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MELD Era Increases the Number of Combined Liver and Kidney Transplantations

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Abstract

Introduction: Combined Liver and Kidney Transplantation (CKLT) procedure is performed in large transplant centers worldwide as a therapeutic option for patients with disease in both organs and is currently the procedure of choice in many centers. The objective of this study was the evaluation of the number of combined transplantations before and after adoption of the MELD score in the Liver and Gastrointestinal Transplant Division of the University of São Paulo (Brazil) and comparison with the State of São Paulo.

Method: Clinical data from 705 transplantations performed from January 2002 to July 2012 were studied. Overall patient survival was analyzed by the Kaplan-Meier method for patients who underwent either combined liver and kidney transplantation or liver transplantation alone. Evaluation of the number of combined transplantations before and after adoption of the MELD score. The mean values and standard deviations were used to examine normally distributed variables. Comparison the incidence results with the CLKT and LT on State of São Paulo.

Results: There was a high prevalence of male patients referred to both modalities of transplantation. The mean age of patients was also similar in both groups, with a predominance of middle-aged males. The predominant reason for transplantation was hepatitis C cirrhosis (25.8%) in the CLKT group. The mean and median survival rates and survival over 10 years were similar between the groups (p= 0.620). The MELD score increases over the course of the period analyzed for patients who underwent both modalities of transplantation (p=0.46). There was an increase in the number of CLKTs after adoption of the MELD score in our institution and in State of São Paulo (p<0.001).

Conclusion: The adoption of the MELD score increase the number of combined transplants performed. The survival rate for Combined Liver and Kidney Transplantation is similar to that of Liver Transplantation alone.

Keywords: Liver transplantation; Kidney transplantation; Kidney failure, Chronic; End stage liver disease

Abbreviations: MELD: Model for End-Stage Liver Disease; CLKT: Combined Liver and Kidney Transplantation; LTA: Liver Transplantation Alone; LT: Liver Transplantation; KT: Kidney Transplantation

Introduction

Liver and kidney disease are responsible for a large number of deaths worldwide and are some of the major cause of hospitalization. In advanced stages of disease, transplantation is the only effective intervention strategy to increase survival [1,2].

The first case of Combined Liver-Kidney Transplantation (CLKT) was described by Margreiter in 1984 [3] Nowadays, CLKT is the standard procedure to patients with concurrent liver and kidney failures, several studies have reported favorable outcomes in these patients [4,5]. However, the presence of renal impairment or hemodialysis in patients undergoing liver transplantation is a predictor of higher mortality [1,4,6,7]. Moreover, the number of patients with renal dysfunction on the liver transplant waiting list increased since the adoption of the Model for End-Stage Liver Disease (MELD) score for allocating liver grafts in 2002 in the U.S. [1,5,8,9].

Some authors have suggested that the transplanted liver can confer a protective immunologic effect on the kidney allograft [1,4,6]. Lower incidence of renal acute cellular rejection during the first year after CLKT in comparison with Kidney Transplantation (KT) alone, even though similar hemodialysis time and immunosuppressive schemes support this idea [6].

Outcomes in CLKT patients seem to be excellent. Graft and patient survival rates can be even higher following CLKT in detriment of Liver Transplantation (LT) alone, most of these series were from North American and Europe [4,10].

In fact, there is no study examining outcomes of CLKT in South America. This is particularly important when considering the potential demographics, ethnic and socioeconomic factors, the varying size of the waiting list and the mean MELD score in the moment of organ allocation. In addition, the different policies used to refer patients for combined transplantation procedures may alter the prognosis and long-term outcomes. In the last year, the average MELD score in patients transplanted in our department was 31.02.

In this study, we aimed to clarify the incidence and outcomes of CLKT performed in a single South American center during pre and post MELD era. Additionally, we also analyzed the results in a larger adjacent area including more than 15 institutions in State of São Paulo.

Methods

Clinical data were retrospectively reviewed from 705 adult Liver

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Transplants (LT) recipients performed from January 2002 to July 2012 in Liver and Gastrointestinal Transplant Division (Department of Gastroenterology) of the University of São Paulo School Of Medicine (Brazil). After exclusion of split-liver transplantation, retransplantation, and living donor LT, we studied 31 CLKT and 592 LT alone. Specifically, we analyzed the variables gender, age, cause of transplantation, MELD score, incidence of LT and CLKT from MELD era and survival rate (overall survival) over the course of this 10 year period.

We collected data from São Paulo Health Secretariat registry in the official government website (www.saude.gov.sp.br/transplante) enrolling 3,961 unselected adult LT recipients performed during the same period within a large adjacent area (Sao Paulo State) including ours and more than 15 institutions.

MELD score is the allocation system in Brazil since July 2006 replacing chronological allocation system. Then we split pre MELD era from January 2002 to July 2006; and MELD era from July 2006 to July 2012.

Almost all procedures were performed with the piggyback technique; UW and HTK were the preservation solution most employed. Immunosuppressive regimen was customized individually, all patients received steroid (ST) bolus during anepathic phase, ST was tapered aiming the complete stop after 3 to 6 months after transplantation; calcineurin inhibitor (Tacrolimus or Ciclosporine) was administered and maintained to all patients; mycophenolate mofetil (MMF) was employed to patients with CLKT or renal dysfunction. The liver and kidney transplantation teams are separated in our institution. That is, one team performs the transplantation of the liver, and the other, the kidney transplant. The indication for CLKT was cirrhosis with end-stage renal disease with glomerular filtration rate < 30 mL/ minute or acute kidney faliure requiring dialysis at least 2 times per week for more than 8 weeks.

The statistical analysis was performed using the SPSS 20.0 software package (SPSS Inc, USA). Overall patient survival analyses were performed by applying the Kaplan-Meier method (Log Rank; Mantel-Cox) to patients who underwent either CLKT or LTA. Mean and median values and standard deviations were used to examine normally distributed variables. Student's t-test for unpaired data was used for comparisons. The chi-square test was used for comparing liver transplantation modality frequencies. P-values lower than 0.05 were considered statistically significant.

Results

Clinical and demographic population profile

In this study, we analyzed all liver transplants performed in our center over the course of 10 years, 31 CLKTs and 592 LTAs. Table 1 shows the main characteristics of these groups of patients. There was a high prevalence of male patients referred to both modalities of transplantation. The mean age of patients was also similar in both groups, with a predominance of middle-aged males.

In patients who underwent CLKT, the average MELD score was 26.2 and the scores ranged from 16 to 37 (Table 1). For CLKT, the warm and total liver ischemia time ranged, respectively, from 35 to 90 minutes (48.29 min ± 11.89) and from 4.5 to 13.7 hours (Mean 7.76 ± 2.30). The predominant reason for transplantation (CLKT) was hepatitis C cirrhosis (25.8%), followed by alcoholic cirrhosis (22.5%), hepatitis B cirrhosis (16.1%), cryptogenic cirrhosis (12.9%), and autoimmune hepatitis (9.7%). HBV + HCV association occurred in one case (3.22%), and other causes such as primary sclerosing cholangitis and Caroli disease occurred in three cases (9.7%).

Patient survival rates

Mean and median survival rates and survival over the 10 years of the study are shown in Figure 1. The overall survival rates of patients in the CLKT and LT alone groups were approximately 68% and 75%, respectively. Survival in the short and long term is similar for the two types of transplantation, although we observed a decrease in the long-term survival in CLKT group (Figure 1). There were no significant differences in survival between the transplantation modalities.

Pre MELD and pos MELD era

In pos MELD era, all patients transplanted in SP State had mean MELD of 28.5, median of 29 and mode of 24. Regarding only LT performed in our institution MELD´s mean, median and mode were 30.5, 29 and 29, respectively.

CLKT was performed more often during pos MELD era, as demonstrated in Table 2. CKLT rate globally rose from 2.1% to 4% in pos MELD era, this increasing was statistically significant ($p<0.0001$).

Discussion

In this study, we examined the outcomes of liver transplantations performed in a large center in Brazil and compared patient survival rates between combined liver and kidney transplantation procedures and liver transplantation alone. Our results showed no differences in the overall survival rates between these transplantation modalities.

CLKT is an effective therapy for end-stage liver disease with chronic renal failure or severe damage to renal function. However, it is a complex surgical procedure, becoming a challenge even to experimented anesthetists, with higher morbidity than liver transplantations alone.

	CLKT (n=31)	LTA (n=592)	p value
Sex (n/%)	M=22 (70.9%)/ F=9 (29.1%)	M=398 (65.8%)/ F=194 (34.2%)	0.19
Ages (years)	49.77 ± 12.96	51.90 ± 13.07	0.39
MELD	26.21 ± 10.16	23.71 ± 12.03	0.50
Liver disease:	HCV 25.8% alcoholic cirrhosis 22.5% HBV 16.1% cryptogenic cirrhosis 12.9% autoimmune hepatitis 9.6% others 9.6% HBV with HCV 3,2%	HCV 35.3% alcoholic cirrhosis 16.5% HBV 8% fulminant hepatitis 11.8% autoimmune hepatitis 4% cryptogenic cirrhosis 9.6% others 14.8%	
Kidney Disease:	chronic renal failure in 24 cases glomerulonephritis membranoproliferative in 2 diabetes mellitus in 1 case hepatorenal syndrome in 2 one case of IgA nephropathy one of pyelonephritis by repetition		

Note: Mean and standard deviations or number and percentage, M: Male; F: Female; HCV: Hepatitis C Cirrhosis; HBV: Hepatitis B Cirrhosis; MELD: Model for End-Stage Liver Disease

Table 1: Demographic parameters for Combined Liver and Kidney Transplantation (CLKT) and Liver transplantation without split, living donor and retransplantation (LTA) in the Liver and Gastrointestinal Transplant Division, University of São Paulo School of Medicine (Brazil), 2002 to 2012.

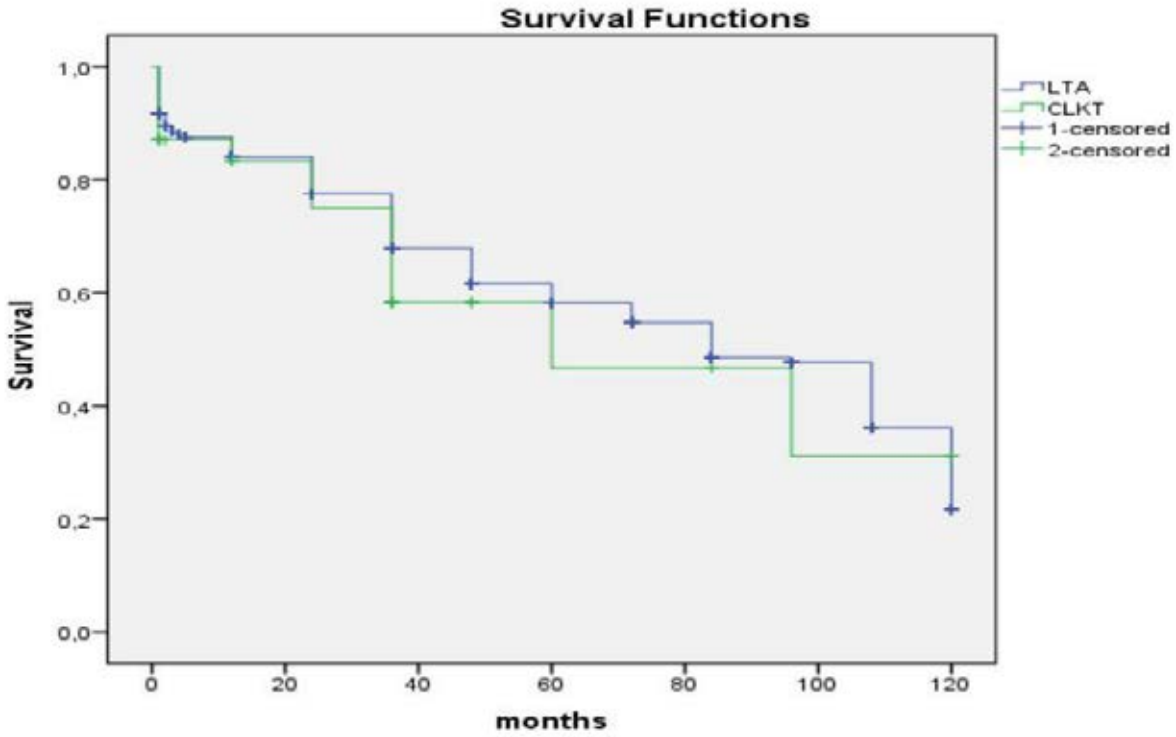

Figure 1: Overall patient survival analyses by the Kaplan-Meier method (Log Rank; Mantel-Cox) of patients who underwent either combined liver and kidney transplantation (CLKT) or liver transplantation alone (LTA) in a University hospital in Brazil Chi-Square=0.245; p-value=0.620.

	Pre MELD LT alone (%)	Pre MELD CKLT (%)	Pos MELD LT alone (%)	Pos MELD CLKT (%)	p value
HCFMUSP	158 (96.3)	6 (3.7)	479 (95)	25 (5)	0.46
SP state	989 (98.1)	19 (1.9)	2201 (96.3)	85 (3.7)	<0.001
Total	1147 (97.9)	25 (2.1)	2680 (96)	109 (4)	<0.001

Note: Number and percentage
MELD era: Model for End-Stage Liver Disease (after 2006).

Table 2: The evaluation of all patients transplanted in State of São Paulo from MELD era and comparison with Combined Liver and Kidney Transplantation (CLKT) in SP State and in the Liver and Gastrointestinal Transplant Division (HCFMUSP), University of São Paulo School of Medicine (Brazil), 2002 to 2012.

Therefore, it is essential to use optimal perioperative fluid tailoring immunosuppressive schemes to improve outcomes [1,4,6,8]. In addition, there is an increased morbidity associated with renal insufficiency, so it would not be surprising if lower survival rates were observed in patients who underwent CLKT. In fact, if the transplanted kidney works, this can minimize these problems and can be better for the patient than undergoing dialysis after transplantation [2,8,10].

The decision to CLKT depends fundamentally on the presence of associated end-stage kidney and liver disease. Indication to combined procedure is straightforward in patients under dialyses. Conversely, in those patients with potentially reversible kidney failure can be difficult to predict whether the native kidney will recovery sufficiently after LT alone [2,4,7,11]. In our institute, we consider more than 8 weeks of dialysis given at least 2 times per week to indicate the CLKT procedure.

This study demonstrated outcomes of LT performed in a large center in Brazil and compared patient survival rates between combined liver and kidney transplantation procedures and liver transplantation alone. Our results showed no differences in the overall survival rates between these transplantation modalities.

The overall 1 and 5 year survival rates of patients who underwent liver transplantation (either combined or alone) were 85% and 60%, respectively. The short-term survival results were similar for both modalities, but we observed better long-term survival in LT alone group. Similar survival in both groups is interesting considering the predictive morbidity factors associated with the patients who underwent CLKT.

The most common cause of liver failure was hepatitis C cirrhosis, corresponding to 25.8% of the CLKT cases. This result contrasts with those reported in other eastern populations. For instance, in China, the most common cause of liver failure has been shown to be hepatitis B cirrhosis, whereas in other western countries, hepatitis C has been reported to be the main cause of end-stage liver disease [1,8,12,13].

CLKT was performed more often over the course of the study period. Specifically, there were only 6 CLKTs during pre MELD era and 25 after introducing of MELD allocation system. Additionally, the MELD scores of those patients who underwent transplantation before 2006 was lower than those referred for an intervention after 2006. This was expected, and as a consequence of the higher degree of severity of those patients transplanted after 2006, their prognosis was poorer. This result is consistent with that reported in other countries [5,7,8].

In Brazil, the absolute number of observed liver transplants is relatively large, approximately 1,500 liver transplants per year. However, the number of donations per million is approximately 10, less

than in the U.S. and Europe [8,9]. In our study, this mismatch between supply and demand caused the MELD to rise and increased the number of double transplants after the adoption of the MELD score. Our work shows a statistically significant increase in the number of CLKTs after 2006 in the State of São Paulo when compared with LTA. To the best of our knowledge, the present study describes the largest series of combined liver transplantations reported in South America to date.

Conclusion

In conclusion, the present results provide important information about the outcomes of combined liver and kidney transplantation in a large center and adjacent area. Specifically, the evaluation and increase incidence of transplants performed after the adoption the MELD score increased the number of simultaneous transplants performed. The survival rate for CLKT is similar to that of LTA.

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