Early Outcomes of Liver Transplants in Patients Receiving Organs From Hypernatremic Donors

Mohammad Bagher Khosravi, Mohammad Firoozifar, Sina Ghaffaripour, Mohammad Ali Sahmeddini, Mohammad Hossien Eghbal

Abstract

Objectives: Uncorrected hypernatremia in organ donors has been associated with poor graft or patient survival during liver transplants. However, recent studies have found no association between the donor serum sodium and transplant outcome. This study sought to show the negative effect donor hypernatremia has on initial liver allograft function. This is the first study to investigate international normalized ratio and renal factors of patients with normal and those with hypernatremic donor livers.

Materials and Methods: This study was conducted at the Shiraz Transplant Research Center in Shiraz, Iran, between May 2009, and July 2011. Four hundred seven consecutive adult orthotopic liver transplants were performed at the University of Shiraz Medical Center.

Results: There were 93 donors in the group with hypernatremia with terminal serum sodium of 155 mEq/L or greater (group 1), and 314 with terminal serum sodium less than 155 mEq/L (group 2). Posttransplant data after 5 days showed that aspartate aminotransferase, alanine aminotransferase, international normalized ratio, and kidney function did not differ between the groups.

Conclusions: Hypernatremia is the most important complication after brain death. Previous studies have suggested donor hypernatremia results in a greater incidence of early postoperative graft dysfunction in liver transplant and is considered one of the extended criteria donor. However, in recent years, this hypothesis has been questioned. Our study shows no difference between patients’ initial results of liver and kidney functioning with normal and hypernatremic donor livers. This is the first study to investigate international normalized ratio as a fundamental factor in defining early allograft dysfunction and renal factors between patients with normal and hypernatremic donor’s livers.

Key words: Donor criteria, Liver function enzymes, Graft dysfunction, Uncorrected hypernatremia, Brain death

Introduction

Our understanding of the pathophysiology of brain death and its effects on donor and recipient organ function has progressed over the last two decades. Several retrospective analyses of the donor have attempted to identify risk factors that are predictive of patient and graft survival after an orthotopic liver transplant.

Dysfunction of the posterior pituitary is common with resultant low to undetectable levels of vasopressin, manifested clinically as diabetes insipidus, and occurring in up to 90% of adult and pediatric organ donors. Uncorrected hypernatremia in organ donors is associated with poor graft or patient survival because of cell swelling and resultant increase of reperfusion-mediated injury. The suggested donor hypernatremia results in a greater incidence of early postoperative graft dysfunction and an increased frequency of graft loss after an orthotopic liver transplant.
Recent studies have shown no association between the donor serum sodium and transplant outcomes, suggesting that acute treatment of hypernatremia near the time of organ procurement ameliorates the negative effect of donor hypernatremia on initial liver allograft function. Here, we report the perioperative outcomes of these allografts, including liver enzyme, international normalization ratio, blood urea nitrogen, and creatinine during 5 days after a liver transplant between hypernatremic donors and controls.

Materials and Methods

After approval of the ethical committee of the University of Shiraz Medical Sciences, between May 2009, and July 2011, four hundred seven consecutive adult orthotopic liver transplants were performed at the University of Shiraz Medical Center in Shiraz, Iran. All protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. All hepatic allografts were perfused and preserved with University of Wisconsin solution using previously described techniques for multiple organ recovery.

The 407 patients involved in this retrospective cohort study were divided into 2 groups according to the terminal donor serum sodium level during their stay in the intensive care unit: group 1 (serum sodium level ≥ 155 mEq/L before organ procurement [n=93]) and group 2 (serum sodium level < 155 mEq/L [n=314]). Early graft function was assessed by daily measurement of patients’ liver function enzymes including aspartate aminotransferase, alanine aminotransferase, and international normalized ratio, and kidney function including blood urea nitrogen and creatinine during the first 5 days after the operation. Patient death for any reason was recorded as a graft loss during 30 days after transplant, because after 30 days, other factors such as rejection, infection, or recurrence of the disease can play a more important role than the quality of the donor organ.

Results

Demographic characteristics of the donor are shown in Table 1. Ninety-three donors comprised group 1, and 314 comprised group 2. There were no differences in age, sex, cause of brain death, and length of stay in the intensive care unit in both groups. Also, recipient patient did not differ by age, sex, model of end-stage liver disease score, length of hospital stay, death during 30 days after transplant (early death), and cold and warm ischemia time in both groups (Table 2). Posttransplant data after 5 days showed that liver enzyme (aspartate aminotransferase and alanine aminotransferase) did not differ between the groups (Figures 1A and 1B).

### Table 1. Donor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Numbers</td>
<td>93</td>
<td>314</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD) (y)</td>
<td>34.0 ± 13.5</td>
<td>32.6 ± 11.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>57/36</td>
<td>201/113</td>
<td>NS</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head trauma (%)</td>
<td>78</td>
<td>75</td>
<td>NS</td>
</tr>
<tr>
<td>ICH (%)</td>
<td>6.5</td>
<td>4.8</td>
<td>NS</td>
</tr>
<tr>
<td>CVA (%)</td>
<td>3.2</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Others (%)</td>
<td>12.30</td>
<td>17.70</td>
<td>NS</td>
</tr>
<tr>
<td>ICU stay (mean ± SD) (d)</td>
<td>5.6 ± 2.6</td>
<td>5.3 ± 2.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** CVA, cerebrovascular accident; ICH, intracranial hemorrhage; ICU, intensive care unit; NS, nonsignificant

**P value < .05 for comparison of groups.**

### Table 2. Recipient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>93</td>
<td>314</td>
<td></td>
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<tr>
<td>Age (mean ± SD) (y)</td>
<td>35.4 ± 13.5</td>
<td>35.9 ± 14.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>58/35</td>
<td>195/119</td>
<td>NS</td>
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<td>Recipient MELD (mean ± SD)</td>
<td>22.1 ± 3.8</td>
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<td>NS</td>
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<td>Hospital stay (mean ± SD) (d)</td>
<td>13.8 ± 7.5</td>
<td>14.4 ± 9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Early death (%)</td>
<td>1</td>
<td>1.90</td>
<td>NS</td>
</tr>
<tr>
<td>Cold ischemia (mean ± SD) (h)</td>
<td>8.3 ± 2.0</td>
<td>8.0 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Warm ischemia (mean ± SD) (min)</td>
<td>47.6 ± 10.1</td>
<td>47.6 ± 10.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** MELD, model of end-stage liver disease; NS, nonsignificant

**P value < .05 for comparison of groups**

**Figure 1.** Posttransplant AST, ALT, and INR in Both Groups

(A)  
(B)  
(C)

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio

Also, levels of international normalized ratio during the 5 days after transplant were similar (Figure 1C). Although there were differences in changes in creatinine levels during the 3 days after transplant between the groups, the values of
creatinine and blood urea nitrogen were not significantly different in either group for the first 5 postoperative days (Figure 2A and 2B). During 30 days after the operation, there were 2 patients deaths in group 1 (2.1%) and 9 patient deaths in group 2 (2.8%), so graft losses were similar between the groups.

Figure 2. Posttransplant BUN and Cr

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine

Discussion

Previously, among the donor criteria, hypernatremia was a significant risk factor for graft loss after liver transplant. For the first time, Avolio and associates suggested that donor hypernatremia may adversely affect the outcome after a liver transplant, and these authors showed a direct correlation between donor serum sodium concentration and liver enzyme levels (aspartate aminotransferase and alanine aminotransferase) after the operation. After this, Gonzalez and associates showed that during a liver transplant, donor hypernatremia correlates with hepatic allograft dysfunction. Figueras and associates reported that donor hypernatremia is associated with high bilirubin concentrations postoperatively, and graft loss within the first month postoperatively.

Totsuka and associates showed that the function and survival of the hepatic graft were improved by correcting donor hypernatremia in donors before recovering the organ, and they suggested that latent changes in hepatocytes induced by hypernatremia are reversible and correction attenuates graft liver injury from donor hypernatremia.

The mechanism of this damage owing to serum hypernatremia in hepatocytes is not clear. One hypothesis states that a sudden change in extracellular osmolality in a liver graft obtained from a hypernatremic donor could cause intracellular water accumulation and cell swelling. However, another hypothesis suggests that serum sodium concentrations may promote accumulation of idiogenic osmoles within liver allograft cells. Subsequent transplant of these livers into recipients with normal serum sodium levels may promote intracellular water accumulation, hepatocyte lyses, and death.

However, recent studies have found that hypernatremia in donors do not affect postoperative graft loss. Tector has reported no increased risk of graft loss in donor livers with peak serum sodium level > 170 mEq/L. Cywinski and associates found no difference in early patient survival, early graft function, intensive care unit stay, and length of stay in the hospital in 51 patients with terminal hypernatremia.

In a final study, Mangus and associates reported that initial posttransplant alanine aminotransferase concentrations did not worsen in recipients who received a liver from donors with peak or terminal hypernatremia (serum sodium level > 160 mEq/L), and there was no correlation between serum sodium and liver damage, which would be expected in the presence of a dose-dependent response.

In our study, we investigated several liver factors including aspartate aminotransferase, alanine aminotransferase, and international normalized ratio, and two renal factors, blood urea nitrogen and creatinine, in 407 patients during 5 days after a liver transplant. This is the first study to investigate international normalized ratio and renal factors between patients with normal and hypernatremic donor livers.

Considering that international normalized ratio and alanine or aspartate aminotransferases are important factors in defining early allograft dysfunction in a liver transplant, this study showed no difference between international normalized ratio value and liver’s enzymes in patents that received livers from donors with serum sodium more or less 155 mEq/L, five days after the operation. Although the level of blood urea nitrogen and creatinine slightly increase after 5 days in both groups, this study indicates that hypernatremia in donors’ livers do not affect the kidneys.

At our center, the time between diagnosing brain death until organ recovery is no more than 1 or 2 days (maximum). The time during which the liver is exposed to high serum sodium in vivo until treatment in the intensive care unit is short. Conversely, mean cold ischemic time was slightly higher in group 1 than it was in group 2 (8.3 h vs 7.5 h), showing that the time the liver is exposed to hypernatremia in vitro leading...
to cell swelling; however, this difference does not significantly affect further outcomes.

References