Transpl Int (2005) 17: 772–778
DOI 10.1007/s00147-004-0715-6

ORIGINAL ARTICLE

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The outcome of 400 consecutive liver grafts using the aortic perfusion-only technique

Received: 7 February 2003
Revised: 13 November 2003
Accepted: 11 March 2004
Published online: 10 February 2005

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Abstract The goal of this study is to establish the effect of cadaveric liver retrieval, using the technique of aortic perfusion only, on liver graft function, and to identify associated potential risk factors for graft dysfunction. The authors reviewed the outcome of 400 consecutive, orthotopic, cadaveric liver transplantation retrieved by the technique of aortic perfusion only. Relevant parameters pertaining to the donor, recipient, procurement, graft and peri-operative variables are analyzed to assess their influence on graft function. The univariant analysis revealed that donor age, body mass index, blood pressure, and vasopressor dependence influence graft function. Furthermore, predictors of dysfunction included prolonged anhepatic phase, transplantation duration and partial grafts. In addition, multivariant analysis revealed significant association between obesity of donors, partial graft, and dysfunction. The technique of aortic perfusion only, is a simple and reproducible procedure. The post-transplantation outcomes appear to be similar to those reported for the traditional liver procurement technique.

Keywords Liver · Graft · Dysfunction · Aortic · Procurement

Introduction

Efficient organ procurement procedures are essential to ensure that undamaged and optimally preserved donor liver and other organs are obtained. In order to face the increasing demand for donor organs, and while the use of donor organ is being optimized, routine multiple organ procurement becomes a necessity. To achieve this, the safest and technically most-straightforward procedures should to be chosen.

Since the earliest description of a standardized technique for multiple organ procurement by Starzl et al. [1], modifications have been suggested to simplify the operative methods and minimize the risk of damage to the graft [2, 3, 4]. The majority of liver procurement teams still consider that the portal vein is mandatory for liver cooling. However the technique of aortic perfusion only (APO) has several theoretical and practical advantages [5, 6]; it is associated with less dissection and cannulation, making it safer in critically unstable donors

[7]. In this study we present our experience with 400 consecutive liver procurements using the APO technique.

Patients and methods

Over a period of 9 years, extending from January 1991 to January 2000, a retrospective study was carried out to review the outcome of 400 consecutive orthotopic liver transplantation, performed in 398 patients, using cadaveric livers retrieved by the aortic perfusion only technique. Patients were provided with appropriate information regarding the procedure to be done and an informed consent was obtained from each patient prior to the operation. Furthermore, the review committee at the Edouard Herriot Hospital approved the study protocol which conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The initial operative steps of retrieval were similar to those described by Starzl et al. However, dissection and ligation of the superior mesenteric artery and dissection and cannulation of the portal vein were not needed. Ligation of the cystic duct was first performed and then a section of the common bile duct, after a limited dissection, was realized allowing flushing of the biliary tree with normal saline. Immediately before cross clamping of the supra-coeliac aorta, cannulation of the infra-renal aorta and inferior vena cava were installed. After cross clamping of the upper abdominal aorta, cooling of the liver along with other intra-abdominal organs was achieved by cold perfusion of 6 l of University of Wisconsin (UW) solution through the aortic canula and by filling the abdominal cavity with sterile ice slush. When perfusion was complete and all intra-abdominal organs were cooled, the liver was removed en bloc with the entire bile duct and the hepatic vascular complex. The kidneys were recovered in all cases. As a final step, the liver was flushed selectively through the portal vein on the back table using 2 l of the UW solution dedicated for the package. Details of the procurement operation, the involvement of other procurement teams and donor and recipient parameters were recorded.

The following donor parameters were analyzed: age, weight, intensive care unit (ICU) stay, body mass index (BMI), peri-operative blood pressure, occurrence of cardiac arrest, occurrence of hypotensive events (systolic pressure < 80 mmHg), use of vasopressive agents (none, low dose: Dobutamine < 5 μg/kg/min or Dopamine < 8 μg/kg/min, high dose: Dobutamine ≥ 5 μg/kg/min or Dopamine ≥ 8 μg/kg/min), and biological value of serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), total bilirubin, prothrombin time (PT), creatinine, and sodium. The recipient parameters included age, donor recipient ABO blood grouping (ABO) compatibility. The procurement parameters included the time for procurement, cold ischemia time, procurement of other organs and the year of procurement. The graft parameters included the condition of the retrieved liver on true-cut biopsy of the graft at the end of transplantation (steatosic: fatty infiltration $> 30\%$, moderate; fatty infiltration between 10–30%, good; fatty infiltration $< 10\%$) and the character of the graft (reduced or split). Peri-operative variables analyzed were intra-operative blood loss, warm ischemia or anhepatic phase time and the duration of transplantation. The blood levels of SGPT, SGOT, GGT, Alkaline phosphatase, PT, and bilirubin were recorded from postoperative day 1 to 7. The functional quality of the graft was determined by the rate of primary non-function and initial poor function. The primary non-function was defined as severe initial poor function leading to death or re-transplantation on days 1–7 [8]. The initial poor function was diagnosed if aspartate transaminase (AST) was greater than 2000 U/l and PT less than 20% on days 2–7 in the absence of artery or vein thrombosis [8].

Different surgeons from a team of 18 surgeons performed procurements, but one surgeon did more than 95% of the transplantations. The regimen of immunosuppressive therapy was variable among patients as they were included in different randomized protocols. Overall 1-year survival was documented and causes of graft and patient losses were analyzed for the whole series. The rate of acute rejection and re-transplantation was recorded.

Data entry was done with Epiinfo software, Release 6 (CDC, Atlanta, USA), statistical analysis was performed with Epiinfo and Stata software, Release 5 (Drive East University, USA). Bilateral statistical tests were used: Chi-square test for dichotomous or multinomial qualitative variables, Mann-Whitney or Wilcoxon test for quantitative variables with non-homogeneous variances or non normal distribution, and ANOVA for quantitative variables of normal distribution and homogeneous variances.

Multivariant analysis was done by stepwise descendent logistic regression, taking into account all factors that had a P value of less than 0.20 in the univariant analysis. Quantitative variables were taken either as superior or inferior to a threshold value (dichotomous), or divided into classes of 10 units (continuous). Quantitative variables are generally better taken into consideration when used as such, because transforming them into dichotomous variables decreases the power of the analysis.

Results

The indications for liver transplantation were: alcoholic cirrhosis (30%), post-viral hepatitis cirrhosis (21.75%),

hepatocellular carcinoma (10%), cholestatic disease (7.5%), congenital biliary atresia (6.25%), fulminant hepatitis (4.25%), cirrhosis of unknown cause (3.5%), metabolic disease (2.5%), autoimmune cirrhosis (1.75%), and other indications (12.5%). In the pediatric age group, 51 (12.75%) transplantations were done. The ABO histocompatibility was positive in 393 transplantations (98%). Of the patients, 362 received whole cadaveric liver, 38 received partial cadaveric liver, either reduced liver size (children) or split liver, and 11 patients received both liver and kidney transplantation. The rate of primary non-function was nil and the rate of initial poor function was of 9.5% (38 patients). Two patients (0.5%) were re-transplanted secondary to hepatic artery thrombosis and 66 patients experienced at least one episode of acute rejection. The 1-year survival of the graft and recipient was 89.25% and 89.75%, respectively, death was mainly due to infection (56.73%). Other causes of death included gastrointestinal bleeding, neurologic accident, multiple organ dysfunction and failure, and recurrence of the initial disease. The donor's demographic characteristics and biological tests values are represented in Tables 1 and 2, respectively, to show their relation to transplantation dysfunction. The effects of the different procurement and transplantation parameters on graft dysfunction are depicted in Tables 3 and 4, respectively.

A univariant analysis of potential risk factors for initial poor function showed that some parameters could predict graft dysfunction. Among the donor parameters, older age (> 60 years), obesity (BMI > 30, which is the BMI of an obese patient), low blood pressure and the need of vasopressors seem to predict dysfunction. There was higher donor PT of borderline significance (≥60%) and a trend towards higher donor GGT levels in case of dysfunction. Among factors related to surgery, prolonged anhepathic phase, partial character of the graft and transplantation duration seem to predict dysfunction.

In addition, a trend of increasing dysfunction in case of steatotic liver graft aspect is noted but it is not statistically significant. Table 5 shows the results of the multivariant analysis for quantitative variables divided into classes of 10 units, whereas Table 6 depicts the result of multivariable analysis for dichotomous quantitative variables.

Significant association was noted between obesity and non-whole cadaveric transplantation with dysfunction, demonstrating that whole cadaveric graft has a protective effect against dysfunction. In addition, there is a trend towards higher dysfunction in the case of elderly donors, steatotic liver aspect and presence of low blood pressure.

Table 1 Baseline donor demographic characteristics [*M (SD)* mean and standard deviation]

Variable	Overall	No dysfunction $n=362$ (90.5%)	Dysfunction $n=38$ (9.5%)	*P* value OR [95%CI]; *P* value*
Age M (SD)	31.3 years	31.2 (13.7)	32.3 (14.7)	0.67
< 60 Years		347 (97.5%)	34 (89.5%)	
≥60 Years		9 (2.5%)	4 (10.5%)	4.54[1.09–17.51];**0.028**
Weight M(SD)	66.55 kg	65.9 (15.8)	72.8 (18.0)	0.007
< 75 kg		229 (70.0%)	20 (54.1%)	
≥75 kg		98 (30.0%)	17 (45.9%)	1.99 [0.94–4.19]; **0.048**
BMI M (SD)	22.58	22.4 (3.5)	24.3 (4.0)	0.013
< 30		298 (97.4%)	35 (94.6%)	
≥30		8 (2.6%)	2 (5.4%)	2.13 [0–11.64]; **0.29**
Gender				
Male	63.5%	233 (65.8%)	21 (58.3%)	0.73 [0.34–1.56]; **0.37**
Female	36.5%	121 (34.2%)	15 (41.7%)	
ICU stay M (SD)	26.43 h	26.1 (32.2)	29.6 (32.4)	0.40
< 48 h		302 (85.6%)	29 (76.3%)	OR1 = 1.0
48–71 h		26 (7.4%)	5 (13.2%)	OR2 = 2.0
≥72 h		25 (7.0%)	4 (10.5%)	OR3 = 1.67; **0.38***
Cardiac arrest				
Yes	66 (16.5%)	58 (16.0%)	8 (21.1%)	1.40 [0.55–3.42]; **0.43**
No	334 (83.5%)	304 (84%)	30 (78.9%)	
Low BP				
Yes	344 (86%)	317 (87.6%)	27 (71.1%)	0.35 [0.15–0.18]; **0.005**
No	56 (14%)	45 (12.4%)	11 (28.9%)	
Vasopressor				
None	57 (14.25%)	46 (12.7%)	11 (28.9%)	
Low	292 (73%)	268 (74%)	24 (63.2%)	**0.02**
High	51 (12.75)	48 (13.3%)	3 (7.9%)	

*Trend test when applicable

Table 2 Donor baseline tests [*M (SD)* mean and standard deviation]

Variable	Overall	No dysfunction $n=362$ (90.5%)	Dysfunction $n=38$ (9.5%)	*P* value OR [95%CI]; *P* value*
SGOT M (SD)	100.36 IU/l	96.2 (158.3)	140 (475.6)	$P=0.41$
<90 IU		276 (78.9%)	30 (78.9%)	
≥90 IU		74 (21.1%)	8 (21.1%)	0.99 [0.40–2.41]; $P=$**0.99**
SGPT M (SD)	66.77 IU/l	66.8 (117.4)	66.5 (132.3)	p=0.98
<90 IU		298 (84.4%)	34 (9.5%)	
≥90 IU		55 (15.6%)	4 (10.5%)	0.64 [0.18–2.00]; $P=$**0.41**
GGT M (SD)	26.98 IU/l	25.97 (25.2)	36.6 (50.6)	$P=0.073$
<90 IU		329 (96.%)	35 (92.1%)	
≥90 IU		11 (3.2%)	3 (7.9%)	2.56 [0.53–10.72]; $P=$**0.16**
Bilirubin M (SD)	15.67 μmol/l	15.8 (12.3)	14.5 (9.2)	$P=0.78$
<2.5 IU		8 (2.3%)	0	
≥2.5 IU		338 (97.7%)	34 (100%)	$P=$**0.99**
Creatinine M (SD)	103 μmol/l	103.0 (55.6)	102.9 (73.0)	$P=0.31$
<103 IU		209 (59.4%)	27 (71.1%)	
≥103 IU		143 (40.6%)	11 (28.9%)	0.60 [0.27–1.31]; $P=$**0.16**
Na+ M (SD)	148.85 mEq/l	145.6 (13.0)	148.30 (9.7)	$P=0.18$
<140		100 (29.1%)	7 (18.9%)	
≥140		244 (70.9%)	30 (81.1%)	1.76 [0.70–4.59]; $P=$**0.19**
PT M (SD)	63.8%	63.1 (20.5)	70.53 (19.57)	$P=0.04$
≥60		191 (55.4%)	26 (72.2%)	
<60		154 (44.6%)	10 (27.8%)	0.48 [0.21–1.08]; $P=$**0.05**

*Trend test when applicable

Table 3 Procurement circumstances [*M (SD)* mean and standard deviation]

Variable	Overall	No dysfunction $n=362$ (100%)	Dysfunction $n=38$ (100%)	*P* value OR [95%CI]; *P* value*
Harvesting duration				
M (SD)	115.8 mn	121.0 (62.8)	66.5 (132.3)	$P=0.66$
<60 min		27 (7.7%)	2 (5.7%)	OR1=1
60–119 min		192 (55.0%)	18 (51.4%)	OR2=1.27
≥120 min		130 (37.3%)	15 (42.9%)	OR3=1.56; $P=$**0.49***
Associated graft retrieval				
NO	29 (7.25%)	24 (7.0%)	5 (13.9%)	$P=0.38$
Kidney	73 (18.25%)	65 (18.8%)	8 (22.2%)	
Kidney–heart	212 (53%)	197 (57.5%)	15 (41.7%)	
Kidney–heart–lung	35 (8.75%)	31 (9.0%)	4 (11.1%)	
Kidney–heart–lung–pancreas	32 (8%)	28 (8.1%)	4 (11.1%)	
Other	19 (4.75%)			
Liver aspect				$P=0.11$*
Steatosic	8 (2%)	6 (1.7%)	2 (5.3%)	OR1=3.43
Moderate	31 (7.75%)	27 (7.5%)	4 (10.5%)	OR2=1.52
Good	361 (90.25%)	329 (90.8%)	32 (84.2%)	OR3=1

*Trend test when it applies

Discussion

The aim of this study is to find out the effect of cadaveric liver retrieval without portal vein cooling on liver graft function, and to identify the potential risk factors for graft dysfunction using this technique of procurement. The reported incidence in the literature of primary non-function (PNF) and that of initial poor function (IPF)

Table 4 Transplantation circumstances [*M (SD)* mean and standard deviation]

Variable	Overall	No dysfunction $n=362$ (100%)	Dysfunction $n=38$ (100%)	*P* value OR [95%CI]; *P*value*
Cold ischemia time				
M (SD)	584.3 mn	585.9 (214.2)	569.13 (237.6)	$P=0.49$
<480 min		104 (29.1%)	15 (39.5%)	OR1=1
480–599 min		69 (19.3%)	5 (13.6%)	OR2=0.50
≥600 min		184 (51.6%)	18 (47.4%)	OR3=0.68; $P=$**0.35***
Blood transfusion				
M (SD)	3867.7 ml	3835.0 (3421.2)	4157.9 (3890.5)	$P=0.64$
<1500 ml		66 (18.6%)	4 (10.5%)	OR1=1
1500–2499 ml		44 (12.4%)	7 (18.4%)	OR2=2.6
≥2500 ml		245 (69%)	27 (71.1%)	OR3=1.8; $P=$**0.64***
Anhepatic				
Duration M (SD)	55.8 mn	54.9 (12.7)	64.4 (19.9)	$P=0.0037$
<60 min		242 (71.8%)	17 (45.9%)	3.00 [1.42–6.34]; $P=$**0.0012**
≥60 min		95 (28.2%)	20 (54.1%)	
Transplantation				
Duration M (SD)	345.65 mn	340.0 (116.0)	399.5 (179.5)	$P=0.041$
<300 min		146 (41.1%)	10 (26.3%)	
≥300 min		209 (58.9%)	28 (73.7%)	1.96 [0.87–4.49]; $P=$**0.076**
Associated graft				
Yes	389 (97.25%)	351 (13.4%)	38 (100%)	$P=$**0.61**
No		11 (86.6%)	0 (0%)	
Liver graft				
Partial liver	38 (9.5%)	23 (6.35%)	15 (39.5%)	4.37 [1.99–9.56]; $P=$**0.000018**
Whole liver	362 (90.5%)	339 (93.65%)	23 (60.5%)	0.23 [0.10–0.50]
ABO compatibility				
Yes	392 (98%)	355 (98.1%)	38 (100%)	$P=$**0.99**
No	8 (2%)	8 (2%)	0 (0%)	

*Trend test when it applies

are quite variable [8, 9, 10, 11, 12, 13, 14, 15, 16, 17]. The rates of PNF in the literature are documented to range from as low as 0.6% to as high as 22%. Most centers present frequency of PNF in the range of 2–10%. The frequencies of PNF and IPF as presented by Ploeg and co-workers were, respectively 6% and 16% [8]. Using the same criteria defined by Ploeg et al. for graft dysfunction, the frequencies of PNF and IPF in this retrospective study were 0% and 9.5%, respectively.

Boillot was the first to report that APO has no detrimental effect on graft dysfunction either in adult or pediatric transplantation [18]. Furthermore, the difference in the rates of PNF and IPF was reported not to be significant when the conventional technique of liver procurement was compared to the aortic perfusion only technique [18]. In addition, Chui et al. in a prospective randomized study showed, that procurement using APO and combined aortic and portal cooling produces equivalent results in terms of postoperative graft function and survival [19].

This present study demonstrates that effective liver perfusion occurs via the aorta and hepatic artery, as well as via the portal vein, after the fluid traverses the intestinal circulatory bed. Moreover, this study confirms the previously made conclusion that the APO procure-

Table 5 Quantitative variables divided into classes of 10 units

Variable	OR adjusted	95% CI of OR	*P* value
Age×10	0.73	0.50–1.07	0.11
GGT×10	1.09	0.96–1.23	0.20
Na×10	1.32	0.86–2.02	0.21
PT×10	1.15	0.91–1.46	0.25
BMI×10	6.00	1.77–20.34	0.004
Anhepatic duration×10	1.31	0.99–1.74	0.058
Good liver aspect	0.37	0.12–1.13	0.081
Low blood pressure	0.37	0.11–1.20	0.099
Partial liver	5.43	1.88–15.72	0.002

Table 6 Dichotomous quantitative variables

Variable	OR adjusted	95% CI of OR	*P* value
Donor age ≥60 years	2.90	0.60–14.09	0.19
Donor GGT ≥90 IU	2.81	0.55–14.37	0.22
Donor Na ≥140 IU	1.51	0.52–4.41	0.45
Donor PT <60	0.78	0.30–2.01	0.61
BMI ≥30	2.62	0.39–17.77	0.32
Anhepatic duration ≥60 min	2.15	0.92–5.05	0.08
Steatosic liver aspect	6.07	0.91–40.56	0.06
Low blood pressure	0.36	0.12–1.04	0.06
Partial liver	5.50	2.00–15.12	0.001

ment technique is a safe method for routine liver harvesting. The APO technique has the advantage of being a simple technique that requires less anatomical dissection, thus resulting in a reduction in the risk of surgical error and hepatic artery injury, let alone an enhancement in the early graft function [18, 20, 21, 22, 23, 24].

The cause of the graft dysfunction is not known. The potential mechanisms incriminated can be divided into donor, procurement and transplantation related factors. Several studies have demonstrated that donor-related factors, such as extremes of age, steatosis, hemodynamic instability and high dose of vasopressive administration are potential risk factors for IPF [8, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35]. However, the shortage of liver donors has lead several liver transplant centers to broaden the definition of liver donor suitability [27, 36]. Thus, abnormal liver function tests, older donor (> 50 years) and hemodynamic instability are not longer considered as absolute contraindications for liver retrieval at some centers.

The univariant analysis of donor related factors in this study showed that age greater than 60 years, BMI > 30, low blood pressure and the need of vasopressive agents seems to predict liver graft dysfunction. Other donor related factors such as the length of ICU stay, occurrence of cardiac arrest, presence of abnormal liver function tests and the presence of abnormal sodium and creatinine levels are not related to the frequency of IPF. Furthermore, a donor PT less than 60% seems to protect against postoperative graft dysfunction.

In the present study, the univariant analysis of peri-operative potential risk factors for graft dysfunction demonstrates that prolonged anhepatic phase, prolonged transplantation duration, and the use of a partial graft (split or reduced) are associated with an increase in the frequency of postoperative graft IPF. The prolonged anhepatic phase, which reflects a prolonged warm ischemia, has a deleterious effect on postoperative graft function.

The blood loss has been identified as a peri-operative risk factor [8]. This present study didn't confirm this finding. In addition, prolonged ischemia time, previously reported to be associated with early postoperative graft dysfunction [8, 18, 20, 21, 22, 23, 24, 26, 33, 34, 35], did not show such an effect in this study. This is not an unexpected finding since all our grafts were preserved in UW solution and no extreme preservation time was necessary. The liver was retrieved along with other organs in 92.75% of the cases presented in this study, this did not affect the postoperative liver graft function. Moreover, the harvesting duration was not regarded, in this study, as a risk factor for liver graft dysfunction. This might be explained by the fact that all harvesting was done with little dissection and within acceptable times (< 3 h).

The experience of the procurement surgeon does not seem to play a role in the prediction of IPF. Eighteen surgeons participated in the liver procurement procedures in the present study; most of them were young surgeons (in training) without significant experience. If anything, the fact that surgeons with little experience could perform liver transplantation without affecting the rate of dysfunction enhances the belief that the APO technique is simple and safe.

The multivariant analysis of all potential risk factors in this study leaves the partial character of liver graft as the only predictive factor for postoperative graft dysfunction. The reason might be that prolonged anhepatic phase, splitting procedure and prolonged transplantation duration are all associated with partial grafts. A relatively high incidence of PNF after split liver transplantation has been reported [37]. Split liver transplantation might be a technique that requires additional surgeon's experience in liver transplantation.

In conclusion, given the shortage of organ donors and the more liberal acceptance of marginal donors, an efficient procurement technique that ensures optimal preservation of undamaged organs is essential. In this study, the APO procurement technique proved to be simple, reproducible and produces satisfactory graft function outcome. Thus, this technique can be recommended for routine use in liver transplantation.

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