 9].

On the other hand, primary dysfunction (PD) of the harvested liver may lead to significant morbidity and mortality after OLT. Primary non function (PNF) is the

Table 1 Univariate analysis: donor variables significantly associated with PD

	Immediate function (n = 193)	IPF (n = 48)	PNF (n = 22)	P-value
Donor age				
< 55 years (n = 229)	78 %	16.5 %	5.5 %	
> 55 years (n = 34)	41 %	32 %	27 %	< 0.001
Steatosis				
No (n = 189)	81 %	14.5 %	4.5 %	
slight to moderate (n = 59)	68 %	27 %	5 %	
Severe (n = 15)	0 %	33 %	66 %	< 0.001
Ischemia time				
< 10 h (n = 185)	84.5 %	10 %	4.5 %	
> 10 h (n = 78)	46.5 %	37 %	16.5 %	< 0.05
Amines (Dopamine)				
< 10 µg/kg/min (n = 168)	81 %	13.5 %	5.5 %	
> 10 µg/kg/min (n = 95)	60 %	27 %	13 %	< 0.05
Oliguria				
No (n = 226)	79.5 %	14 %	6.5 %	
Yes (n = 37)	35 %	46 %	19 %	< 0.05
Hypotension				
< 60 min (n = 184)	82 %	13 %	5 %	
> 60 min (n = 79)	53 %	30.5 %	16.5 %	< 0.03
ICU stay				
< 5 days (n = 191)	84 %	11.5 %	4.5 %	
> 5 days (n = 72)	46 %	36 %	18 %	< 0.03

most serious form of PD occurring in 10–23 % and resulting in rapid death of the patient unless an urgent retransplantation is performed. In other cases the graft shows a borderline function immediately after OLT and in these cases the graft may recover after a variable period of dysfunction, retransplantation may be required or the patient may die. These forms are defined as 'delayed function' (DGF) or 'initial poor function' (IPF) and are characterized, in the firtst week, by high transaminase levels, prolonged prothrombin time and nearly absent bile production. The genesis of these conditions are most likely multifactorial including donor- and recipient-related factors as well as various surgical events [4, 7, 8]. In the present study, a number of variables widely associated with the entire procedure and their correlation with graft dysfunction were analyzed with the aim of defining modern criteria for liver donation and their impact on the results of transplantation.

Materials and methods

Between 1985 and 1995, 282 orthotopic liver transplants (OLT) were performed in our department on 256 adult patients, and of these 32 were urgent cases (acute hepatic failure, urgent retransplantation, ICU patients). Organs were harvested according to the rapid or standard techniques of Starzl et al. [10, 11]. UW solution was used in all except the first 30 procedures. All organs were ABO identical or compatible with the recipients. No reduced or 'split' livers were transplanted. The majority of donor livers were procured by the Niguarda team, only three being procured by others and sent to our institution. All livers had biopsies which were evaluated retrospectively or immediately before surgery, when required. The OLT operations were performed using standard techniques and venovenous bypass (234 cases) or the 'piggy-back' technique (48 cases). Quadruple induction immunosuppression (RATG, azathioprine, cyclosporine and steroids) and cyclosporine monotherapy after the 6th month were routinely adopted.

The following donor parameters were considered: age, sex, cause of death, hospital of procurement, amines, days in ICU, hypotension, oliguria, transaminases, protime, grade of steatosis, macroscopic appearance of the liver, MEGx test (100 cases) and type of cold storage solution. Other parameters considered were recipient age, sex, UNOS and Child status, preservation time, time of anastomosis, blood losses and number of donor/recipient mismatches. These data were compared with patient survival during the 3 months posttransplant and with immediate graft function. In particular IPF was defined as a form of dysfunction with AST > 1500 U/l, AP 20–30 %, and nearly absent bile flow; PNF was defined as an irreversible dysfunction causing death or retransplantation within 8 days. Excluded from the analysis were 4 cases of early death and 15 cases of vascular complications.

Statistical univariate analysis was carried out using the Chi-squared, log-rank and Mantel-Haenzel tests (significance assumed for $P < 0.05$). Multivariate analysis was carried out using a multiple linear regression model (MS-BMDP vers. 1.0) and significance assumed for $P < 0.02$.

Results

Median donor age was 33 years (range 4–66); 34 (12.9 %) were older than 55 years. Steatosis was absent in 189 livers; mild to moderate steatosis was present in 59 grafts (22.4 %) and severe steatosis in 15 (5.7 %). Me-

dian ischemia time was 480 min (range 180–1320) and 78 livers (29.6 %) had an ischemia time longer than 10 h. Median ICU stay was 3 days (range 1–24) and 72 donors (27.3 %) had a prolonged ICU stay of more than 5 days. Donor dosage of amines of more than 10 μg/kg/min of dopamine or oliguria were present, respectively, in 95 (36.1 %) and 37 (14.1 %) cases (Table 1). PD occurred in 70 cases (26.6 %) including 22 PNF (8.4 %) and 48 IPF (18.2 %) and within 3 months of transplantation, 43 of these 70 PD grafts (61.4 %) failed (22/22 PNF and 21/48 IPF) compared with 29 of 193 (15 %) with immediate function ($P < 0.05$; Table 2).

Univariate analysis of IPF grafts performed with both discrete and continuous variables showed the following factors to have a statistically significant effect: donor age, ICU stay, amines, hypotensive episodes, steatosis, ischemia time, oliguria, appearance of the liver, blood losses and UNOS status (Table 1). Multivariate analysis of IPF grafts showed donor age, steatosis, ischemia time, hypotensive episodes and amine dosage to be significant independent variables.

Univariate analysis of PNF grafts showed donor age, amines, hypotension, steatosis, ischemia time, oliguria and UNOS status to be significant (Table 1). Multivariate analysis of PNF grafts showed steatosis, ischemia time and amine dosage to be independent risk factors (Table 3).

Table 2 Incidence of primary dysfunction in 263 OLT (*PNF* primary non function, *IPF* initial poor function)

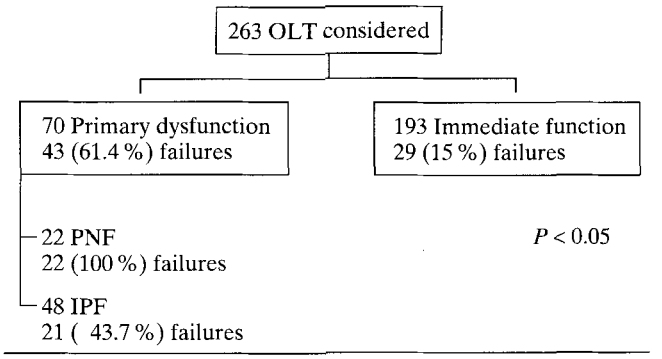

Table 3 Multivariate analysis: variables independently corelated with PNF

	Correlation coefficient	*P*-value
Steatosis	0.72	0.0002
Ischemia time	0.29	0.001
Amine dosage	0.03	0.02

Discussion

The selection of liver donors is a process in which several parameters have to be weighed in order to maximize the chances of success to the procedure. Currently used criteria are not well defined and it is difficult to establish how much each individual parameter contributes to graft function within the context of all the available parameters [1, 4, 9]. The clarification of this dilemma is critical, as the demand for OLT is increasing in the face of a constant donor pool. To remedy the shortage of suitable donors many centers have widened their acceptance criteria. It is crucial to define how much this is possible and what its impact is on the results of transplantation [1, 4, 8, 9]. From our data, PD occurred in a relevant percentage of cases as in other series (20 %). Together with PNF which by definition resulted in failure of the graft, IPF is also a major complication of OLT and is associated with a significantly higher mortality, graft insufficiency and retransplantation rate than observed in patients with immediate liver function.

Several historical parameters [3, 7, 13] are associated with the occurrence of dysfunction, such as the donor hemodynamic instability (amine dosage, hypotension, oliguria), preexisting or death-induced conditions (donor age, steatosis, appearance of the liver, ICU stay) and recipient variables (UNOS status, blood losses). All these parameters can induce different grades of damage to the liver that may result in dysfunction after harvesting, cold storage and transplantation. However, multivariate analysis showed only steatosis, amines and ischemia time to be significant as independent variables associated with PNF. Donor age was independently correlated with IPF and not with PNF [1, 7, 13], reflecting the fact that an old but healthy donor should not routinely be rejected. A long ischemia time, even since the introduction of UW solution, has a detrimental effect on graft function, and this is especially evident with poor condition donors in whom different parameters are altered [4, 7]. Undoubtedly UW solution has had an invaluable effect in improving the results of OLT, but care must be taken not to overextend preservation time when this is not necessary [3, 7].

Moderate to severe fatty changes in the liver graft, as in previous studies, was significantly related to PD [2, 12]. Since steatosis is not easily evaluable macroscopically, biopsies have to be obtained in every uncertain case [2]. The MEGx test was not predictive in our experience of graft function [6].

In conclusion, the acceptance of marginal donors increases the risks of PD and negatively influences the results of OLT. Their rejection, however, would reduce by about 30 % the actual transplantation rate in our center leading to unacceptable increases in mortality in the waiting list. The data should be used as background information to facilitate clinical judgement for an individ-

ual case. The combination of significant factors should be avoided when possible. Preservation time, as the only variable that can be controlled, shoul be kept as short as possible.

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