Severe Hypernatremia in Deceased Liver Donors Does Not Impact Early Transplant Outcome

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Background. There may be an increased risk of primary nonfunction in livers procured from donors with hypernatremia. The purported mechanism for this effect is undefined. This study analyzes early graft function for donor livers procured from patients with severe hypernatremia.
Methods. The organ procurement records for 1013 consecutive deceased liver donors between 2001 and 2008 were reviewed. Both peak and terminal serum sodium levels were categorized as (1) severe for a level 170 mEq/L or higher, (2) moderate for 160 to 169 mEq/L, and (3) normal for less than 160 mEq/L. Outcomes included 30-day posttransplant alanine aminotransferase and total bilirubin, primary nonfunction, and 30-day and 1-year graft survival.
Results. Within the severe hypernatremia group, there were 142 (peak) and 50 (terminal) donors, whereas the moderate group had 233 (peak) and 162 (terminal) donors. The study groups did not differ in recipient age, model for end-stage liver disease score, steatosis, and ischemia times for the peak or terminal serum sodium groups. The differing levels of hypernatremia severity did not differ importantly, for peak or terminal serum sodium, in posttransplant alanine aminotransferase or total bilirubin, or the risk of intraoperative death and primary nonfunction. Thirty-day and 1-year graft survival did not demonstrate a negative impact from donor hypernatremia.
Conclusions. Posttransplant measures of early liver function and risk of failure, up to 1-year posttransplant, did not differ significantly based on peak or terminal donor serum sodium levels. These results suggest that donor serum sodium level likely has little clinical impact on posttransplant liver function.

Keywords: Orthotopic liver transplant, Extended criteria donor, Transplant outcomes, Hypernatremia, Graft survival.

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In an effort to offer liver transplantation to a greater number of persons in need, Indiana University has increased its use of extended criteria donor (ECD) livers during the past 8 years. Initial results from this expansion demonstrate a dramatic increase in liver transplant volume, with a concomitant decrease in recipient waitlist time and decrease in center waitlist volume without a change in graft or patient survival (*1*). As a result of this approach, our center accepts a large number of liver allografts that have been rejected by other centers. Based on the previous research, a commonly observed reason for deceased donor liver allograft nonuse is severe donor hypernatremia (*1*,*2*). Donor hypernatremia was first identified in the 1990s as a possible factor increasing the risk of primary nonfunction (*3*–*7*). These early studies were later supported by reports of increased graft loss for hypernatremic donors at two centers, including a review of 59 patients at the University of California, Los Angeles (UCLA) with peak serum sodium of 170 mEq/L or higher and 120 patients in Austria with peak serum sodium greater than 155 mEq/L (*8*, *9*). However, three recent studies have found no association between donor serum sodium and transplant outcome (*1*, *10*, *11*). This includes a study at Indiana University of 72 patients between 2001 and 2005 with a peak serum sodium level of 170 mEq/L or higher with no difference in graft survival.

It has been suggested that donor hypernatremia results in cell swelling, resulting in exacerbation of reperfusion-mediated injury. One report from Pittsburgh and another from UCLA suggest that acute treatment of hypernatremia near the time of organ procurement ameliorates the negative effect of donor hypernatremia on initial liver allograft function (*7*, *12*). Between 2001 and 2008, our center used liver allografts from 375 deceased donors with peak serum sodium of 160 mEq/mL or higher (37% of all transplants) and 213 donors with terminal serum sodium of 160 mEq/mL or higher (21%). This article reports perioperative outcomes for these allografts, including early graft function, and graft survival up to 1-year posttransplant.

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MATERIALS AND METHODS

The medical records for all adult, deceased donor orthotopic liver transplants performed between July 1, 2001, and December 31, 2008, were reviewed (n=1013). Extracted data came from the comprehensive transplant recipient registry at our center, individual written and electronic medical records, and the original donor medical history. Donor sodium levels were recorded from the original on-site donor intensive care unit flow sheet as provided by the organ procurement organization. Peak serum sodium level was the highest value recorded at any time after admission, whereas the terminal serum sodium level was the last recorded value before procurement. No effort was made by our center to influence the management of serum sodium levels although levels were corrected per routine protocol by the physician providing care for the patient. Median donor hospital stay was 2 days and did not differ among the study groups. Recipient inclusion criteria for this analysis included all transplant recipients 18 years and older receiving a deceased donor liver transplant during the study period. Graft function and survival data were collected from the transplant database. For patients receiving retransplantation within 30 days of the original transplant, the analysis included only data for the first transplant.

All recipients were listed for transplantation according to standard procedures and protocols as established by the United Network for Organ Sharing. Mean model for end-stage liver disease (MELD) score at transplant was 18 (range 6–48). Donor livers were recovered using standard procurement techniques including aortic and portal vein flushing and cold storage as described previously (*13*). Our primary preservation solution is histidine-tryptophan-ketoglutarate (HTK) solution, but many of our import livers are preserved in University of Wisconsin solution, and our use of HTK started in May, 2003 (*14*). The piggyback hepatectomy approach was used in 95% of the transplants and has been described previously (*15*). Posttransplant immunosuppression included induction with rabbit antithymocyte globulin (total dose 6 mg/kg) with a rapid steroid taper of three doses of solumedrol (500, 250, and 120 mg) and maintenance with tacrolimus monotherapy (*16*). Approximately one half of the recipients received a single dose of rituximab on postoperative day 3 as part of the induction protocol.

Primary transplant outcomes included early graft function and survival up to 1-year posttransplant. Perioperative graft function was assessed by daily measurement of liver function enzymes in the immediate posttransplant period, followed by twice weekly laboratory values for outpatients up to 30 days posttransplant. All occurrences of graft loss were included in the final analysis regardless of cause, comorbidities, or timing. Patient death for any reason was recorded as a graft loss. Specifically, there were no exclusions for perioperative mortality or graft loss or for nonliver-related deaths. We have previously reported no difference in survival for import and local donor livers at our center (*2*). A portion of the data from this article was published previously in a review of our ECD experience (*1*). Although many perioperative deaths are technical in nature, the possibility of the hypernatremic liver contributing to an early demise necessitates the inclusion of all recipients. Recipients were compared by level of hypernatremia (normal [<160 mEq/L], moderate [160–169 mEq/L], and severe [>170 mEq/L or higher]) using chi-square testing for graft loss. Serum alanine aminotransferase (ALT) and serum total bilirubin (TB) levels were assessed using one-way analysis of variance. Statistical testing was performed on SPSS software (SPSS version 17.0 for Windows, SPSS Inc., 2009, Chicago, IL). Retrospective use of data from the transplant center database was reviewed and approved by the institutional review board of the Indiana University School of Medicine.

TABLE 1. Baseline demographic data for liver transplant donors and recipients stratified by donor peak serum sodium (total n=1013)

	Donor peak serum sodium level (mEq/L)				Donor terminal serum sodium level (mEq/L)			
	<160	160–169	≥170 and higher	P[a]	<160	160–169	≥170	P[a]
Total overall	646 (64%)	230 (23%)	137 (13%)		803 (79%)	162 (16%)	48 (5%)	
Recipient gender, male (%)	67	66	69	0.84	66	74	77	0.08
Recipient age (yr), median (range)	52 (18–76)	54 (18–74)	53 (24–72)	0.23	52 (18–76)	54 (20–72)	52 (27–70)	0.11
Recipient BMI (kg/m^2), median	27.8	28.2	28.1	0.65	28	27.9	26.3	0.63
Recipient diagnosis (%)								
Hepatitis C	46	45	54	0.74	46	48	42	0.83
Hepatocellular carcinoma	22	21	22	0.98	22	19	24	0.76
Recipient MELD at transplant, median (range)	16 (6–45)	17 (7–44)	16 (7–48)	0.56	16 (6–45)	16 (7–42)	17 (8–48)	0.44
Donor gender, male (%)	59	55	47	0.04	60	48	51	0.02
Donor age (yr), median (range)	42 (5–81)	42 (6–79)	38 (6–68)	0.17	41 (5–81)	43 (6–79)	34 (7–68)	0.23
Donor cause of death (%)								
Stroke	41	44	39	0.64	41	45	35	0.72
Trauma	38	36	35		39	35	39	
Other	21	20	26		20	20	26	
Donor liver steatosis								
Steatosis >20%	3%	2%	2%	0.12	3%	2%	0%	0.66
Preservation with HTK (%)	61	71	65	0.02	60	72	77	<0.01
Total cold ischemia time (hr), median (range)	7 (3–17)	6 (3–18)	7 (3–20)	0.51	7 (3–18)	6 (3–20)	6 (3–9)	0.01
Total warm ischemia time (min), median (range)	30 (9–142)	28 (8–106)	30 (14–203)	0.07	30 (8–142)	29 (13–203)	30 (14–106)	0.92

[a] *P* value calculated using χ^2 test for categorical variables and one-way analysis of variance for continuous variables.
BMI, body mass index; MELD, model for end-stage liver disease; HTK, histidine-tryptophan-ketoglutarate.

RESULTS

Of the 1013 deceased donor liver transplants between 2001 and 2008, there were 375 (37%) recipients who received a liver allograft from a deceased donor with a peak serum sodium level of 160 mEq/L or higher. Preservation solution for these livers included 64% HTK and 36% University of Wisconsin solution. There use of HTK was greater in the hypernatremic livers when compared with the nonhypernatremic livers. The median cold ischemia time was 7 hr, and the median warm ischemia time was 30 min. There were 213 (21%) liver allografts from donors with terminal sodium level of 160 mEq/L or higher (Table 1). Comparison of recipient demographic data stratified by severity of donor hypernatremia demonstrated no important differences in recipient age, gender, body mass index, diagnosis of hepatitis C or hepatocellular carcinoma, or MELD among the three study groups. Similarly, there were no important differences by level of hypernatremia for donor age, gender, cause of death, or level of hepatic steatosis. The three groups also did not differ significantly in total cold or warm ischemia time. Follow-up time ranged from 12 months to 8 years (median 50 months).

Liver transplant outcomes are listed in Table 2. The study groups did not differ significantly for the risk of intraoperative death, primary nonfunction, or in graft survival at 30 days and 1-year posttransplant. These findings were consistent for both peak and terminal donor serum sodium levels. Figures 1 and 2 display the 1-year Cox proportional hazards survival based on the peak and terminal levels of donor hypernatremia. Statistical modeling for these graphs demonstrate no significant difference in graft survival based on peak or terminal donor serum sodium levels when controlling for recipient and donor age and recipient MELD score. To evaluate the impact of change in donor serum sodium levels, the difference between the peak and terminal levels were calculated, and this value was included as a covariate in the regression model. The change in serum sodium carried a *P* value of 0.98 and was, therefore, removed from the final model as a nonsignificant factor. Previous studies have

TABLE 2. Liver transplant outcomes stratified by peak and terminal donor serum sodium levels in 1013 consecutive adult, deceased donor liver transplants

	N (%)	Intraoperative death (%)	*P*	Graft failure within 7 d (%)	*P*	Graft failure within 30 d (%)	*P*	Graft failure within 1 yr (%)	*P*
Donor peak serum sodium (mEq/L)									
<160	646 (64)	1	0.87	4	0.75	7	0.87	17	0.15
160–169	230 (23)	1		3		6		13	
≥170	137 (13)	2		3		7		12	
Donor terminal serum sodium (mEq/L)									
<160	803 (79)	1	0.71	4	0.21	7	0.32	17	0.05
160–169	162 (16)	1		2		4		12	
≥170	48 (5)	0		0		5		5	

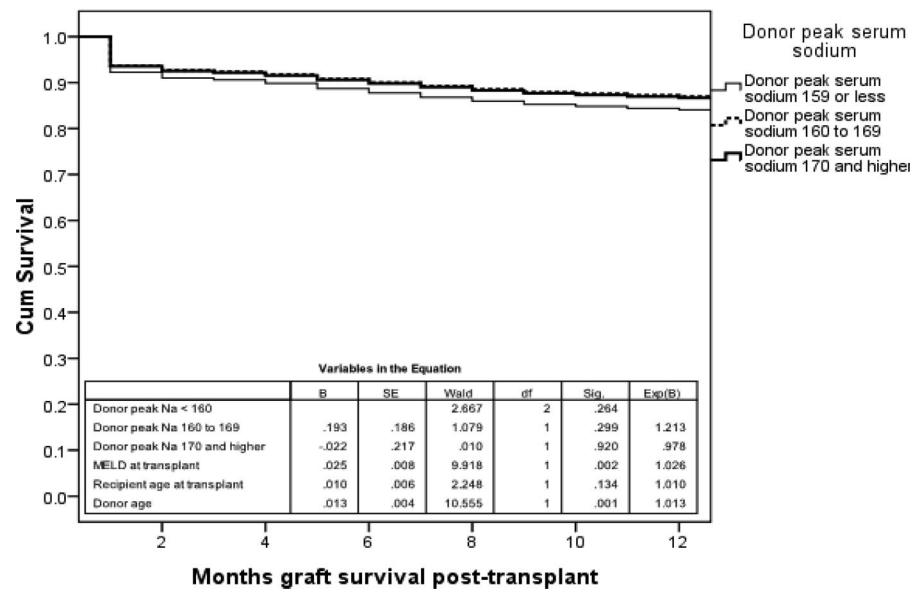

FIGURE 1. Cox proportional hazards graft survival stratified by donor peak serum sodium level (n=1013). MELD, ●●●.

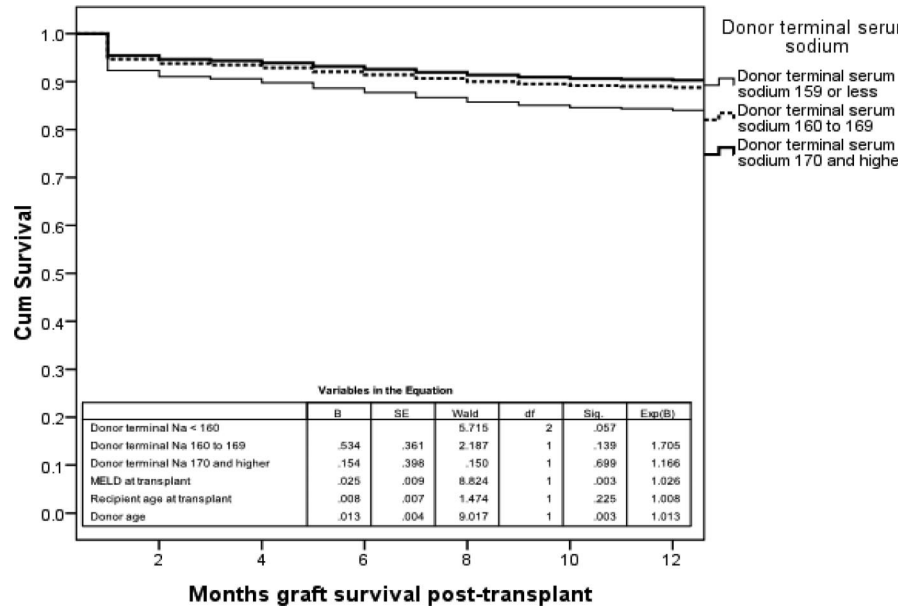

FIGURE 2. Cox proportional hazards graft survival stratified by donor terminal serum sodium level (n= 1013). MELD, ●●●.

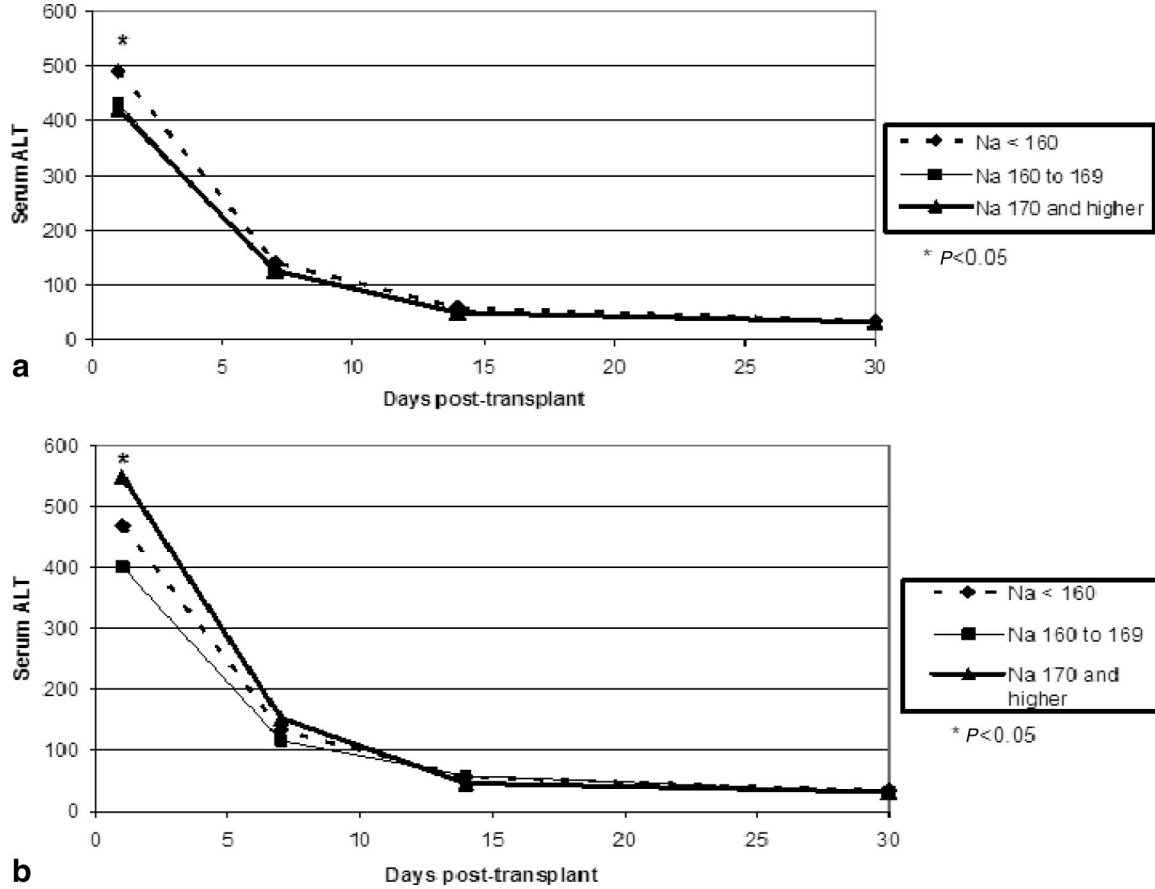

FIGURE 3. Thirty-day posttransplant median serum alanine aminotransferase (ALT) by peak (a) and terminal (b) donor serum sodium level for 1013 consecutive deceased donor liver transplants.

used an upper threshold of 155 mEq/L for normal donor serum sodium level. These two regression analyses were recalculated using the alternative 155 mEq/L threshold for normal and moderate hypernatremia, and there were no meaningful differences in the outcomes. Posttransplant serum ALT levels are displayed graphically in Figure 3 (a and b). For peak and terminal serum sodium levels, the ALT levels differ significantly on posttransplant day 1, but then they are

similar by day 7 and thereafter. TB levels are highest for the low donor serum sodium level and remain higher throughout the first 30 days, although the group difference does not reach statistical significance (data not shown).

Of the 375 allografts from all donors with peak serum sodium level of 160 mEq/L or higher, 24 were lost within 30 days of transplant (6%; Table 3). This compares with a 7% graft loss rate for the remaining cohort of donor livers with both peak and terminal serum sodium levels less than 160 mEq/L. The causes of recipient graft loss are listed individually, and these do not demonstrate a pattern of graft failure different from the entire population.

DISCUSSION

The clinical effect of donor hypernatremia on the transplant liver allograft is unclear. Although retrospective data from the 1990s suggested an increased risk of graft loss for liver allografts procured from donors with hypernatremia, the studies were weak both in size and methodology. Essentially, these studies were database reviews that incidentally found hypernatremia to be a factor associated with graft loss. Totsuka et al. (*7*) (University of Pittsburgh) provided the first systematic review of donor hypernatremia, with an attempt to distinguish transplant outcomes based on terminal (corrected) donor serum sodium level (final donor serum sodium level at procurement). This study suggested an increased risk of liver graft loss for donors in whom the serum sodium had not been corrected to less than 155 mEq/L. Two recent studies have found that donor serum sodium does not have an effect on clinical outcomes. Tector et al. (*1*) found no increased risk of graft loss in 72 donor livers with peak serum sodium level 170 mEq/L or higher. Cywinski et al. (*17*) found no difference in early graft function, length of intensive care unit stay, length of hospital stay, and early patient survival in 51

TABLE 3. Graft loss within 30 d of transplant for donor livers with peak or terminal serum sodium level ≥160 mEq/L

Patient No.	Peak ≥160	Terminal ≥160	Recipient age (yr)	Graft survival (d)	Cause of graft loss
1	×	×	71	0	Intraoperative death; hyperacute rejection, history of kidney transplant
2	×	×	64	0	Intraoperative death; cardiac, history of myocardial infarction; normal graft appearance
3	×	×	61	0	Intraoperative death; arrest, cause unclear
4	×		56	0	Intraoperative death; arrest, cause unclear
5	×		49	0	Intraoperative death; arrest, cause unclear
6	×		45	1	Death; portal vein thrombosis leading to liver failure
7	×	×	44	2	Death; primary nonfunction; steatotic donor liver
8	×	×	69	2	Death; massive perioperative hemorrhage; normal graft function
9	×		41	5	Death; sepsis, normal graft function
10	×		66	7	Death; cardiac dysrrhythmia with sudden death; normal graft function
11	×		51	8	Death; portal vein thrombosis leading to liver failure
12	×		59	9	Death; massive intraoperative hemorrhage and necrotizing pancreatitis
13	×	×	56	12	Death; postoperative stroke, normal graft function
14	×		55	12	Death; cardiac dysrrhythmia with sudden death; normal graft function
15	×		41	13	Graft loss; hepatic artery thrombosis, retransplant; alive and well
16	×	×	50	14	Death; cardiac dysrrhythmia with sudden death; normal graft function
17	×		48	14	Death; vascular thrombosis and hepatic necrosis
18	×		54	14	Death; sepsis, ICU-acquired infection
19	×	×	60	19	Graft loss; hepatic artery thrombosis, retransplant; alive and well
20	×	×	58	21	Death; bile duct necrosis and sepsis
21	×		48	22	Death; hepatic artery thrombosis, died at the end of retransplant from cardiac dysrrhythmia
22	×		59	27	Death; sepsis related to ischemic necrosis of the colon
23		×	62	29	Death; recurrent hepatic artery thrombosis, multisystem organ failure
24	×	×	61	30	Death; sepsis related to biliary leak

ICU, intensive care unit.

patients with terminal serum sodium 155 mEq/L or higher. Unfortunately, all these studies are inadequately powered to demonstrate clinically important differences in outcomes. In addition, no published study has ever evaluated a dose or response effect in which an increasing donor sodium level is compared with transplant outcomes. No large scale national database studies have addressed this issue because donor serum sodium levels are not routinely reported for data entry. Finally, there have been no prospective, randomized studies in which treated and nontreated donors are assigned to recipients.

Totsuka et al. suggested that allograft injury related to donor hypernatremia occurs at the time of procurement, during cold storage, or at reperfusion, because donor hypernatremia does not affect measured liver enzymes before the procurement procedure. These authors state that it is likely an increased intracellular osmolality that causes hepatocyte death and graft dysfunction in the presence of uncorrected donor hypernatremia (*7*). Busuttil and Tanaka (*12*) (UCLA) agree with this suggestion as they hypothesize that cell swelling occurs in relation to the donor hypernatremia, and this swelling exacerbates reperfusion injury. Gonzalez et al. suggest that a sudden change in extracellular osmolality in a liver graft obtained from a hypernatremic donor could cause intracellular water accumulation and cell swelling. This difference in intracellular and extracellular osmolality then exacerbates reperfusion injury (*4*). Results from the present analysis do not support the occurrence of clinically important hepatocyte injury related to donor hypernatremia. Initial posttransplant liver enzymes did not worsen for the hypernatremic groups, and there is no suggestion of an increasing ALT or TB with increasing levels of hypernatremia, which would be expected in the presence of a dose response effect. The posttransplant serum aspartate aminotransferase levels are not shown but were similar to those for serum ALT.

We completed a detailed review of all graft losses within 30 days of transplant for recipients of liver allografts from donors with severe hypernatremia. There were five patients who experienced intraoperative arrest, one related to hyperacute rejection, one cardiac in nature, and three unexplained. Two of the three unexplained arrests occurred in allografts from donors with peak serum sodium greater than 160 mEq/L but a terminal serum sodium less than 160 mEq/L, whereas one occurred with an allograft from a donor with peak sodium 169 mEq/L and terminal sodium of 162 mEq/L. These results did not differ significantly from the entire population as evidenced by the comparison of early graft loss in Table 2.

One possible explanation for the disparity in published outcomes is related to the length of time for which the liver is exposed to the hypernatremia and cell swelling. As transplant systems have become more efficient, donor organs can be procured, transported, and transplanted in a more timely fashion when compared with a decade ago. At our center, the organ procurement procedure rarely lasts more than 2 hr, followed by rapid transport and transplantation with a median cold ischemia time of 7 hr and warm ischemia time frequently less than 30 min. As with all ECD allografts, efficient procurement, transport, and transplantation of the organ, with minimization of cold ischemia time, are critical to its successful use. A large proportion of donor liver allografts transplanted at our center are imported regionally or nationally. We have previously demonstrated no difference in clinical outcomes as a result of the geographic origin of the donor liver (*18*). Results from our study suggest that deceased donor liver allografts exposed to severe peak and terminal hypernatremia before procurement can be transplanted routinely without negative sequelae related to the hypernatremia.

REFERENCES

1. Tector AJ, Mangus RS, Chestovich P, et al. Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. *Ann Surg* 2006; 244: 439.
2. Mangus RS, Fridell JA, Vianna RM, et al. No difference in clinical transplant outcomes for local and imported liver allografts. *Liver Transpl* 2009; 15: 640.
3. Avolio AW, Agnes S, Magalini SC, et al. Importance of donor blood chemistry data (AST, serum sodium) in predicting liver transplant outcome. *Transplant Proc* 1991; 23: 2451.
4. Gonzalez FX, Rimola A, Grande L, et al. Predictive factors of early postoperative graft function in human liver transplantation. *Hepatology* 1994; 20: 565.
5. Figueras J, Busquets J, Grande L, et al. The deleterious effect of donor high plasma sodium and extended preservation in liver transplantation. A multivariate analysis. *Transplantation* 1996; 61: 410.
6. Briceno J, Lopez-Cillero P, Rufian S, et al. Impact of marginal quality donors on the outcome of liver transplantation. *Transplant Proc* 1997; 29: 477.
7. Totsuka E, Dodson F, Urakami A, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: Effect of correction of donor hypernatremia. *Liver Transpl Surg* 1999; 5: 421.
8. Markmann JF, Markmann JW, Markmann DA, et al. Preoperative factors associated with outcome and their impact on resource use in 1148 consecutive primary liver transplants. *Transplantation* 2001; 72: 1113.
9. Pokorny H, Langer F, Herkner H, et al. Influence of cumulative number of marginal donor criteria on primary organ dysfunction in liver recipients. *Clin Transplant* 2005; 19: 532.
10. Tekin K, Imber CJ, Atli M, et al. A simple scoring system to evaluate the effects of cold ischemia on marginal liver donors. *Transplantation* 2004; 77: 411.
11. Renz JF, Kin C, Kinkhabwala M, et al. Utilization of extended donor criteria liver allografts maximizes donor use and patient access to liver transplantation. *Ann Surg* 2005; 242: 556.
12. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transpl* 2003; 9: 651.
13. Mangus RS, Tector AJ, Agarwal A, et al. Comparison of histidine-tryptophan-ketoglutarate solution (HTK) and University of Wisconsin solution (UW) in adult liver transplantation [see comment]. *Liver Transpl* 2006; 12: 226.
14. Mangus R, Fridell, JA, Vianna RM, et al. Comparison of histidine-tryptophan-ketoglutarate solution and University of Wisconsin solution in extended criteria liver donors. *Liver Transpl* 2008; 14: 365.
15. Mangus RS, Fridell JA, Vianna RM, et al. Use of the piggyback hepatectomy technique in liver transplant recipients with hepatocellular carcinoma. *Transplantation* 2008; 85: 1496.
16. Tector AJ, Fridell JA, Mangus RS, et al. Promising early results with immunosuppression using rabbit anti-thymocyte globulin and steroids with delayed introduction of tacrolimus in adult liver transplant recipients. *Liver Transpl* 2004; 10: 404.
17. Cywinski JB, Mascha E, Miller C, et al. Association between donor-recipient serum sodium differences and orthotopic liver transplant graft function. *Liver Transpl* 2008; 14: 59.
18. Mangus RS, Fridell JA, Vianna RM, et al. No difference in clinical transplant outcomes for local and imported liver allografts. *Liver Transpl* 2009; 15: 640.