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Native renal function after combined liver-kidney transplant for type 1 hepatorenal syndrome: initial report on the use of postoperative Technetium-99 m-mercaptoacetyltriglycine scans

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Summary

Type 1 hepatorenal syndrome (HRS) is characterized by rapid deterioration of renal function. We sought to assess native kidney function after combined kidney-liver transplant (CLKTx) performed for type 1 HRS. We performed a retrospective, cross-sectional, single-center study. All patients with Type 1 HRS who received a CLKTx at the University of California, San Francisco from 1997 to 2007 were screened for enrollment. Patients with a baseline estimated glomerular filtration rate (eGFR) $\geq$30 ml/min/1.73 m^2 were eligible. Twenty-three patients were identified and consented to receive a Technetium-99 m-mercaptoacetyltriglycine (MAG3) nuclear scan to measure the native kidney contribution to overall renal function. Only 4 of the 23 subjects (17.4%) demonstrated native renal function that consisted of a contribution $\geq$50% of total renal function. Several factors and comorbidities such as age, gender, race, duration of HRS, need for and duration of renal replacement therapy, need for pressors, urine sodium, proteinuria, and use of octreotide/midodrine were analyzed and not found to be significant in predicting native renal function. The assessment of post-transplant native renal function following CLKTx may allow for improved accuracy in identifying the patients in need of CLKTx, and thus allow for greater optimization of dual-organ allocation strategies in patients with concomitant liver and renal failure.

Introduction

Nearly three decades have passed since the first report of combined liver-kidney transplantation (CLKTx) [1]. With the implementation of the Model for End-Stage Liver Disease (MELD) scoring system in February of 2002, which emphasized prioritization of liver allocation for patients with renal insufficiency, the number of CLKTx has demonstrated nearly consistent annual increases. Indeed, the increased mortality in liver transplant alone (LTA) patients with renal insufficiency can be obviated through the successful application of CLKTx; however, it is recognized that this form of dual-organ transplantation comes at the cost of deprivation of transplantation for patients with end-stage renal disease. The latter portends even greater significance in the setting of potential native renal recovery in a CLKTx recipient [2].

With the growing application of CLKTx has come concern for the excessive use of dual-organ transplantation, and thus a misappropriation of this limited resource [3]. In

2006, a consensus conference on CLKTx was held in the United States, in an attempt to help define recipients best suited for this form of dual-organ transplantation [4]. Although there is little disagreement for the benefit of CLKTx in end-stage liver disease (ESLD) patients with long-standing chronic renal failure, there remains little data on defining the ESLD patient with hepatorenal syndrome (HRS) best suited for CLKTx, especially those patients with Type 1 HRS, who are largely believed to have reversible renal disease.

Single-center retrospective studies have suggested that HRS with the need for renal replacement therapy (RRT) >8 weeks defines the appropriate candidate for CLKTx. Furthermore, data regarding native renal function following CLKTx are limited [5], but hold potential through this form of retrospective assessment to accurately assess the benefit of CLKTx, and help guide future allocation strategies. We sought to determine the extent of native renal function following CLKTx in patients with Type 1 HRS.

Patients and methods

We performed a retrospective, cross-sectional, single-center study. All patients who received a CLKTx at the University of California, San Francisco (UCSF) from 1997 to 2007 were screened for enrollment. Twenty-three patients diagnosed with Type 1 HRS prior to transplant, with a baseline-estimated glomerular filtration rate (eGFR) $\geq$ 30 ml/min/1.73 m^2 prior to the onset of HRS, consented for study participation. The baseline eGFR was calculated using the modification of diet in renal disease (MDRD) formula and determined from review of outpatient records obtained during a period of clinical stability in the 6-months prior to hospital admission. Given the critical nature of the ESLD patient with Type 1 HRS, native kidney biopsy is rarely performed at our institution. Type 1 HRS was defined according to the criteria outlined by the International Ascites Club [6].

The CLKTx was performed in the standard fashion, with implantation of the liver allograft prior to the kidney allograft. Only donation after brain-death donors were used for dual-organ transplant recipients for the time period studied, with both the liver and kidney allograft originating from the same donor for all CLKTx recipients. Induction therapy was not used, and standard immunosuppression consisted of steroids, mycophenolate mofetil, and a calcineurin inhibitor.

Subjects underwent a Technetium-99 m-mercaptoacetyltriglycine (MAG3) renogram to measure the native kidney contribution to overall renal function. Dynamic renogram images were obtained from the anterior and posterior projections simultaneously. Because of the proximity to the gamma camera detectors, the transplant kidney was assessed using data from the anterior projection, while the native kidneys were assessed using data from the posterior projection. Regions of interest were drawn manually around each kidney, and allowed for the quantitative assessment of renal function. Photon counts within each region of interest were processed using renogram analysis software, which also takes into account the number of kidneys, location of the kidneys, patient age, height, weight, radiotracer dose injected, and corrects for background activity. Quantitative indices of estimated renal plasma flow, relative uptake and contribution, time to peak height, and the clearance half-time for each kidney were assessed. The images of both native kidneys were processed as one single unit separately from the kidney transplant. The relative function of all three kidneys was defined as the relative attenuation corrected counts in the renal parenchyma between 2 and 3 min after injection of MAG3, similar to the method described by Francis, *et al.*[5] Native contribution $\geq$ 50% to overall kidney function was considered significant and labeled as 'high'.

This study was approved by the UCSF Committee on Human Research. Outpatient and inpatient records were reviewed including: clinic visit notes, hospital notes, discharge summaries, laboratory results, and medication histories. Data obtained included: demographics, urine and serum electrolytes, urine and serum creatinine, liver function tests, MELD score, need for renal replacement therapy, pretransplant use of octreotide/midodrine, significant perioperative hospital events (such as sepsis and need for pressors) baseline immunosuppression and graft outcomes. Categorical variables were compared between groups using the Fisher's Exact test and continuous variables were compared with the Wilcoxon rank-sum test. Statistical analyses were performed with Stata 11 (Stata Corp., College Station, TX).

Results

During the time period of 1997–2007, 100 patients underwent CLKTx at UCSF (Table 1). Twenty-three subjects with Type 1 HRS were consented and able to undergo a MAG3 renogram. At the time of the MAG3 renogram 100% of the liver allografts were functioning and no patient developed end-stage renal disease requiring renal replacement therapy. Baseline patient characteristics are seen in Table 2.

Nineteen subjects (82.6%) demonstrated low contribution of native kidney function to overall renal function (Native-low), while four subjects (17.4%) had a high contribution of native kidney function to overall renal function (Native-high). The mean time $\pm$ SD from CLKTx to MAG3 renogram was 1200 $\pm$ 822 days for the Native-low cohort, and 1179 $\pm$ 1341 days for the Native-high cohort

Table 1. CLKTx as a percentage of total deceased donor liver transplants performed at UCSF from 1997–2007.

Year of transplant	Deceased donor liver transplants at UCSF (*n*)	CLKTx at UCSF (*n*)	% CLKTx
1997	79	3	3.8
1998	85	4	4.7
1999	87	4	4.6
2000	76	7	9.2
2001	90	8	8.9
2002	82	9	11.0
2003	104	11	10.6
2004	106	16	15.1
2005	143	13	9.1
2006	138	15	10.9
2007	118	10	8.5

CLKTx, combined liver-kidney transplant; UCSF, University of California, San Francisco.

Table 2. Baseline patient characteristics.

	Native-low (*n* = 19)	Native-high (*n* = 4)	*P* value
Mean age, years (SD)	54.9 (7.8)	55.8 (6.8)	0.85
Male gender, *n* (%)	12 (63.2)	3 (75)	1.00
Race, *n* (%)			
African-American	3 (15.8)	1 (25)	1.00
Caucasian	12 (63.2)	2 (50)	1.00
Latino/Hispanic	2 (10.5)	0 (0)	1.00
Other	2 (10.5)	1 (25)	0.45
Cause of ESLD, *n* (%)			
Hepatitis B	0 (0)	1 (25)	0.17
Hepatitis C	10 (52.6)	1 (25)	0.59
Alcohol	6 (31.6)	0 (0)	0.54
Other	3 (15.8)	2 (50)	0.19
Comorbid conditions, *n* (%)			
Diabetes mellitus	4	1	1.00
Hypertension	6	2	0.59
Mean MELD Score (SD)	38.2 (3.2)	36.8 (4.3)	0.46

SD, standard deviation; ESLD, end-stage liver disease.

($P = 0.97$). The percent contribution of native renal function to overall renal function based on the MAG3 renogram was 21.9 ± 14.3% and 64.0 ± 17.7% for the Native-low and Native-high groups, respectively ($P < 0.001$). There was no significant difference in the median eGFR at the time of imaging between the two groups (Native-low 72 ml/min/1.73 m^2 vs. Native-high 65.5 ml/min/1.73 m^2; $P = 0.47$). The two groups demonstrated similar MELD scores at the time of CLKTx with values of 38.2 ± 3.2 and 36.8 ± 4.3 for the Native-low and Native-high cohorts, respectively ($P = 0.46$).

Table 3. Baseline and time of Type 1 HRS onset renal characteristics.

	Native-low (*n* = 19)	Native-high (*n* = 4)	*P* value
Baseline eGFR, ml/min/1.73^2			
Median (IQR)	48 (35–58)	52 (40–72)	0.50
Baseline eGFR, *n* (%)			
≥ 60 ml/min/1.73^2	3 (15.8)	1 (25%)	1.00
30–59 ml/min/1.73^2	16 (84.2)	3 (75%)	1.00
Duration of HRS, days			
Median (IQR)	25 (20–46)	36 (22–49)	0.72
Need for RRT, *n* (%)	14 (73.7)	2 (50)	0.56
Duration of RRT, days			
Median (IQR)	19 (13–25)	17 (10–33)	0.80
Urine Sodium at HRS onset, mEq/l			
Median (IQR)	10 (10–30)	8.5 (15–22.5)	0.42
Urine Protein: Creatinine ratio, g/g at HRS onset			
Median (IQR)	0.37 (0.17–0.65)	0.73 (0.29–1.16)	0.30

eGFR was calculated using the MDRD equation.
HRS, hepatorenal syndrome; eGFR, estimated glomerular filtration rate; IQR, interquartile range; RRT, renal replacement therapy; MDRD, modification of diet in renal disease.

Baseline renal characteristics, as well as need for RRT and duration of RRT, can be found in Table 3. There was no difference in the median baseline eGFR prior to the development of HRS (Native-low 48 ml/min/1.73 m^2 vs. Native-high 52 ml/min/1.73 m^2; $P = 0.50$). The median duration of HRS in days prior to CLKTx was 25 and 36 for the Native-low and Native-high groups, respectively ($P = 0.72$). There was also no difference between the groups with regard to the need for RRT (Native-low $n = 14$, 73.7% vs. Native-high $n = 2$, 50%; $P = 0.56$) or the median duration of RRT prior to CLKTx (Native-low 19 days vs. Native-high 17 days; $P = 0.80$).

Hospital events and characteristics were also similar between the two groups. There was no difference between the two groups in the incidence of sepsis pretransplantation (Native-low $n = 6$, 31.6% vs. Native-high $n = 2$, 50%; $P = 0.59$) or hypotension requiring pressor therapy (Native-low $n = 10$, 52.6% vs. Native-high, 1, 25%; $P = 0.59$). The onset of sepsis and need for pressor therapy occurred in all cases after the onset and diagnosis of Type 1 HRS. Two patients (10.5%) in the Native-low group received octerotide/midodrine as therapy for Type 1 HRS prior to CLKTx compared with 1 patient (25%) in the Native-high group ($P = 0.45$).

Univariate analysis was performed to determine the effect of several factors on native renal function. The factors in the analysis included: age, gender, race, baseline eGFR, diagnosis of diabetes, duration of HRS, need for RRT,

Table 4. Univariate analysis of pretransplant factors to predict high versus low native renal function following CLKTx.

	OR	95% CI	*P* value
Age (per 1 year)	1.02	0.88–1.20	0.84
Recipient gender (male)	1.75	0.15–20.23	0.65
Recipient race (Caucasian)	0.58	0.07–5.11	0.63
Baseline eGFR			
<60 vs. ≥60	1.78	0.07–20.90	0.66
<50 vs. ≥50	1.38	0.14–13.6	0.77
<40 vs. ≥40	1.38	0.14–31.3	0.80
Urine protein: creatinine ratio (≤0.5 g/g)	0.30	0.01–3.79	0.36
Urine sodium (per 1 mEq/l)	0.99	0.89–1.04	0.71
Diabetes mellitus	2.17	0.24–19.28	0.49
Duration of HRS (per 1 day)	1.00	0.94–1.03	0.84
Need for RRT	0.36	0.03–3.62	0.36
Duration of RRT (per 1 day)	0.99	0.92–1.06	0.74
Sepsis	2.17	0.24–19.28	0.49
Pressors	0.30	0.03–3.43	0.33
Octreotide/midodrine treatment	2.83	0.19–41.99	0.45

CLKTx, combined liver-kidney transplant; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; RRT, renal replacement therapy.

duration of RRT, sepsis, need for pressors, urine sodium concentration on admission, urine protein:creatinine ratio on admission, and use of octreotide/midodrine pre-CLKTx (Table 4). No factors analyzed were found to be significant in predicting high versus low native renal function following CLKTx.

Discussion

The proportion of patients undergoing liver transplantation with renal insufficiency has significantly increased since the implementation of the MELD scoring system for organ allocation in February of 2002. With the increased use of this form of dual-organ transplantation has come the heightened awareness for identifying those with the greatest benefit from CLKTx to minimize the ineffective use of the renal allograft in CLKTx [3]. Despite established guidelines recommending consideration for CLKTx in patients with chronic renal failure and a creatinine clearance <30 ml/min/1.73 m^2, as well as patients with acute kidney injury and the need for RRT >6 weeks [7], there still remains difficulty in defining the most appropriate candidates for CLKTx. The latter is especially true when the cause of renal disease remains controversial and/or potentially reversible such as Type 1 HRS.

Although the indications for CLKTx are yet to be firmly delineated, the benefit of CLKTx when used for the appropriate population is well described. Given the limits of organ availability, and the long waitlist times associated with transplantation, CLKTx is best performed when native renal recovery is not expected, thus allowing for justification dual-organ allocation to a single recipient, and the consequent leaving of an end-stage renal disease patient on dialysis [2,8]. Indeed, the increased postoperative mortality with LTA in ESLD patients with renal dysfunction is well established [4,9,10]. Combined allocation of a liver and kidney allows for improved survival in the ESLD population with renal insufficiency/failure. However, further studies investigating the degree of native renal recovery in the entire CLKTx population will allow for greater delineation of the population best suited to benefit from dual-organ transplant.

The HRS can be defined as the functional renal failure manifested in patients with advanced cirrhosis that remains potentially reversible, and can be further characterized by 2 types [6]. Type 1 HRS is characterized by the rapid and progressive decline in renal function with an associated median survival of only 2 weeks. In contrast, Type 2 HRS is characterized by a slower and less severe onset, with a median survival of approximately 6 months [11]. Patients with HRS were classically not included as candidates for combined transplantation because of the perceived reversibility of their renal dysfunction following liver transplantation. However, CLKTx has been shown to be of benefit to the ESLD patient with HRS who has a duration of renal replacement therapy >8 weeks [12]. The latter study is limited in that subclassification into Type 1 and Type 2 HRS was not performed, and neither was postoperative assessment of native renal function. In our current study we sought to assess the degree of native renal function in recipients of CLKTx for Type 1 HRS. Surprisingly, we demonstrate that despite all 23 of our patients remaining dialysis free at approximately three years post-transplant, only 4 of the 23 patients demonstrated a significant degree (>50%) of native renal function. Although we demonstrated a low contribution of native renal function in patients undergoing CLKTx for Type 1 HRS, we were unable to determine factors significant for predicting the degree of native renal function within this cohort. Furthermore, the exact etiology of clinical decompensation leading to HRS was unable to be ascertained in the current study given the potential for multiple etiologies leading to development of HRS.

Our study is limited by its retrospective nature and the overall small cohort size. Indeed, the small cohort size of HRS patients lends itself to the possibility of a type 2 error when interpreting the data. It is clear that larger scale assessments of CLKTx recipients with more diverse etiologies of renal failure, as well as in comparison to matched controls of LTA recipients with pretransplant renal dysfunction and nontransplanted waitlist candidates with dual-organ dysfunction, is warranted. Previous studies have focused on survival comparisons between CLKTx and LTA groups as a surrogate for justification of renal allograft

transplantation concomitant with liver transplantation, and thus without consideration of postoperative native renal function recovery. This initial study remains unique as it represents the largest study thus far assessing the degree of native renal function following CLKTx through the technique of MAG3 renal scan evaluation. Although our practice has been to classify native contribution to overall kidney function $\geq 50\%$ as evidence of recovery, previous reports have used the arbitrary cut-off of $\geq 40\%$ [5]. Even with the application of a cut-off of $\geq 40\%$, 74% of the 23 patients identified would not have had evidence of high contribution of native kidneys to overall renal function. It should be noted, as well, that although a standardized criteria was employed for interpretation of the MAG3 renal scans by a single radiological team, there may be a component of intraobserver or interobserver variability in the interpretation of results as this was not carried out in a blinded fashion.

Liver transplantation alone had been considered the treatment of choice for patients with cirrhosis and Type 1 HRS. Although some centers have reported HRS resolution post-transplant from 58% to 98% of patients [13,14], our study clearly demonstrates a distinct population of ESLD patients with Type 1 HRS who at approximately three years post-transplant fail to have significant native renal function. The ideal time for renal scanning post-transplant is yet to be determined, and requires further investigation and likely serial renal scans. By employing MAG3 renogram scanning in both the Native-high and Native-low groups on average over 3 years post-transplant from CLKTx, we minimize the risk of too early an assessment of postoperative renal function which can capture both a.) a transplanted renal allograft with delayed graft function or b.) native kidney function which has yet to fully recover. There remains the potential that an assessment of renal function too far removed from post-transplant may allow for recovered native renal function to progressively deteriorate, and thus increase the population perceived to have no evidence of renal recovery. However, we believe this population of patients still benefits from CLKTx, as they constitute what would traditionally manifest as delayed kidney failure in the LTA population, with an associated significant increase in risk of death post-transplant. Undoubtedly, further studies comparing patients with Type 1 HRS who undergo LTA versus CLKTx are needed to help further define the population of Type 1 HRS patients who would benefit from CLKTx.

It should be noted that upon examination of the entire cohort of Type 1 HRS patients who underwent CLKTx, there was a median duration of HRS of 29 days, and a need for RRT of approximately 3 weeks. Previous reports have documented a median survival time of 14 days for patients with Type 1 HRS [15]. Our study is similar to more recent data demonstrating improved success rate in the intensive management of this patient population to allow them to proceed to transplant [13,16].

In summary, we demonstrate that patients with Type 1 HRS can demonstrate low contribution of native renal function, and thus benefit from combined transplant of both liver and kidney allografts. Although this individual benefit comes at the cost of depriving organ allocation to the kidney transplant waitlist, there remains a demonstrated benefit for the CLKTx recipient as evidenced by the low rate of native renal function at 3 years post-transplant. Prospective randomized controlled trials in patients with concomitant liver and renal dysfunction comparing LTA versus CLKTx are not possible. However, to allow for optimization of dual-organ allocation strategies future studies analyzing a wide cohort of CLKTx recipients are needed. Specific attention to preoperative parameters and decision-making analysis, as well as postoperative native renal function contribution by MAG3 renograms may allow for refinement in allocation to yield the greatest benefit from dual-organ allocation.

Authorship

PAV: participated in the research design, writing of the manuscript, performance of the research, and data analysis; JJQ: participated in the research design and performance of the research; DMC, CMA: participated in the performance of the research; RH: participated in the performance of the research and the research design; FV: participated in the research design and the writing of the manuscript; DW: participated in the research design, writing of the manuscript, performance of the research, and data analysis.

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