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Prognostic Impact of Peritransplant Serum Sodium Concentrations in Liver Transplantation

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Background: Serum sodium (Na) is considered to reflect the severity of liver cirrhosis. In the last few years, much effort has been made to integrate this association into prognostic models after liver transplantation. The aim of this study was to investigate the associations between peritransplant Na and neurological complications, as well as short-term survival, after liver transplantation.


Material/Methods: A total of 306 liver transplantations between 2012 and 2015 were evaluated. Pre- and posttransplant sodium concentrations were investigated with regard to 3-month survival and incidence of posttransplant neurological complications, along with other factors present in the operative side of the recipient and donor.

Results: The 3-month survival rate was 94%. Neither hyponatremia (<130 mEq/L) nor hypernatremia (>145 mEq/L) at pretransplantation predicted 3-month survival. A large amount of intraoperative blood transfusion and a large delta Na showed a significant association with poor outcomes at 3 months. On multivariate analysis, the requirement of blood transfusion and warm ischemia time remained independent prognostic factors for 3-month mortality. Hyponatremia and a large delta Na tended to lead to the frequent development of neurological complications. These complications, secondary to rapid Na correction, were concerning and potentially led to a prolonged hospital stay and early mortality.

Conclusions: Rapid change in the sodium level might be caused by large amounts of blood transfusion products. This leads to a diminished short-term survival, as well as a higher rate of neurological complications.

MeSH Keywords: Hyponatremia • Liver Cirrhosis • Liver Transplantation

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Background

Incidence rates of neurologic complications after liver transplantation (LT) are reported to be between 13% and 47% [1]. There are various etiologies of posttransplant encephalopathy, including calcineurin inhibitor (CNI) toxicity, infections, electrolyte disorders, and cirrhosis type. Hyponatremia is common in cirrhosis patients [2]. The severity of hyponatremia is related to the severity of cirrhosis [2]. It is well known that rapid correction of hyponatremia can lead to severe neurological consequences, ranging from subclinical confusion to severe seizure, osmotic demyelination syndrome (ODM), and death.

For the last decade, a significant association between pretransplant hyponatremia and outcomes after liver transplantation has been emphasized. It was reported that hyponatremia at LT was associated with higher waitlist mortality [3,4]. While the prognostic impact of pretransplant hyponatremia in LT patients is confirmed in many reports [5], it remains to be elucidated if poor outcomes in patients with hyponatremia would be just sequel to severe cirrhosis or associated with complications secondary to rapid changes in peritransplant serum sodium levels. Liver transplant surgery often requires large amount of blood transfusion, fluid resuscitation, and albumin infusion, which potentially lead to rapid changes in the levels of electrolytes, especially serum sodium. We hypothesized that rapid changes (increases) in serum sodium levels would more likely happen in patients with low sodium levels and that these changes could lead to posttransplant neurological complications, a prolonged hospital stay, and eventually, a poor posttransplant outcome. While the association between poor posttransplant outcomes and low serum sodium has been investigated and confirmed in many reports, there were few reports specifically assessing the impact of peritransplant changes in serum sodium levels on short-term outcomes after LT. The aim of this study was to investigate the effect of pretransplant hyponatremia on LT outcomes, focusing especially on the changes in peritransplant serum sodium levels, in terms of neurological complications and early posttransplant mortality.

Material and Methods

Patient selection

A retrospective single-center review of the electronic medical records of all patients who received a liver transplant from 2012-2015 at the University Hospital IUPUI Indianapolis was performed. A total of 306 liver transplant recipients were enrolled in this study. Multivisceral transplant patients who received a liver graft with an intestinal and/or pancreatic graft were excluded. Combined liver and kidney transplant patients

were included. The whole retrospective analysis of all liver transplants was approved by the Institutional Review Board at the Indiana University School of Medicine (protocol no. 1011003619R006).

Intraoperative management

We utilized the piggy-back technique with preservation of the vena cava without usage of a V-V bypass and vena cava clamping in more than 90% of the patients [6]. During surgery, we tried to maintain a central venous pressure of less than 10 mmHg throughout the whole procedure. During surgery, we also tried to not exceed the recommended limit for increasing the serum sodium, which was 0.5–1.0 mEq/L/h.

Aminocaproic acid (Amicar) infusion was used, which can subsequently reduce blood transfusion usage [7]. After surgery, these patients were routinely sent to the transplant intensive care unit (ICU).

Posttransplant management

Our immunosuppression protocol was described elsewhere [8]. Briefly, it consists of 3 equal doses of rabbit antithymocyte globulin (RATG) given on postoperative days (POD) 2, 4, and 6 (total dose=6 mg/kg). Tacrolimus was used as a primary immunosuppressive agent with goal level of 7–10 ng/mL in the first 3 months and 6–8 ng/mL thereafter. All patients received fluconazole and valganciclovir as prophylaxis. In the immediate postoperative days, CVP was kept as low as possible with maintaining adequate urine output. Evaluation of neurological complications was done by ICU staff and neurologists. Radiological exams such as CT and MRI head were done upon neurologist request. The severity of hepatic encephalopathy (HE) was graded with West Haven Criteria. All neurological complications were divided into minor (tremor, headache, sleep disorder) and major (ODM, grade III and IV of West Haven Criteria, seizure). Preadmission HE was also evaluated. We defined it as any altered mental status in the last 6 months prior to LT.

Analysis of outcomes

The pre- and post-LT variables included in this analysis were data on recipient characteristics, including sex, age, primary cause of cirrhosis, MELD score prior LT, and pretransplantation encephalopathy (yes/no), as well as data on operative factors such as type and quantity of fluids, packed red blood cells (PRBCs), fresh frozen plasma (FFP), and albumin usage. Posttransplant factors included the serum sodium level immediately after LT surgery and tacrolimus/cyclosporine A levels. These factors were analyzed as possible risk factors for neurologic complications, graft loss, and patient death. We defined severe hyponatremia as a pre-LT sodium level <130 mEq/L and

mild hyponatremia as a pre-LT sodium level of 130–134 mEq/L). The difference between pre- and posttransplant serum sodium concentrations was defined as delta sodium. Delta Na was considered to be indicative of increased risk for developing neurological complications and possible CPM [9,10]. Thus, patients were categorized according to delta sodium (>+10 mEq/L; +5 to +10 mEq/L; –5 to +5 mEq/L; <–5 mEq/L), and the association between delta Na and posttransplant outcomes was evaluated. We also evaluated the intubation period, as well as the ICU stay and total hospital stay durations, for impact on the peritransplant serum sodium level and changes in this level.

Statistical analysis

These data were summarized using the median and range for continuous variables and using the percentage for discrete variables. Association of the variables with an altered mental status was analyzed using a logistic regression model. We used the Kaplan-Meier method to estimate the patient and graft survival rates. The log-rank test was used to analyze differences in the curves. All independent variables with a *p* value less than 0.01 were included in the multivariate model, and clinically relevant factors likely affecting the endpoints were also included in the multivariate analysis. EZR version 1.22 (Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria), was used for the statistical analysis, and the level of significance was set at 0.05.

Results

A total of 306 patients were evaluated. All patients received deceased donor liver transplant, of whom 12 patients were transplanted by using a liver graft from a donation after cardiac death (DCD) donor. Of these 306 patients, 10 patients underwent retransplant. The median age at the time of transplantation was 57.7 years (interquartile range [IQR]: 51.2–62.6 years). The median model for end-stage liver disease (MELD) score was 22 (IQR: 18–23). Twenty-six patients received combined liver and kidney transplantation.

Short-term survival

Of these 306 patients, the 3-month patient survival rate was 94.2%. Possible risk factors for 3-month mortality were investigated, focusing on peritransplant serum sodium levels. While neither pretransplant hyponatremia (<130 mEq/L) nor hypernatremia (>145 mEq/L) predicted 3-month survival (*p*=0.93 and 0.99, respectively), a large amount of intraoperative PRBCs (*p*<0.001, hazard ratio [HR]=1.07) and large delta Na (>10 mEq/L) (*p*=0.045, HR=3.74) showed a significant association with poor outcomes at 3 months. Figure 1 shows the patient survival curves according to delta Na up to 3 months.

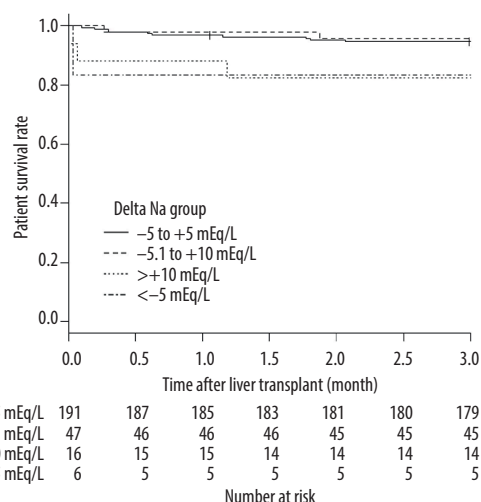


Figure 1. Short term survival after LT in according to Delta Sodium.

On multivariate analysis, delta Na more than 10 mEq/L did not remain as an independent predictive factor for 3-month mortality, whereas intraoperative estimated blood loss (EBL) (*p*=0.04, HR=1.02 per 100 mL) and warm ischemia time more than 25 min (*p*=0.02, HR=5.13) were considered to be independent risk factors for 3-month mortality (Table 1).

Delta Na and intraoperative management

The association between delta Na and intraoperative blood transfusion requirement was assessed. Eighteen patients (7%) showed a delta Na of more than 10 mEq/L, which was considered to be a large delta Na. The requirements for the PRBCs and FFP were significantly larger in patients who showed a large delta Na than in those with a delta Na of less than 10 mEq/L. This can be explained by the higher sodium concentration in these fluids. For instance, the sodium concentration in packed RBCs is 150 mmol/L, that in FFP is 170 mmol/L, that in 5% albumin is 150 mmol/L, and that in plasmalyte is 140 mmol/L. In all patients with a pretransplant serum sodium <130 mmol/L, the main OR for fluid was D5% half of normal saline. In all other cases, the main intravenous fluid was half normal or normal saline. The median requirements for PRBCs and FFP were 9.4, 4.4, and 2.4 units (*p*<0.001) and 5.5, 2.2, and 0.9 units (*p*<0.001) in patients with a large delta Na (>10 mEq/L), those with a moderate delta Na (+5.1 to +10 mEq/L), and those in the control group (–5 to +5 mEq/L), respectively. Possible risk factors for a large delta Na were evaluated. Intraoperative EBL (*p*=0.01, odds ratio [OR]=1.02 per 100 mL blood loss), intraoperative transfusion; FFP (*p*<0.001, OR=1.16 per unit), PRBCs (*p*<0.001, OR=1.09 per unit), platelets (*p*=0.03, OR=2.07 per unit); operative time (*p*<0.001, OR=2.63 per hour), low pretransplant sodium level

Table 1. Risk factor for 3-month mortality.

Variables	Univariate		Multivariate	
	p*	HR (95%CI)	p*	HR (95%CI)
Recipient age (per year)	0.29	0.98 (0.95–1.01)		
Female recipient	0.09	3.41 (0.82–14.3)		
Hepatitis C				
MELD score	0.16	1.05 (0.98–1.13)		
MELD-Na score	0.22	1.05 (0.97–1.13)		
Donor age (per year)	0.23	1.02 (0.99–1.06)		
DCD	1.0	N/A		
Combined kidney transplant	0.71	0.68 (0.09–5.18)		
Pre-transplant serum sodium				
130–145 mEq/L (Ref.)				
<130 mEq/L	0.93	0.93 (0.21–4.11)		
>145 mEq/L	0.99	N/A		
Delta Na				
–5 to +5 mEq/L (Ref.)				
+5 to +10 mEq/L	0.78	0.81 (0.18–3.68)		
>+10 mEq/L	0.045	3.74 (1.03–13.6)	0.49	0.29 (0.01–9.71)
<–5 mEq/L	0.22	3.64 (0.47–28.5)		
Intraoperative EBL (per 100 mL)	<0.001	1.02 (1.01–1.03)	0.04	1.02 (1.0–1.04)
Intraoperative transfusion (per unit)				
PRBC	<0.001	1.07 (1.04–1.11)		
FFP	<0.001	1.12 (1.06–1.16)		
Platelet	0.001	1.81 (1.26–2.59)		
Cold ischemia time				
6 hours or less (Ref.)				
6–8 hours	0.13	2.34 (0.78–6.98)		
>8 hours	0.76	1.29 (0.25–6.63)		
Warm ischemia time				
25 min or less (Ref.)				
>25 min	0.007	4.29 (1.49–12.4)	0.02	5.13 (1.33–19.8)
Operative time (per hour)	<0.001	1.92 (1.32–2.79)	0.79	0.9 (0.42–1.93)

* Cox proportional hazard regression model. MELD – model for End-Stage Liver Disease score; DCD – donation after cardiac death donor; EBL – estimated blood loss; PRBC – packed red blood cell; FFP – fresh frozen plasma; HR – hazard ratio; CI – confidence interval.

of less than 130 mEq/L ($p < 0.001$, OR=12.5), MELD-Na score ($p < 0.001$, OR=1.14), and combined kidney transplant ($p = 0.04$, OR=3.63) were associated with a large delta Na (> 10 mEq/L). Operative time ($p = 0.004$, OR=2.85 per hour) and a pretransplant sodium level less than 130 mEq/L ($p < 0.001$, OR=29.6) remained independent risk factors (Table 2). Intraoperative blood transfusion was not regarded as an independent predictive factor for a large delta Na. The MELD-Na score was not included in the multivariate model considering its potentially

significant interaction with the pretransplant serum sodium level, which was included in the model.

Posttransplant course and neurological complications

In 22 (7%) patients, dialysis was started for acute kidney injury. All dialysis treatments were initiated after 48 h from OLT, so that it did not impact the delta sodium calculation. None of the patients received preoperative dialysis as a way to control pretransplant hyponatremia. Posttransplant neurological

Table 2. Association with large Delta Na (more than +10 mEq/L).

Variables	Univariate		Multivariate	
	p*	HR (95%CI)	p*	HR (95%CI)
Pre-transplant serum sodium 130–145 mEq/L (Ref.) <130 mEq/L	<0.001	12.5 (4.37–35.6)	<0.001	29.6 (6.69–131.0)
MELD score	0.06	1.07 (1.0–1.15)		
MELD-Na score	<0.001	1.14 (1.06–1.23)		
Intraoperative EBL (per 100 mL)	0.01	1.02 (1.01–1.04)		
Intraoperative transfusion (per unit)				
PRBC	<0.001	1.09 (1.04–1.13)	0.78	1.02 (0.91–1.13)
FFP	<0.001	1.16 (1.07–1.25)	0.49	1.06 (0.9–1.25)
Platelet	0.03	2.07 (1.08–3.99)		
Intraoperative albumin infusion (per 100 mL)	0.06	1.04 (1.0–1.09)		
Operative time (per hour)	<0.001	2.63 (1.7–4.08)	0.004	2.85 (1.4–5.8)
Warm ischemia time 25 min or less (Ref.) >25 min	0.03	1.98 (0.53–7.36)		
Cold ischemia time <6 hours (Ref.) 6–8 hours >8 hours	0.07 0.09	3.05 (0.91–10.2) 3.41 (0.81–14.3)		
Combined kidney transplant	0.04	3.63 (1.08–12.2)		
Intraoperative renal replacement therapy	0.16	2.23 (0.74–6.75)		

* Logistic regression model. MELD – model for End-Stage Liver Disease score; EBL – estimated blood loss; PRBC – packed red blood cell; FFP – fresh frozen plasma; OR – odds ratio; CI – confidence interval.

complications, including altered mental status (AMS) and ODS were assessed with regard to a possible relationship with peritransplant serum sodium levels. Posttransplant AMS was observed in 41 patients (13%). Pretransplant hyponatremia (<130 mEq/L) was significantly associated with the occurrence of posttransplant AMS ($p=0.004$, $OR=3.52$), whereas a large delta Na (>10 mEq/L) was not associated with the occurrence of posttransplant AMS ($p=0.46$, $OR=1.64$) (Table 3). History of hepatic encephalopathy was significantly associated with posttransplant AMS. History of alcoholic cirrhosis was not associated with AMS ($p=0.12$). On multivariate analysis, pretransplant hyponatremia (<130 mEq/L) ($p=0.009$, $OR=3.15$) and pretransplant hepatic encephalopathy ($p=0.009$, $OR=2.68$) were considered to be independent risk factors for posttransplant AMS. No obvious ODS was observed in our series. All patients with posttransplant neurological complications were followed by a neurologist for their entire hospital stay. Thirty-two (10%) patients received CT/MRI head evaluation for possible ODS after presenting a persistent altered mental status. In all patients, the image evaluation for ODS was negative. There was

no difference in posttransplant intubation period according to pretransplant sodium levels or delta Na between the groups. In the group with a larger delta Na, hospitalization was longer than it was in the control group (10, 12, and 19.5 days in the control group [± 5 mEq/L], moderate delta Na group [$+5.1$ to $+10$ mEq/L], and large delta Na group [$>+10$ mEq/L], respectively [$p=0.04$]). The pretransplant sodium level was not associated with a prolonged hospital stay (12 days in the low sodium group [<130 mEq/L] vs. 10 days in the control group [130 – 145 mEq/L], $p=0.31$).

Discussion

In this study, we investigated the impact of intraoperative serum sodium changes on short-term mortality after OLT, as well as on neurological complications. Low serum sodium concentration is a common finding prior OLT in cirrhotic patients and is closely associated with ascites, encephalopathy, and hepatorenal syndrome (Guerva et al., 2009). In the last

Table 3. Risk factors for post-transplant altered mental status.

Variables	Univariate		Multivariate	
	p*	HR (95%CI)	p*	HR (95%CI)
Recipient age >65 yo	0.77	1.16 (0.42–3.24)		
Primary liver disease				
Alcoholic cirrhosis	0.12	1.86 (0.85–4.06)		
Pre-transplant serum sodium				
130–145 mEq/L (Ref.)				
<130 mEq/L	0.004	3.52 (1.51–8.25)	0.009	3.15 (1.32–7.49)
MELD score	0.24	1.03 (0.98–1.09)		
MELD-Na score	0.07	1.05 (1.0–1.12)		
Pre-transplant hepatic encephalopathy	0.002	3.04 (1.48–6.23)	0.009	2.68 (1.28–5.62)
Intraoperative EBL (per 100 mL)	0.44	0.99 (0.96–1.02)		
Operative time (per hour)	0.13	0.68 (0.42–1.11)		
Delta Na				
–5 to +5 mEq/L (Ref.)				
+5 to +10 mEq/L	0.39	1.46 (0.61–3.5)		
>+10 mEq/L	0.46	1.64 (0.44–6.19)		
<–5 mEq/L	0.99	N/A		
Combined kidney transplant	0.45	1.57 (0.5–4.95)		
Intraoperative renal replacement therapy	0.17	1.81 (0.78–4.16)		

* Logistic regression model. MELD – model for End-Stage Liver Disease score; EBL – estimated blood loss; OR – odds ratio; CI – confidence interval.

decade, the prognostic impact of pretransplant hyponatremia after OLT has been emphasized. It was reported that low sodium is associated with higher waiting list mortality among LT candidates [3,4]. In addition, the significant impact of low sodium has been confirmed by Sharma et al. [5], who examined the relationship between serum sodium and survival benefit. They found that the LT survival benefit increased significantly with decreased serum sodium values when the MELD score is more than 11. According to the results from this study, there was a significant correlation between a large delta Na and 3-month mortality. In agreement with other studies in the literature, we found that predictors for diminished short-term survival included intraoperative EBL and blood product transfusion and operative time. There was a tight correlation between a large delta Na and the usage of intraoperative blood products, operative time, and pretransplant hyponatremia (<130 mEq/L). These results emphasized the importance of careful management of the peritransplant serum sodium level. Intraoperative anesthetic management could play a significant role in the prevention of serious sequelae.

It is not uncommon to see that large amounts of blood products in transfusion are required in OLT surgery, which is considered to be related with higher infection rates, sepsis, abdominal complication, and decreased patient survival [11,12]. The usage of blood products was correlated with a large delta Na. We observed that patients with a large delta Na received more than the average amount of blood products in transfusion. Overall, in accordance with other studies in the literature, we observed a diminished short-term survival in patients with a large amount of blood products in transfusion. This can be explained by the large delta sodium value and their serious consequences, cases that are technically difficult and a prolonged operative time.

Hyponatremia in cirrhotic patients is very common [2]. This can be mainly explained by systemic vasodilatation and the consecutive release of antidiuretic hormone (ADH), which promotes water retention and a decrease in serum sodium. The severity of hyponatremia is related to the severity of cirrhosis [2]. It is well known that fast correction of hyponatremia can lead to serious neurological consequences, of which the most severe complication would be ODS [13]. The main mechanism

for hyponatremia is still unknown, but hyponatremia can be explained by cerebral edema, disruption of the myelin sheath, and opening of the blood-brain barrier, allowing entry of complement and other cytotoxic plasma components. All of these could be caused by a fast osmolality change during sodium correction. The clinical manifestations of brain demyelination are typically delayed for 2–6 days after an overly rapid elevation of the serum sodium concentration [14]. The clinical consequences can vary from benign nausea, confusion and disorientation to ‘locked in’ syndrome [14].

In our study, 41 patients (15%) developed AMS. In the literature, the reported rate of neurologic complications after OLT is between 13% and 47% [1]. While there is still disagreement in the classification of different neurological events after LT, we defined AMS as any significant neurological event, such as seizure, confusion, or loss of consciousness. In our study, low pretransplant sodium and history of hepatic encephalopathy were significantly associated with the occurrence of posttransplant AMS. Interestingly, no correlation was found between a large delta Na and AMS. Posttransplant AMS can be multifactorial, including factors such as CNI toxicity, infections, electrolyte disorders, and type of cirrhosis, and it would be difficult to determine an exact reason for each of the episodes, whereas it should be emphasized that the pretransplant serum sodium level showed a certain association with posttransplant AMS. In regard to ODS, this complication is regarded as the most serious AMS event most likely associated with rapid changes in the serum sodium level. It was reported that the incidence after LT was correlated with severity of pretransplant hyponatremia (Yun, et al.), whereas we did not observe ODS in any of the patients. Because all patients with AMS did not always receive an MRI or CT scan, an underestimation or misdiagnosis of ODS is possible. Further investigations into association between posttransplant AMS, especially ODS, and delta Na are warranted.

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The results from this study encourage us to change and ameliorate our current approach, especially regarding intraoperative management, with patients with a low pretransplant serum sodium level. Currently, all patients with a Na <120 mEq/L are temporarily suspended on the LT list and admitted for correction of hyponatremia until their serum sodium level becomes 125 mEq/L or higher. During OLT surgery, the liver transplant anesthesia team frequently checks the blood gas and serum sodium levels and tries to avoid an excessive amount of blood products and/or albumin infusions to prevent overcorrecting the serum sodium level, especially for patients with pretransplant hyponatremia. In terms of posttransplant management, it is important to promote high suspicion for ODS and to consider prompt initiation of plasmapheresis and immunoglobulins as a treatment for ODS [15,16].

The limitations of this study include its retrospective data collection and possible bias due to unmeasured patient characteristics in the clinical evaluation of neurological complications. Additionally, there was no standardized protocol for the pre- and posttransplant correction of hyponatremia, so we did not determine whether the correction of serum sodium was intentional. Even so, the prognostic impact of the peritransplant delta Na and the association between the pretransplant sodium level and occurrence of posttransplant AMS were remarkable. These warrant more attention and need to be further investigated in future studies.

Conclusions

Our results indicate that neurological complications secondary to a pretransplant low serum sodium level and intraoperative rapid serum sodium correction were concerning, which potentially led to prolonged hospitalization and early mortality. Because intraoperative factors, such as large amounts of blood loss and transfusion and a prolonged operative time, were associated with a significant increase in the serum sodium level, careful intraoperative monitoring of the serum sodium level is crucial to avoid adverse events.

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