Insulin Decreases the Serum Potassium Concentration during the Anhepatic Stage of Liver Transplantation

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Background: Severe hyperkalemia is a serious problem during orthotopic liver transplantation. The effectiveness of insulin in decreasing serum potassium concentration during the anhepatic stage of orthotopic liver transplantation was investigated.

Methods: Forty patients with serum potassium concentrations greater than 4.0 mEq/L at the onset of the anhepatic stage were randomized into two groups. Control group patients (n = 20) received no treatment, and treatment group patients (n = 20) received an intravenous bolus of regular insulin (20 u) 10 min into the anhepatic stage, followed by a glucose infusion (500 ml 5% dextrose in water) over 15 min.

Results: In the control group, the potassium concentration did not change, whereas in the treatment group, it decreased from 4.70 ± 0.54 to 4.18 ± 0.63 mEq/L (mean ± SD) within 15 min and to 3.57 ± 0.55 mEq/L 60 min after therapy. The potassium concentration was less in the treatment group than in the control group within 30 min of treatment (3.97 ± 0.52 vs. 4.49 ± 0.45 mEq/L, respectively; P < 0.05). The potassium concentration increased similarly 30 s after graft reperfusion in both groups of patients, but was less in the treatment group (5.91 ± 1.63 vs. 7.37 ± 1.67 mEq/L, respectively; P < 0.05). The potassium concentration returned to prer eperfusion levels within 5 min after graft reperfusion.

Conclusions: In patients undergoing orthotopic liver transplantation, the administration of insulin rapidly decreases serum potassium concentration, even in the absence of the liver, suggesting an important contribution by extrahepatic tissues in the insulin-stimulated uptake of potassium. (Key words: Insulin; hyperkalemia; potassium. Liver. Transplantation. Metabolism: glucose; hormones; insulin.)

SEVERE hyperkalemia is a serious complication during orthotopic liver transplantation (OLT) and is usually the result of the large potassium (K+) load during massive blood transfusion or during reperfusion of the grafted liver, especially in patients with renal insufficiency.1-3 For example, during 1987 and 1988, a 0.7% intraoperative mortality rate was reported to be related to massive transfusion-induced hyperkalemia.4 The very short-lived but severe hyperkalemia of greater than 7-8 mEq/L caused by washout of K+ from the graft may be a factor in the circulatory impairment associated with reperfusion.5,6 Therefore, successful treatment of hyperkalemia, particularly during the anhepatic stage, can be of vital importance during OLT. Management strategies for decreasing serum K+ concentration include the administration of washed packed cells,7,8 hemodialysis, exchange autotransfusion,9 diuretics, and promotion of redistribution of K+ by alkalinization, or beta2-adrenergic agonist or insulin administration. However, some of these techniques are cumbersome or have not been well studied in the setting of OLT.

Insulin decreases serum K+ concentration in healthy persons and in patients with renal failure.9,10 The effect of insulin on serum K+ in patients with liver disease is unknown; in normal patients, the liver accounts for about 70% of the K+ removed from the circulation during the first hour after insulin administration.9 Other metabolic actions of insulin are abnormal in the setting of hepatic dysfunction: patients with liver disease are frequently resistant toward the glucose-decreasing effects of insulin.11 Furthermore, during OLT, the anhepatic stage excludes any hepatic function. Thus, the
purpose of this study was to determine the effectiveness of insulin in decreasing the serum K⁺ concentration during the anhepatic stage of OLT.

Materials and Methods

Following approval by the Institutional Review Board and with the patients' informed consent, 40 adult patients undergoing OLT with serum K⁺ concentrations greater than 4.0 mmol/L at the onset of the anhepatic stage were studied. Patients with diabetes mellitus were excluded because of abnormal glucose metabolism, and patients with renal insufficiency were excluded because of the potential for decreased renal excretion of K⁺. Anesthesia was maintained with isoflurane (0.2–0.8%), fentanyl, and vecuronium. Intraoperative management followed the standard care used during OLT at our institution and included the use of pulmonary arterial and femoral arterial catheters with frequent determination of hemodynamic variables. Normocarbia was maintained (Paco₂ of 35–40 mmHg), and pH was kept within the normal range (7.3–7.45). Venovenous bypass was used during the anhepatic stage in all cases.

Patients were randomized into two groups: control group patients (n = 20) received no insulin therapy, and treatment group patients (n = 20) received an intravenous bolus of regular insulin (20 u) 10 min after the start of the anhepatic stage, immediately followed by an intravenous glucose infusion (500 ml 5% dextrose in water) over 15 min. No other technique designed to deliberately decrease K⁺ concentration was used in any patient. Serum K⁺ and glucose concentrations were determined at the following times: 5 min before administration of insulin and glucose (IG - 5'); 5, 10, 15, 30, 45, and 60 min after the administration of insulin and glucose (IG + 5', IG + 10', IG + 15', IG + 30', IG + 45', and IG + 60', respectively); and 30 s and 5 and 30 min after graft reperfusion (III + 30', III + 5', and III + 30', respectively). Blood urea nitrogen and creatinine concentrations were determined at the beginning of the procedure. Urine output and urine K⁺ concentration were measured during the anhepatic stage. Transfusion requirements during the anhepatic stage and the K⁺ concentration in the transfused blood mixture (packed erythrocytes/fresh frozen plasma: PlasmaLyte A²⁻ = 300:200:250) were noted. Results, presented as mean ± SD, were analyzed using one-factor analysis of variance and analysis of variance for repeated measures. A P value less than 0.05 was considered statistically significant.

Results

The two patient groups were similar regarding age, weight, height, baseline blood urea nitrogen and creatinine, urine output during the anhepatic stage, K⁺ concentration in the urine, renal excretion of K⁺ during the anhepatic stage, transfusion requirements during the anhepatic stage, and K⁺ concentration in the blood mixture (table 1).

Immediately before the administration of insulin and glucose (IG - 5'), serum K⁺ concentration was slightly less in the control group than in the treatment group (4.38 ± 0.32 vs. 4.70 ± 0.54 mmol/L, P < 0.05; fig. 1. table 2). Serum K⁺ concentration was ≥5.0 mmol/L in one control group patient (5.3 mmol/L) and in five treatment group patients (range 5.0–6.3 mmol/L). During the anhepatic stage, K⁺ concentration did not change in the control group. It increased 30 s after graft reperfusion (7.37 ± 1.67 mmol/L) then returned to prereperfusion levels at 5 and 30 min after reperfusion. In the treatment group, K⁺ concentration decreased within 15 min after the insulin administration, and it was less than in the control group within 30 min after treatment. Immediately after graft reperfusion, K⁺ concentration increased in the treatment group to the same degree as in the control group. However, because the K⁺ concentration in the treatment group was less before reperfusion, the peak K⁺ concentration (5.91 ± 1.63 mmol/L) was less than that in the control group (P < 0.05).

Hypokalemia (K⁺ ≤ 3.0 mmol/L) was not seen in the control group. In the treatment group, however, hy-

Table 1. Demographic Data of the Two Patient Groups: Baseline Blood Urea Nitrogen (BUN) and Creatinine; Urine Output, Urine Potassium (K⁺) Concentration, and Renal Excretion of Potassium during the Anhepatic Stage; Transfusion Requirements during the Anhepatic Stage; and Potassium Concentration of the Blood Mixture

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Treatment Group</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>44.1 ± 10.9</td>
<td>49.9 ± 11.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.7 ± 14.6</td>
<td>70.4 ± 9.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.9 ± 9.3</td>
<td>170.9 ± 8.6</td>
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<tr>
<td>Baseline BUN (mg/dL)</td>
<td>23.4 ± 19.3</td>
<td>26.2 ± 23.1</td>
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<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.5 ± 2.0</td>
<td>1.4 ± 1.3</td>
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<tr>
<td>Urine output (ml)</td>
<td>188.0 ± 190.2</td>
<td>258.3 ± 187.7</td>
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<tr>
<td>Urine K⁺ (mmol/L)</td>
<td>42.2 ± 10.0</td>
<td>41.5 ± 12.8</td>
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<tr>
<td>Renal excretion of K⁺ (mmol)</td>
<td>6.7 ± 5.4</td>
<td>9.2 ± 5.4</td>
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<td>Packed red blood cells (U)</td>
<td>6.1 ± 4.2</td>
<td>6.9 ± 5.0</td>
</tr>
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<td>Blood mixture K⁺ (mmol/L)</td>
<td>11.6 ± 2.6</td>
<td>10.9 ± 3.8</td>
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Values are mean ± SD. No statistically significant difference was found between the two patient groups.
pokalemia was observed in one patient during the anhepatic stage (serum K+ concentration of 2.7 mm/L), and in five patients at 5 or 30 min after graft reperfusion, but this was not associated with cardiac arrhythmias.

Glucose levels are presented in table 2. Hypoglycemia was not observed in any patient. Two control group patients had low-normal serum glucose concentrations (74 and 76 mg/dL, respectively) during the anhepatic stage. Hyperglycemia (serum glucose concentrations ≥250 mg/dL) was seen before or after graft reperfusion in 3 control patients and in 13 treatment patients; however, this hyperglycemia was usually mild, and only one patient in each group had glucose levels >300 mg/dL after graft reperfusion. pH values were similar in both groups (table 2).

Two patients in each study group required small boluses of epinephrine (≤30 μg) upon graft reperfusion to treat transient hypotension (systolic blood pressure ≤70 mmHg).

Discussion

Hyperkalemia secondary to massive transfusion, renal insufficiency, and a sudden release of K+ from the graft on reperfusion, remains an important cause of intraoperative morbidity and mortality during OLT. A short-lived, severe postreperfusion hyperkalemia may contribute to hypotension and bradycardia, called the "postreperfusion syndrome." A severe form of postreperfusion syndrome results in cardiac arrest, caused by a brief episode of hyperkalemic "cardioplegia" in addition to other metabolic and hemodynamic changes. Because of the severe potential complications of hyperkalemia during OLT, it is of utmost importance to decrease the baseline K+ concentration effectively and quickly before graft reperfusion.

In healthy persons, total body K+ content depends on the balance between intake and renal excretion. The plasma K+ concentration is a function of total body K+ content and its distribution between the extracellular and intracellular compartments. Normally, about 2% of total body K+ is in the extracellular fluid compartment. Intracellular K+ concentration depends mainly on the activity of sodium-potassium ATPase and is influenced by the acid-base status and by hormones such as epinephrine, aldosterone, and insulin. After an acute K+ load, homeostasis is maintained by an insulin-dependent translocation of K+ into the intracellular space, with liver and muscle representing the major buffering systems.

Frequently, K+ homeostasis is abnormal in patients with liver cirrhosis. Decreased total body K+ content results in chronic hypokalemia and is probably due to hyperaldosteronism, diuretic therapy, and gastrointestinal losses. Furthermore, tolerance to exogenous K+ loading is reduced due to a decreased K+ uptake by the
Table 2: Serum Potassium and Glucose Levels, and pH Values during Liver Transplantation in the Control Group and Treatment Group (IG)

<table>
<thead>
<tr>
<th>K⁺ (mEq/L)</th>
<th>Group</th>
<th>IG</th>
<th>IG + 60 min</th>
<th>IG + 30 min</th>
<th>IG + 60 min</th>
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<th>IG + 45 min</th>
<th>IG + 30 min</th>
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<tbody>
<tr>
<td>Control</td>
<td>IG</td>
<td>4.39 ± 0.21</td>
<td>4.37 ± 0.19</td>
<td>4.18 ± 0.19</td>
<td>4.23 ± 0.22</td>
<td>4.13 ± 0.24</td>
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<td>4.14 ± 0.25</td>
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<tr>
<td>IG</td>
<td>4.70 ± 0.19</td>
<td>4.67 ± 0.19</td>
<td>4.62 ± 0.19</td>
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<tr>
<td>Glucose (mg/dL)</td>
<td>Control</td>
<td>95 ± 19</td>
<td>96 ± 18</td>
<td>97 ± 18</td>
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<td>96 ± 18</td>
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<tr>
<td>PH</td>
<td>Control</td>
<td>7.37 ± 0.04</td>
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Values are mean ± SD. IG = IG + 30 min before administration of insulin and glucose (IG); IG = IG + 45 min after administration of insulin and glucose (IG + 30 min). *P < 0.05 compared with control group.

Cirrhotic liver, possibly because of reduced sensitivity to insulin, and to a reduced muscle mass.11,15,16

Therapy for hyperkalemia is directed both at decreasing the harmful effects of hyperkalemia on the heart and at decreasing the K⁺ concentration. Calcium chloride, epinephrine, and magnesium sulfate may decrease the effects of hyperkalemia on the myocardial cells.18,19 The K⁺ load may be decreased by the use of fresh blood products or by washing packed cells before their administration,20 because K⁺ concentration in 35-day-old packed cells (with ±70 mL of plasma) may reach 76 mmol/L. Potassium can be removed by the use of hemodialysis, exchange transfusion, and diuretics.8 Hemodialysis is the most efficient way to rapidly decrease K⁺ concentration.10 Exchange autotransfusion also has been used effectively to decrease the K⁺ concentration during OLT.8 Dialyzing the effluent blood from the liver on graft reperfusion before it enters the systemic circulation reduced the degree of hyperkalemia and incidence of cardiac arrest in an animal model.6 However, all the techniques described above are fairly complicated and impractical in the clinical setting. In addition, diuretics are relatively ineffective and have a slow onset. Finally, K⁺ concentration can be decreased by promoting redistribution of the K⁺ using alkalinization, beta-adrenergic agonists, and insulin.9,10,15,14

Alkalosis decreases the plasma K⁺ concentration by shifting K⁺ to the intracellular compartment in addition to increasing distal tubular K⁺ excretion by the kidney.20 However, intravenous sodium bicarbonate seems to be ineffective in rapidly treating hyperkalemia in patients with renal insufficiency.10 Moreover, its hypertonicity may raise K⁺ concentration as a result of cellular dehydration, which leads to increased intracellular K⁺ concentration followed by passive diffusion of K⁺ out of cells.21

Epinephrine directly stimulates K⁺ uptake by skeletal and cardiac muscle cells and hepatocytes by a beta₂-adrenergic receptor-mediated increase in cAMP, resulting in activation of sodium-potassium ATPase.22,23 However, epinephrine resulted in a small decrease in K⁺ concentrations in only 50% of the patients with renal failure.10 Tachycardia is a common side effect of epinephrine.22 Ritodrine and albuterol, more selective beta₂-sympathomimetic agents, may have more predictable results with fewer side effects.25,24

Insulin quickly and effectively decreases serum K⁺ concentrations in healthy volunteers.9,15 In patients with renal failure, insulin is effective within 10 min.
and is much more effective than epinephrine.\textsuperscript{10} The effect of insulin on hyperkalemia is dose related,\textsuperscript{8} even in patients with diabetes mellitus.\textsuperscript{25} Insulin-induced K\textsuperscript+ uptake is mediated by the direct stimulation of the activity of sodium-potassium ATPase\textsuperscript{14,26} and is independent of insulin-stimulated glucose uptake.\textsuperscript{9} Both insulin and beta\textsubscript{2}-adrenergic agonists stimulate the sodium-potassium ATPase, but their effects are additive, indicating that their intracellular signals are different.\textsuperscript{26}

Under normal conditions, the cellular uptake of K\textsuperscript+ by splanchnic tissues during the first 60 min after insulin administration accounts for approximately 70% of the total decrease in extracellular K\textsuperscript+ content;\textsuperscript{25} thereafter K\textsuperscript+ is taken up predominantly by skeletal and cardiac muscle and adipose tissue.\textsuperscript{9,10,15} Obviously, glucose should be administered along with insulin to avoid hypoglycemia. Because the injection of 50% glucose may lead to hypotonicity, it may be advantageous to administer a 5% solution of glucose as a continuous infusion.

The results of this study demonstrate that insulin effectively decreases the serum K\textsuperscript+ concentration within 15 min, and for at least 60 min, even in the absence of the liver, in patients who have abnormal K\textsuperscript+ homeostasis and insulin resistance. The reduction in K\textsuperscript+ concentration is not explained by increased renal excretion of K\textsuperscript+, because the renal excretion of K\textsuperscript+ was similar in both groups. Many tissues (including skeletal and cardiac muscle and adipocytes) probably contribute to the decrease in the serum K\textsuperscript+ concentration. In this study, we used an intravenous bolus of 20 u of regular insulin, which is equivalent to the dose used in two other studies (0.005 u · kg\textsuperscript{-1} · h\textsuperscript{-1}).\textsuperscript{9,10} It is unknown whether larger doses of insulin are more effective or have a faster onset of action. This study did not include patients with renal insufficiency or with insulin-dependent diabetes mellitus; however, our clinical experience indicates that insulin is also effective in decreasing K\textsuperscript+ concentration in these patients. Although K\textsuperscript+ concentration 30 s after graft reperfusion was greater in the control group, the incidence of hemodynamic instability (defined as the need for epinephrine to maintain arterial blood pressure) did not differ between the groups. The number of patients in our study may have been too small to reveal such a difference. Also, it is possible that the degree of potassium increase is more important that the potassium level itself, and the gradual decrease in K\textsuperscript+ concentration by insulin followed by a rapid increase in K\textsuperscript+ concentration on reperfusion might lead to more cardiac irritability. Finally, arrhythmias and hemodynamic disturbances at the time of reperfusion are due to several factors, and not to potassium shifts alone. For all of these reasons, it is too early to recommend the routine administration of insulin during the anhepatic stage to attenuate the acute hyperkalemia at reperfusion. This issue requires further study. However, we believe that, if hyperkalemia develops during the anhepatic stage, insulin should be administered.

Several patients in the treatment group had hyperglycemia. This probably could be avoided by administering a smaller amount of glucose or by decreasing the infusion rate of 5% dextrose in water. Also, hypokalemia (≤3.0 mm/L) was observed in 25% of the treatment group patients during the nehepatic stage, but was not associated with cardiac arrhythmias.

In conclusion, the administration of insulin rapidly decreases serum K\textsuperscript+ level during the anhepatic stage of OLT, suggesting an important contribution by extrahepatic tissues in the insulin-stimulated uptake of K\textsuperscript+.

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References


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