ORIGINAL ARTICLE

Simultaneous Liver-Kidney Transplantation for Adult Recipients With Irreversible End-Stage Renal Disease

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Hypothesis: Combined liver-kidney transplantation is safe (low morbidity and acceptable mortality) and effective in patients with end-stage liver disease. Although refinements in surgical technique have resulted in better patient and allograft outcomes, the negative impact of renal insufficiency on survival in patients undergoing liver transplantation has been widely reported, although some aspects are controversial.

Design: Analysis of the clinical characteristics and outcome in the management of patients undergoing combined liver-kidney transplantation. The end points were operative mortality, morbidity, and long-term survival.

Setting: University Hospital 12 de Octubre.

Patients: Between May 1986 and December 2001, 820 liver transplantations were performed. There were 16 cases (1.96%) of combined liver-kidney transplantations, which represent the sample of this study.

Results: Mean ± SD follow-up of 42.2 ± 29 months: 6 patients died (37.5% mortality rate). There were 4 (25%) hospital deaths within 6 months following surgery and 2 after 6 months (4 sepsis, 1 refractory heart failure, and 1 recurrent hepatitis C virus disease). Univariate analysis related to mortality included age, sex, etiology, preoperative creatinine level, United Network for Organ Sharing status, Child-Pugh score, type of hepatectomy (piggyback), intraoperative blood product administration, and the presence of postoperative complications. The only 2 significant factors were the presence of postoperative complications ($P = .01$) and the United Network for Organ Sharing status ($P = .02$). Crude survival rate was 62.5%. Actuarial survival rates were 80%, 71%, and 60% at 1, 3, and 5 years, respectively.

Conclusion: Because end-stage renal disease is not a formal contraindication for liver transplantation, a combined liver-kidney transplantation for adults with end-stage renal disease can be done safely and effectively.

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ALTHOUGH REFINEMENTS IN surgical technique and improvement in medical management have resulted in better short-term and long-term patient and allograft outcomes,[1] the negative impact of renal insufficiency on survival in patients undergoing liver transplantation has been widely reported,[2-4] although some aspects are still controversial.[5-7]

Although renal failure was initially considered a contraindication, after the first combined liver-kidney transplantation (CLKT) reported by Margreiter et al[8] in 1984, it became clear that renal failure was no longer absolute, and this restrictive policy was soon reconsidered by the majority of institutions worldwide. Moreover, additional advantages have been proposed[9] by those who advocate its wider application, such as the immunological benefit (the supposedly protective effect of the liver allograft), the reduction in intensive care unit and in-hospital stay, and the overall consumption of health care resources by combining liver and kidney transplants, in comparison with an isolated liver transplantation in the context of simultaneous renal failure.

However, during the renal failure workup in candidates for liver transplantation who have end-stage liver disease (ESLD), it is important to clearly distinguish[10] patients with potentially reversible renal failure from those patients in whom renal dysfunction is associated with advanced, irreversible end-stage renal disease (ESRD). Moreover, there is a group of patients with mimetic liver and kidney lesions within the context of a systemic disease[11] (polycystic adult kidney liver disease, familial amyloidotic polyneuropathy, amyloidosis, or primary hyperoxaluria), in

Table. Etiology of Liver and Renal Failure (1986-2001)

Liver Failure	%	Kidney Failure	%
Cirrhosis	56.2	Chronic glomerular disease	56.2
Hepatitis C virus induced	18.8		
Alcohol induced	18.8		
Hepatocellular carcinoma* and hepatitis C virus	12.5		
Hepatitis B virus induced	6.3		
Polycystic adult kidney liver disease	37.5	Polycystic adult kidney liver disease	37.5
Recurrent cholangitis (hepatic artery thrombosis)†	6.3	Chronic allograft rejection	6.3

*Incidence findings (2 cases); the main indication was hepatitis C virus–induced cirrhosis.

†A re-orthotopic liver transplantation owing to late hepatic artery thrombosis.

which the indication for transplantation of 1 of the affected organs is not the irreversible failure itself but the presence of unmanageable symptoms (polycystic adult kidney liver disease), untreatable complications (familial amyloidotic polyneuropathy), or the cause of the kidney failure itself (primary hyperoxaluria). In this clinical scenario, a detailed evaluation needs to be done to weigh up the pros and cons before proceeding with a CLKT.

The present series compiles our experience with CLKT since the beginning of the Abdominal Organs Transplantation Program in 1986. Our study (retrospective review of a prospectively designed database) is a longitudinal and observational one that was conducted to analyze the clinical characteristics and outcome in the management of patients who had undergone a CLKT according to our protocol (first case performed in September 1987 at the University Hospital 12 de Octubre, Madrid, Spain). The end points of the present clinical research study were operative mortality rate, morbidity rate, and long-term patient and graft survival.

METHODS

STUDY SAMPLE

Between May 1986 and December 2001, 820 liver transplantations were performed in our service, and 35 cases (4.3%) included other abdominal organs: the pancreas after the kidney (n=1, 0.1%), the liver after the kidney (n=1, 0.1%), simultaneous pancreas-kidney transplants (n=17, 2.1%), and CLKT (n=16, 1.96%). These 16 CLKT cases represent the sample studied here.

All patients suffered simultaneously from ESLD and kidney failure or ESRF as a manifestation of the same systemic disease responsible for the liver disease (with identical lesions in both organs or a direct complication of the disease affecting the liver).

INCLUSION CRITERIA AND ETIOLOGY OF LIVER/KIDNEY FAILURE

Our criteria for liver transplantation have been described elsewhere.[12-15] A kidney allograft was added in patients with chronic renal failure (glomerular rate filtration <20 mL/min) who might benefit from preemptive CLKT in anticipation of further worsening of renal function with the introduction of calcineurin competitors as induction immunosuppression therapy in the posttransplantation setting.

Etiology of liver failure is shown in the **Table**. In most instances in the present series, the cause of liver failure was hepatitis C virus–induced cirrhosis (18.8%), alcohol-induced cirrhosis (18.8%), hepatocellular cancer (12.5%), hepatitis B virus–induced cirrhosis (6.3%), or ischemic recurrent cholangitis after late hepatic artery thrombosis (6.3%). Polycystic adult liver-kidney disease represents the remaining causes for liver replacement. Concerning the etiology of kidney failure (Table), the indications for renal replacement were chronic glomerular disease (56.2%), polycystic adult liver-kidney disease (37.5%), and chronic rejection of a prior renal allograft (6.3%).

EXCLUSION CRITERIA

We excluded patients who underwent a renal transplantation and afterward a liver transplantation but not simultaneously (within an interval of months or years).

ALLOGRAFT ALLOCATION AND DONOR CHARACTERISTICS

All allografts come from ABO-compatible cadaveric donors (both grafts from the same donor). Cross-matching was performed in only 3 cases, all of which were negative.

IMMUNOSUPPRESSION REGIME

A calcineurin-competitor (in addition to steroids) was the baseline regimen adopted in the present series as an induction therapy, which essentially does not differ from that used in isolated liver or kidney transplantation.

A double regimen was used in 50% of cases (tacrolimus + steroids), a triple one in 43.8% (cyclosporine + steroids + azathioprine/mycophenolate mofetil), and a fourth drug was added in 6.3% (antithimoglobulin + cyclosporine + steroids + azathioprine/mycophenolate mofetil).

STUDY DESIGN, VARIABLES, AND STATISTICAL ANALYSIS

A retrospective, longitudinal, and observational study was conducted. A database was compiled including 63 variables (nominal and numerical). Values are shown as mean/standard deviations, ranges, or percentages. Categorical data were compared by means of the χ^2 test and numerical data by the t test. Survival curves were constructed with the Kaplan-Meier method, and the log-rank test was used for survival comparisons by means of the SPPS for Windows (SPSS Inc, Chicago, Ill) (P values $<.05$ were considered significant).

RESULTS

DEMOGRAPHICS AND PREOPERATIVE CHARACTERISTICS

Sixteen patients were the focus of this study (population sample). The mean±SD age was 48.7±11.2 years (range, 34-55 years). The female:male ratio was 5:11 (68% male). The mean±SD pretransplant Child-Turcotte-Pugh score was 8.88±2.47 (range, 6-12). The mean±SD pretransplant serum creatinine level was 4.98±1.38 (range, 3.01-8.9). United Network for Organ Sharing

(UNOS) statuses were UNOS 1 (18.8%), UNOS 2a (16.3%), UNOS 2b (40%), and UNOS 3 (25%).

INTRAOPERATIVE CHARACTERISTICS

A piggyback technique was carried out in 75% of the cases, venous by-pass in 12.5%, and total clamping in 12.5%. During the liver transplantation phase, intraoperative dialysis was required in 62.5% of patients, and administration of blood products was required as follows: fresh frozen plasma in 100% of cases (mean±SD units perfused, 29.4±20.7), platelets in 50% (mean±SD units perfused, 22±11.3), and units of packed red cells in 100% (mean±SD units perfused, 17.3±14.9).

POSTOPERATIVE COURSE

Immunological complications (cellular rejection) occurred in 1 case (6.3%), a moderate-grade biopsy proven and treated by intravenous methyl-prednisolone (1g/3d). Nonimmunological complications occurred in 4 patients (25%), consisting of acute pancreatitis (1), cytomegalovirus colitis (1), catheter-related sepsis (1), and severe pulmonary edema (1) secondary to right heart failure (unrecognized pulmonary hypertension with intraoperative mean pulmonary artery pressure of 28 mm Hg). Surgical complications occurred in 2 cases (12%), consistent with conservatively managed limited bile leak. The overall mean±SD intensive care unit stay was 9±8.4 days (range, 4-36 days). For those who survived the postoperative period (from CLKT to hospital discharge), the mean±SD length of hospital stay was 33±9.7 days (range, 23-59 days).

MORTALITY AND SURVIVAL ANALYSIS

After a mean±SD follow-up of 42.2±29 months (range, 1-90 months), 6 patients died (actual mortality rate, 37.5%). There were 4 (25%) operative in-hospital deaths (within 6 months after the transplantation) and 2 late mortality cases (beyond the 6 months after hospital discharge). The causes were sepsis (4 cases: 3 postoperative and 1 in later follow-up), refractory heart failure (1 postoperative), and recurrent liver disease (hepatitis C virus–induced severe recurrence) during follow-up (1). Univariate analysis for factors related to operative mortality was performed; factors included age, sex, etiology of liver or kidney failure, preoperative creatinine level, UNOS status, Child-Pugh score, type of hepatectomy (piggyback vs others), intraoperative administration of blood products, and the presence of postoperative complications. The only 2 significant factors were the presence of postoperative complications ($P=.01$) and UNOS status ($P=.02$).

Crude survival rate was 62.5%. Actuarial survival rates (calculated for those who survived the postoperative period) were 80%, 71%, and 60% at 12, 36, and 60 months, respectively (**Figure 1**), and actuarial mean survival time was 65 months (95% confidence interval, 46-53). Sex ($P=.47$), UNOS status ($P=.91$), etiology of liver disease ($P=.92$), etiology of renal failure ($P=.76$), type of hepatectomy (piggyback vs others, $P=.51$), and type of immunosuppression ($P=.83$) were not related to long-term survival, according to the log-rank test.

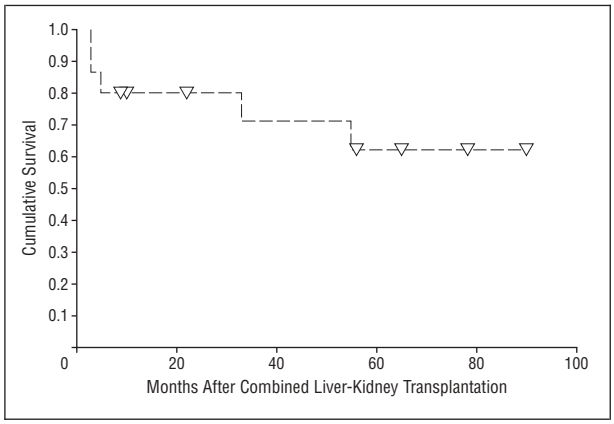

Figure 1. Actuarial survival rates after combined liver-kidney transplantation (University Hospital 12 de Octubre, Madrid, Spain). Triangles indicate survival times.

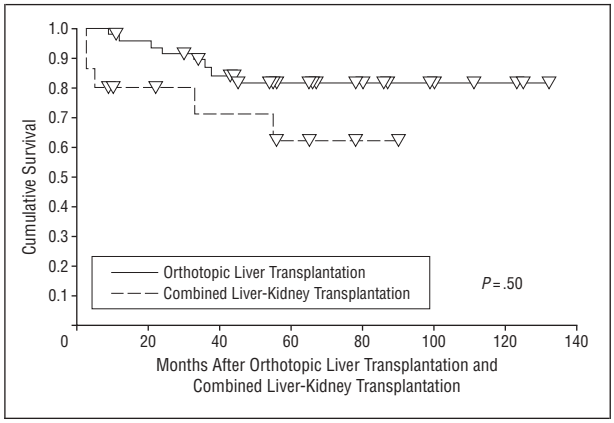

Figure 2. Survival rates after orthotopic liver transplantation and combined liver-kidney transplantation. Triangles indicate survival times.

To compare this group of CLKT with those who underwent an isolated liver transplantation during the same period (avoiding the effect of overall improvement in results with time), a control group was constructed with patients who underwent a liver transplantation immediately before or after CLKT. A total of 48 patients served as controls (2 cases after the CLKT and 1 case before). There were no differences ($P=.50$) in survival (**Figure 2**).

In addition to this, we carried out a comparison concerning survival between 2 periods: 1986-1993 (7 cases) and 1994-2001 (9 cases). There were no differences in actuarial or actual survival among them (**Figure 3** and **Figure 4**).

COMMENT

Treatment of ESLD is occasionally complicated by the presence of concomitant renal insufficiency, and mortality of hepatic transplant recipients in the context of an acute renal failure (ARF) has been found to reach 90%.[16] For this reason, it is especially important not only to assess the functional reserve of patients with ESLD (by methods other than the classical methods of measuring plasma creatinine levels or creatinine clearance) but also to study the underlying cause of the renal insuffi-

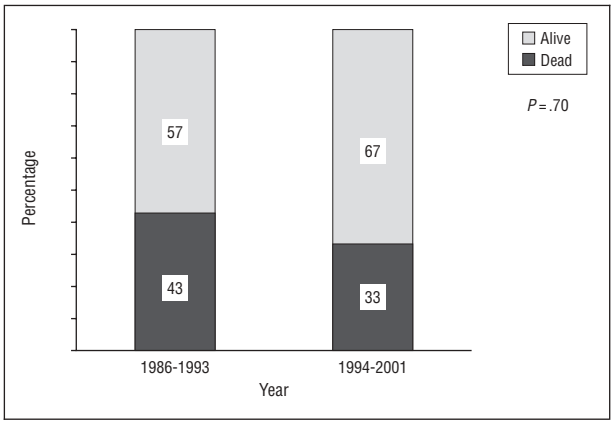

Figure 3. Actual survival rates of 2 periods.

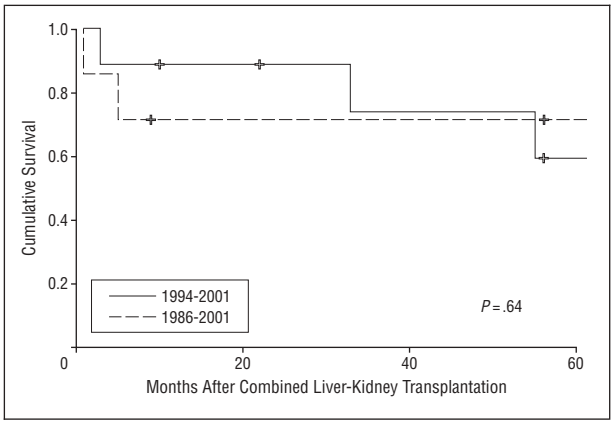

Figure 4. Actuarial survival rate: a comparison of 2 periods.

ciency.[17] This is achieved by using alternative methods to assess functionality (inulin clearance or isotopic studies) and a thorough investigation of the causes (prerenal, intrinsic renal, postrenal, hepatorenal syndrome, chronic glomerulonephritis, etc) that can trigger ARF in these patients.

In a retrospective study conducted by Cuervas-Mons et al[18] in 1986, the rise in serum creatinine before liver transplantation was associated with an increased mortality after the intervention, and these authors established a cutoff at 1.72 mg/dL (prediction of survival or mortality in 79% of cases). In a multivariate study performed by Rimola et al[19] of the predictive factors of mortality after liver transplantation performed on a sample of 102 patients, it was also shown that, in addition to the presence of postoperative infections and hepatic graft rejection, pretransplant renal insufficiency was another independent prognostic factor. In a comparative study including 111 liver transplant recipients with ARF and 196 without ARF before transplantation, Fraley et al[20] concluded that ARF was associated with an increased mortality consistent with the known adverse prognostic effect of ARF on ESLD. But this effect was remarkably reduced in patients who received a functioning orthotopic liver transplant.

The first successfully performed CLKT was reported in 1984 by Margreiter et al,[8] who concluded that this procedure could be performed in patients with simultaneous failure of both organs. Since then, publications in English have compiled the results of several institutions (corresponding to around 800 transplants) where this procedure has been performed successfully during the last 2 decades. It is shown that CLKT not only reduces morbidity and the costs associated with renal insufficiency[21] but also offers immunological benefits because there is a lower incidence of rejection. However, the indications for this intervention are still controversial.[21]

In our experience, of 820 liver transplantations performed between May 1986 and December 2001, CLKT was only done in 16 (approximately 2%), representing a very small proportion, in accordance with data from other series.[22-32] All live patients at the end of this study (62.5%) had functional grafts, and the only functional loss was that related to patient death: actuarial survival was comparable to that obtained in patients receiving only liver transplants (controls) during the same period (Figure 2). Only 1 patient had cellular rejection that responded well to steroid treatment. We can therefore confirm that CLKT is a suitable treatment for patients who, according to our criteria (irreversible ESLD and ESRD), require a double transplant and who would otherwise have a very small chance of survival.

However, this achievement is by no means without complications. In the present series, the operative mortality (25%) and morbidity rates were much higher than those recorded in our experience[22] and others' experience[22] with orthotopic liver transplantation, although similar to those reported in CLKT. Also, the use of blood and blood products was very high, and intensive care unit and in-hospital stays were more prolonged. In the univariate analysis, age, sex, etiology of liver or kidney failure, preoperative creatinine level, Child-Pugh score, type of hepatectomy (piggyback vs others), and the amount of blood products intraoperatively given did not have any significant effect on operative mortality. However, the presence of postoperative infectious complications (sepsis) and the UNOS status (UNOS 3 vs UNOS 1 and 2) of the patient did have a significant influence.

We conclude that (1) the criteria used for CLKT in our group gave good short-term and long-term results; (2) these results are susceptible to improvement by reducing the rate of infectious complications and the length of the waiting list (UNOS status); (3) given that CLKT seems to confer a degree of immunological tolerance, it would be appropriate to develop more specific immunosuppresion protocols that would result in better immunocompetence against the possible infections that produce a high operative mortality; and (4) we do not consider hepatorenal syndrome or ARF (of prerenal or intrinsically renal cause) that occasionally complicates the course of chronic liver disease to be an indication for double transplant. On the contrary, as suggested by our group elsewhere,[33] in these circumstances the correct perioperative management, consisting of intraoperative dialysis and/or hemofiltration, use of the surgical hepatectomy technique that conserves renal flow (piggyback), and the introduction of renal function–sparing protocols after orthotopic liver transplantation with ARF, gives satisfactory results without having to use a renal graft and could be more beneficial for patients with chronic renal failure following a dialysis program.

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