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Comparison of results of combined liver-kidney transplantation *vs.* isolated liver transplantation

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ABSTRACT

Introduction. Combined liver-kidney transplantation (LKT) is the best therapeutic option for patients with end-stage liver and kidney disease. Objectives. To analyze baseline characteristics and clinical outcome of LKT compared to isolated liver transplantation (LT). **Material and methods.** The study included 16 LKT performed between 1998 and 2006 and 32 LT matched by age, sex, date and indication for transplantation. Demographic, pretransplant, post-transplant and survival variables were analyzed. **Results.** As planned by the study design, mean age, distribution by sex and indication for LT were similar between groups. The most common indication for LT was HCV- and/or alcohol-induced cirrhosis. The most common indication for KT was renal failure, in most cases secondary to glomerulonephritis. Twelve patients (69%) were on dialysis before LKT. Hepatocellular carcinoma and diabetes mellitus pre-transplantation were similar between groups. However pretransplant arterial hypertension (AHT) was higher in LKT than LT (50% vs. 19%; p = 0.02). In the post-transplant: reoperation due to bleeding, bacterial infections, liver rejection, AHT and median creatinine levels at 1st and 3rd years were similar in LKT and LT. In contrast, early post-transplant dialysis was higher in LKT than LT (31% vs. 3%; p = 0.01). Survival rates at 1st, 3rd, 5th and 7th years were similar in both groups (87.5%, 74%, 74% and 66% vs. 81%, 75%, 75% and 75% in LT and LKT, respectively). **Conclusions.** LKT is an effective therapeutic option in patients with end-stage liver and kidney disease. Most early and late complications and long-term survival are similar to those observed with LT.

Key words. Kidney transplantation. Liver transplantation. Outcome. Metabolic complications.

INTRODUCTION

Liver-kidney transplantation (LKT) is the best therapeutic option for patients with end-stage liver and kidney disease.[1] Despite the fact that results in terms of long-term post-transplant survival are comparable to those of liver transplantation (LT) and kidney transplantation (KT) alone,[2-8] the growing demand associated with the organ shortage requires a correct selection of candidates for combined transplantation. Increased post-LT morbidity and mortality has been reported in patients with pre-LT renal dysfunction.[9-11] However, the optimal moment to perform a simultaneous combined transplantation is not well defined and there are no clinical guidelines on this topic. Furthermore, it is difficult to predict which candidates for LT with renal dysfunction will improve their renal function after transplant. In recent years, with the introduction of the MELD system for organ allocation, the number of combined LKT has progressively increased.[12,13]

The first transplant performed in our institution was in 1998. Since then, the number has increased over the last years. The objective of this study was to review our experience in combined LKT from the point of view of survival and post-transplant complications and to compare it with a control group of LT alone.

MATERIAL AND METHODS

Between January 1998 and December 2006, 16 LKT (15 adult and 1 pediatric) were performed at

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our institution. This group of LKT was compared to a control group of LT matched by date and indication for liver transplantation, age and sex in a ratio of 2:1 (n = 32).

The indication of LKT was established by the liver and kidney transplant selection committees of our hospital. Candidates for LKT were patients with an indication for liver transplantation due to end stage of liver disease with Child-Pugh ≥ B9 or symptomatic portal hypertension with or without hepatocellular carcinoma (within the Milan criteria) and with concomitant chronic renal failure: < 30 mL/min in the glomerular filtration rate or > 30% of glomerulosclerosis or fibrosis on hemodialysis for more than 8 weeks, or with a glomerular filtration rate less than 30 mL/min. Moreover, patients with polycystic liver-kidney disease with criteria of simultaneous liver-kidney transplantation and patients with hiperoxaluria were also considered candidates for combined LKT.

The number of LKT performed was analyzed by periods and compared with total isolated LT.

The data analyzed were collected retrospectively by review of patient medical records. The data collected included:

- Recipient demographic data (age, sex) and indication for liver and kidney transplantation.
- Pretransplant data related to the liver were (presence of cirrhosis, Child-Pugh stage, MELD (model of end stage liver disease) score pretransplantation, presence of hepatocellular carcinoma) and kidney (pretransplant need for dialysis, creatinine clearance calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula.
- Pretransplant diabetes mellitus (DM) or arterial hypertension (AHT).
- Donor demographic data (age, sex), cold and warm ischemia times of the kidney and liver.
- Immediate post-transplant data (surgical data, cross-match, days of intensive care unit (ICU) stay and days of hospitalization, need for reoperation due to bleeding, creatinine at 1 month, post-transplant need for dialysis and development of bacterial infections in the first month.
- Induction and maintenance immunosuppression.
- Late post-transplant data (incidence of liver and kidney rejection, incidence of DM defined as the need of insulin therapy, oral antidiabetics or dietetic treatment to mantain fasting glucose levels below 120 mg/dL and AHT defined as systolic blood pressure ≥ 140 mmHg and a diastolic pressure ≥ 90 mmHg at 1st and 3rd years, late cardiovascular complications (ischemic heart disease, cerebrovascular accidents), development of *de novo* tumors, creatinine at 1st and 3rd years), and
- Survival rates in both patient groups.

The standard induction immunosuppression used at our center in LKT is three-drug-based therapy [calcineurin inhibitor (target levels between 250-350 ng/mL), mycophenolate mofetil (1,000 mg tid) and steroids (prednisone 20 mg/day)] and the maintenance immunosuppression is based on two-drug therapy [calcineurin inhibitor (100-200 ng/mL) and mycophenolate mofetil (1,000 mg tid)] with low doses of steroids. In isolated LT induction is usually based on calcineurin inhibitors and steroids and maintenance with calcineurin inhibitor monotherapy when possible.

Combined LKT was always performed with a cadaveric donor and the same donor for both grafts. The standard surgical technique for liver transplantation was orthotopic liver transplantation with preservation of the vena cava, followed by implantation of the renal allograft, usually in the right iliac fossa.

The SPSS 19 statistical package was used for statistical analysis. Categorical variables were compared using the χ^2 test or Fisher's exact test when appropriate. Continuous variables were expressed as mean ± SD if they followed a normal distribution, and compared using Student's t test. If these variables did not follow a normal distribution, they were expressed as median and range, and compared using the Mann-Whitney test. A p-value ≤ 0.05 was considered significant.Kaplan-Meier curves were used for survival analysis and the log-rank test to compare survival curves.

RESULTS

Sixteen LKT patients (15 adult and 1 pediatric) were performed from January 1998 to December 2006 and were matched to 32 isolated LT by date, age, sex and indication for liver transplantation.

Rate of LKT over time

The number of LKT has increased over time in our center compared to total isolated LT (0.9% of total between 1998-2000, 1.30% between 2001-2003, 2.7% between 2004-2006).

Baseline characteristics

Table 1 shows the demographic characteristics and indications for LKT. The main indication for LT was HCV- and/or alcohol-induced cirrhosis. In turn, the main indication for KT was chronic renal failure, and this chronic renal failure was associated with chronic glomerulonephritis in most of our cases.

Comparison between LKT and LT

Tables 2 and 3 show recipient demographic characteristics, indications for transplantation and pre-

Table 1. Indications for liver and kidney transplantation (n = 16).

	Age (years)/ Sex	Date of LKT	Indication for LT	Indication for KT	Follow-up
1	42/M	1998	HCV + alcohol C	Chronic GN	Alive
2	40/F	1999	Polycystic liver disease	Polycystic kidney disease	Dead (sepsis)
3	55/F	1999	Polycystic liver disease	Polycystic kidney disease	Dead (sepsis)
4	15/M	2001	Hyperoxaluria type 1	Hyperoxaluria type 1	Alive
5	48/M	2002	HCV + alcohol C	Diabetic nephropathy	Dead (Haemorrhage)
6	65/M	2003	Alcohol C	Glomerulopathy (90% sclerosis)	Alive
7	49/M	2003	HCV C + HCC	IgA GN	Alive
8	42/M	2004	HCV + Alcohol C	Proliferative GN	Death (Decompensated cirrhosis)
9	65/M	2004	Alcohol C	Mesangial IgA GN	Alive
10	58/M	2005	Alcohol C + HCC	Diffuse glomerulosclerosis	Alive
11	54/M	2005	HCV + alcohol C + HCC	Cryoglobulinemic GN	Death (Lung neoplasia)
12	44/M	2005	Alcohol C	Hypocomplementemic glomerular nephropathy	Alive
13	67/M	2005	Alcohol C	Extracapillary proliferative GN	Alive
14	59/F	2006	HCV C	Membranoproliferative GN	Alive
15	57/M	2006	HBV C	Mesangial IgA GN	Alive
16	55/M	2006	Alcohol C	Chronic GN	Alive

HCC: hepatocellular carcinoma. GN: glomerulonephritis. C: cirrhosis. CRF: chronic renal failure. HRS: hepatorenal syndrome. LT: isolated liver transplantation. LKT: liver and kidney transplantation. HCV: hepatitis C virus. HBV: hepatitis B virus. M: male. F: female.

Table 2. Pretransplant patient characteristics.

Pretransplant recipient variables	LKT (n = 16)	LT (n = 32)	
Age (mean, years)	55 (15-67)	54 (13-66)	NS
Sex (male, %)	81%	78%	NS
Indication for LT	Alcohol = 7 HCV = 4 HBV = 1 CHC = 2 Other = 2	Alcohol = 12 HCV = 12 HBV = 1 CHC = 3 Other = 4	NS
Follow-up time (mean, years)	5.7 (0-14)	6.3 (0-14)	NS
Hepatocellular carcinoma	5 (31%)	9 (28%)	NS
Cirrhosis	13 (87.5%)	30 (94%)	NS
MELD (mean)	22	17	0.004
Child-Pugh stage (C, %)	1 (6%)	16 (50%)	< 0.001
Pretransplant AHT	8 (50%)	6 (19%)	0.02
Pretransplant DM	5 (31%)	9 (28%)	NS
Pretransplant dialysis (%)	11 (69%)	-	-

DM: diabetes mellitus. AHT: hypertension. LT: liver transplantation. LKT: liver-kidney transplantation.

Table 3. Post-transplant complications.

	LKT	LT	P
Days in ICU	5 (2-44)	4 (1-21)	0.05
Days of hospitalization	21 (11-70)	20 (0-99)	NS
Reoperation due to bleeding	3 (19%)	5 (16%)	NS
Bacterial infections in the first month post-transplant	9 (60%)	16 (52%)	0.06
Need for dialysis	5 (31%)	1 (3%)	0.01
Rejection			
Liver	2 (12.5%)	4 (12.9%)	NS
Kidney	0 (0%)		
DM in first year	6 (46%)	9 (32%)	NS
AHT in first year	5 (39%)	12 (43%)	NS
Late complications (2 years)	3 (25%)	5 (16%)	NS
Ischemic heart disease	1	2	
Stroke	-	2	
De novo tumors	2	2	
Deaths	5 (31%)	11 (34%)	

ICU: intensive care unit. DM: diabetes mellitus. AHT: hypertension. LT: liver transplantation. LKT: liver-kidney transplantation.

Table 4. Baseline donor and surgical characteristics.

	LKT (n = 16)	LT (n = 32)	P
Age (years)	40.5 (17-69)	44.5 (14-81)	NS
Sex (% male)	10 (63%)	22 (69%)	NS
CIT (mean) (liver) (min)	370 (125-650)	302 (105-710)	NS
WIT (mean) (liver) (min)	35 (20-65)	40 (20-80)	NS
CIT (mean) (kidney) (min)	408 (180-600)	-	-
WIT (mean) (kidney)	0	-	-
Positive cross-match	0%	-	-

CIT: cold ischemia time. WIT: warm ischemia time. LKT: liver-kidney transplantation. LT: liver transplantation.

transplant and post-transplant variables in both patient groups. The percentage of patients with Child-Pugh stage C was higher in patients with isolated LT (56% *vs.* 6% in LKT; p = 0.001). MELD score before LT was 22 in LKT *vs.* 17 in LT (p = 0.004). Of patients with LKT, 11 (69%) were on hemodialysis more than three months before transplantation and in the rest, the glomerular filtration rates were < 30 mL/min. Pretransplant DM was present in 31% of LKT and 28% of LT patients (p = ns). Pretransplant arterial hypertension was present in 50% of LKT *vs.* 19% of LT patients (p = 0.02).

Table 4 shows donor and surgical variables, with no significant differences between both groups.

Survival

With a median follow-up of 6.1 years (range: 0-13.9), LKT survival was 81% and 75% at 1st and 3rd,5th and 7th years respectively and LT survival was 87.5%, 74%, 74% and 66% at 1st, 3rd, 5th and 7th years respectively.

In LKT group, 3 patients (19%) died in the first year (during the first month post-LKT) and five patients (31%) during the overall follow-up *vs.* 4 (12.5%) patients in the first year and 11 patients (34%) during the overall follow-up in the LT group. Causes of death in the LKT group were: septic shock in three patients and subsequent multiorgan failure, all after post-transplant bleeding. Particularly, the two patients that were transplanted due to polycystic liver and kidney disease died during the first month due to sepsis. One LKT patient died in the 6th year post-LKT due to recurrent hepatitis C cirrhosis and kidney renal failure and the other patient died due to metastatic lung neoplasia two years after LKT. In the LT group, causes of death were sepsis (n = 1), multiorgan failure (n = 2), recurrence of hepatocellular carcinoma (n = 1) chronic rejection (n = 1), primary recurrent disease

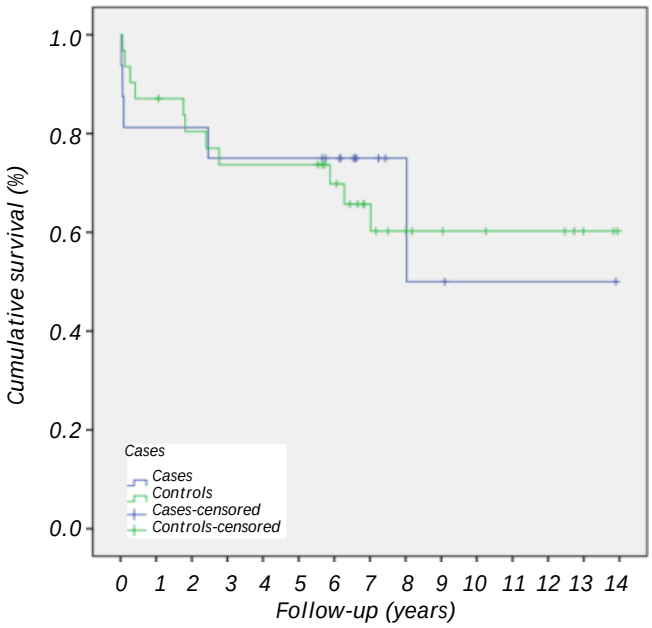

Figure 1. *Survival of combined liver-kidney transplant and isolated liver transplant. LKT: liver-kidney transplantation. LT: liver transplantation. Survival of LKT* vs. *LT. LKT survival: 81%, 75%, 75%, 75% at 1st, 3rd, 5th and 7th year. LT survival: 87%, 74%, 74% and 66% at 1st, 3rd, 5th and 7th year.*

(n = 3) and others (n = 3). Survival in the first 3 months post-transplant was lower in the LKT group (81% *vs.* 97% in LT). No differences were observed between groups after the third month post-transplantation (p = ns) (Figure 1).

Liver graft survival was the same as no patients were re-transplanted. Kidney graft survival was similar at 1, 3, 5th year post-kidney transplant. Only one patient lost his kidney the 7th year post-LKT and died four months later because of decompensated cirrhosis and renal failure.

Post-transplant complications

- ICU stay was longer in LKT [5 (2-44) days *vs.* 4 (1-21) days; p = 0.05] and bacterial infection nearly reached the statistical significance (60 *vs.* 52%, p = 0.06). In contrast, hospital stay, reoperations due to bleeding in the first month were similar in both groups. Five patients (31%) in the LKT group required temporary hemodialysis after transplantation versus 1 patient (3%) in the LT group (p = 0.01). The incidence of liver rejection was similar in both groups (12.5% in LKT *vs.* 12.9% in LT), and there was no case of kidney rejection. The incidence of DM and AHT at 1st and 3rd years was similar in both groups.
- Induction and maintenance immunosuppression showed differences between isolated LT and LKT because of the standard practice in our hospital. Induction immunosuppression was based on cyclosporine in 25% and tacrolimus in 75% of LKT, whereas cyclosporine was used in 62% and tacrolimus in 38% of LT (p = 0.03). Mycophenolate use was greater in LKT than LT both in the induction and maintenance phase (87% *vs.* 6%; p = 0.1) and (83% *vs.* 41%; p = 0.01), respectively. Prednisone duration was greater in LKT [579 (246-1,286) days *vs.* 364 (32-2,510) days in LT; p = 0.4).
- Median creatinine at 1 and 3 years post-transplant was similar in both groups.

Table 5. Glomerular filtration rates after LKT calculated by MDRD 4 (modification of Diet in Renal Disease).

	Date of LKT	GF 1st month	GF 1st year	GF 3rd year	GF 5th year
1	1998	81	77	85	62
2	1999	Dead	Dead	Dead	Dead
3	1999	Dead	Dead	Dead	Dead
4	2001	98	105	83	74
5	2002	Dead	Dead	Dead	Dead
6	2003	103	64	89	70
7	2003	35	30	33	54
8	2004	193	97	69	63
9	2004	18	49	46	42
10	2005	6	91	120	145
11	2005	124	93	Dead	Dead
12	2005	43	43	Not available	Not available
13	2005	64	53	94	89
14	2006	68	54	50	59
15	2006	66	72	71	71
16	2006	93	66	66	81

- Glomerular filtration rates calculated by MDRD 4 in LKT are shown in table 5 with a mean filtrate at five years of 72 mL/min.

DISCUSSION

Simultaneous LKT is an appropriate therapeutic option for patients with end-stage liver and kidney disease. Since the first LKT was performed by Margreiter in 1983, outcomes in terms of morbidity and mortality have improved mainly as a result of refinements in the surgical technique, with long-term survival rates comparable to those for LT and KT alone.[2-8] Survival rates at 3 and 5 years vary depending on the series and range from 72-82% and 62-78%, respectively, percentages similar to ours. Moreover, although LKT still represents a very small proportion of total LT and KT, the number of LKT has increased over time, coinciding with the introduction of the MELD system in most centers.

The indications for LKT are:

- Hereditary diseases affecting both organs, of which the most common is hepatorenal polycystic disease, especially when there is renal insufficiency and symptomatic incapacitating hepatomegaly.
- Metabolic diseases, such as primary type I hyperoxaluria; and
- Coexisting liver and kidney diseases which are the more frequent indications.

Functional renal disorders concomitant to liver disease, such as hepatorenal syndrome or pre-renal acute renal failure are generally not indications for LKT, except in cases that do not improve after 3 months on hemodialysis.[1,14] While the number of simultaneous LKT has increased, there are not many studies dealing with this special population. We have decided to perform a case-controlled study comparing our series of LKT control patients undergoing LT alone. The main findings of our study can be summarized as follows:

- Patient and graft survival are similar in patients undergoing LKT compared to patients undergoing LT alone.
- Early complications including stay in ICU, bacterial infections and need of dialysis are more frequent in LKT patients.
- Late complications are comparable in both groups.

In our series, the most common indications for liver and kidney transplantation in LKT were HCV associated cirrhosis and alcoholic cirrhosis as the indication for LT and chronic glomerulonephritis as the indication for KT. Hepatorenal polycystic disease accounted in two patients (12.5%) LKT, and there was only one LKT for hyperoxaluria because most LKT were performed in adults. These results are in agreement with other series reported in the literature.[15-18] One limitation of our case-controlled study is that Child-Pugh was different between groups. This is likely explained by the fact that the presence of cirrhosis is currently considered a contraindication for isolated kidney transplantation and hence LKT indication usually takes place in patients with better liver function. However MELD score was higher in LKT than in isolated LT due to the weighting of serum creatinine in the model. Although, at our center the MELD system for LT alocation was fully implemented in 2007, the increase in the number of LKT performed after 2004, reported as well in other series, could be a consequence that the implementation of the MELD system was being introduced at those years in our center.

Although patients who underwent LKT spent more days in the ICU, possibly due to the greater complexity of the surgical procedure, the overall hospital stay and the rate of immediate postoperative complications, and need for reoperation (variables related to early mortality in other series), were similar in both groups.[4] Bacterial infections were more frequent in the LKT patients, even though with no statistical significance. This finding might be related to a more potent immunosuppressive treatment in LKT patients. Steroids were with draw in LT during the 6th and 12th month post-liver transplant but in LKT, low doses of steroids are maintained in the long term.

It is interesting to note that there were no significant differences in the incidence of metabolic complications, such as hypertension, diabetes, long-term development of cardiovascular problems or occurrence of *de novo* tumors. These complications are generally more frequent in kidney transplant patients due to the typical arteriosclerotic complications of chronic renal failure,[19,20] but generally appear during long-term follow-up.

Factors that have been associated with a poorer short-term survival in LKT are infections in the immediate postoperative period, intraabdominal hemorrhage and a more advanced liver disease (Child-Pugh stage C).[4,21] Our series confirmed a poorer early survival in LKT than isolated LT due to sepsis

and intraabdominal hemorrhage. However, although the percentage of bacterial infections were higher in the LKT group, it did not reach statistical significance and the percentage of reoperations due to bleeding was similar between groups. It should be noted that the indication for transplantation in 2 of 5 patients who died in the LKT group was hepatorenal polycystic disease, a condition that is sometimes accompanied by severe malnutrition and has been associated with poorer survival rates after LKT.[22] In our series, the two patients with polycystic disease died in the post-operative period due two sepsis. Malnutrition and a more potent immunosuppression may have been contributing factors. From the second year post-transplant, survival was similar in both groups, with good rates being achieved after 3 and 5 and 7 years of follow-up.

Numerous articles have reported the advantage of combined LKT in providing immunological protection to the renal graft.[23,24] Possible mechanisms to explain this effect are the trapping of anti-HLA antibodies in the liver graft and the passage of lymphocytes with the liver graft, resulting in a greater microchimerism and consequently greater tolerance.[25-27] This advantage is more evident in simultaneous combined transplants, and less evident in transplants performed sequentially.[21,24] In our series, there were no kidney graft rejections and the incidence of liver graft rejection was very low, results that are consistent with those previously reported in the literature.

In more than a third of patients who underwent LKT, the indication for LT was HCV-induced cir-rhosis. Although post-transplant protocol biopsies are performed in our center in patients whose indication for LT is HCV-induced cirrhosis, they are not routinely performed in patients with LKT due to the a priori absolute contraindication for interferon treatment to avoid the risk of inducing renal rejection.[28,29] To date, 3 of 6 patients are alive and have no evidence of advanced liver disease, however the histologic situation is unknown.

In conclusion, LKT is an effective therapeutic option in patients with end-stage liver and kidney disease. Late complications as well as medium-term survival are comparable to those obtained with isolated LT and although two organs are used in the same recipient, the good results should not discourage this practice in patients in need of both organs. The difficulty in clinical practice remains in when to decide in each patient when she/he actually needs a simultaneous LKT.

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