Glucose Metabolism and Associated Outcome After Pediatric Liver Transplantation

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ABSTRACT

Background. Despite hypoglycemia and hyperglycemia being frequently observed in the early postoperative phase, information on glucose metabolism after pediatric liver transplantation (pLT) is scarce.

Methods. The goal of this retrospective single-center study, which included 46 patients who consecutively underwent 55 liver transplantations, was to gather data on glucose uptake, the prognostic relevance of hyperglycemia, and the safety of insulin administration in patients after pLT.

Results. In this study population, glucose intake to keep blood sugar levels (BSLs) within the targeted range of 120 to 200 mg/dL (6.7–11.1 mmol/L) increased rapidly over the first few postoperative days and was significantly correlated with graft function. There was no association between a postoperative daily mean BSL >200 mg/dL and specific posttransplant complications (acute rejection, infection, need for retransplantation, and/or death). High postoperative mean 7-day BSLs were associated with poor glucose metabolism and an increase in morbidity and 6-month posttransplant mortality. Hypoglycemia was not observed under insulin administration.

Conclusions. With high BSLs being associated with poor glucose metabolism, it is likely that the critical illness itself, in addition to poor graft function, causes the increase in morbidity and mortality, with hyperglycemia serving as a marker.

HYPOGLYCEMIA and Hyperglycemia are frequent problems in critically ill children. Both conditions are associated with an increase in morbidity and mortality [1,2]. Due to depleted graft glycogen stores, poor glycogenolysis, poor gluconeogenesis, and increased postoperative consumption, pediatric patients are at a high risk for hypoglycemia in the first few days after liver transplantation. Conversely, hyperglycemia in the early phase after liver transplantation seems to increase the risk of (surgical site) infections, allograft rejection, and death in adult patients [3–5]. However, after several multicenter studies failed to reproduce the initially reported positive effects of tight glucose control on morbidity and mortality in surgical intensive care unit patients, most international liver transplant centers recommended a glucose level between 6 and 10 mmol/L in the early posttransplant course; this approach was endorsed by the British Transplantation Society Guidelines of 2011.

To date, no data are available on the kinetics of postoperative glucose intake, the incidence and prognostic relevance of postoperative hypoglycemia and hyperglycemia, and the risk of insulin administration in the early phase after pediatric liver transplantation (pLT). The objective of the present study therefore was to gather data on the following: (1) the correlation of glucose intake and graft function; (2) the incidence and prognostic relevance of postoperative hypoglycemia and hyperglycemia; and (3) the safety of insulin administration in the early phase after pLT.

PATIENTS AND METHODS

Study Design

This retrospective, single-center, observational study was performed at the KUNO University Children's Hospital Regensburg,

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.08.013

Regensburg, Germany. Patients were aged 0 to 17 years and were included in the study after a liver transplantation between 2008 and 2011. Data from medical records were collected from the peritransplant period up to day 182 after transplantation. The study was approved by the local institutional review board (11-101-0120).

Immunosuppression Protocol

Due to a change in our standard immunosuppression protocol, some of the included patients received an intraoperative bolus of prednisolone (300 mg/sqm, with a maximum of 500 mg). After transplantation, all patients were treated intravenously with prednisolone in a high- or low-dose regimen (starting with 15 or 60 mg/sqm), basiliximab on postoperative days 0 and 4 (<35 kg body weight, 10 mg; >35 kg body weight, 20 mg), and cyclosporine (starting with 50 mg/sqm every 12 hours). Indications for high-dose prednisolone treatment included acute liver failure, cystic fibrosis, retransplantation, and autoimmune hepatitis. Other patients at high immunologic risk also underwent this treatment.

Glucose Management

After admission to the pediatric intensive care unit, all patients received glucose infusions at a rate of 5 g glucose/kg/d (3.5 mg/kg/min). In the first 7 days after transplantation, our aim was to keep the BSL between 120 and 200 mg/dL (6.7–11.1 mmol/L) with a minimum supply of 3 g glucose/kg/d (2.1 mg/kg/min). Glucose levels were obtained from the arterial or central venous line at least every 2 h and measured with point-of-care glucometers (ABL800 FLEX analyzer [Radiometer Medical A/S, Copenhagen, Denmark] or ACCU-CHEK Inform II [Roche Diagnostics, Mannheim, Germany]). BSLs >200 mg/dL were considered an indication for continuous administration of insulin. The initial insulin rate of 0.02 to 0.05 U/kg/h as well as all further changes were determined by the attending intensivist. The daily calculation comprised additional glucose amounts from transfusions (including erythrocyte concentrate and fresh frozen plasma) and enteral feeding, as well as glucose loss through drains. Glucose levels in drain fluids were equalized to serum levels.

Outcome Data

To evaluate the graft's synthetic and detoxification function we used daily mean Quick values, coagulation factor V values, and the decrease in bilirubin levels after pLT. Acute rejection was diagnosed based on clinical and biochemical data, as well as results of the liver biopsy, if indicated. Infection was defined as clinical or laboratory suspicion with the need to modify the existing prophylactic antibiotic therapy. Hypoglycemia was defined as a single episode with a BSL <50 mg/dL (<2.8 mmol/L). The postoperative mean 7-day (postoperative days 1–7) BSL and an episode of hyperglycemia defined as a mean BSL >200 mg/dL (>11.1 mmol/L) on at least 1 day within the first 8 days after transplantation were assessed as variables influencing outcome.

The following complications were defined as endpoints: infection within the first 30 days after transplantation, acute rejection, need for retransplantation, or death within the first 6 months after transplantation. The length of stay in the pediatric intensive care unit and duration of mechanical ventilation were used for further outcome assessments.

Statistical Analysis

Outcome assessment, graft function, and statistical differences between groups were tested by using linear regression analysis and Mann-Whitney or χ^2 tests depending on the type of variables. A P value <.05 was considered statistically significant. Data are represented as mean ± standard deviation. All analyses were performed by using SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, United States).

RESULTS

Baseline Characteristics

The study included 46 pediatric patients who consecutively underwent 55 liver transplantations. Nine patients were excluded because of incomplete data. Indication for transplantation is summarized in Table 1. Living donations (n = 15) were performed as left lateral (n = 13) or right (n = 2) segment transplantation. Deceased liver transplantations were either performed as whole (n = 12) or split (n = 28) liver transplantation. Intraoperative administration of prednisolone was performed in 34 transplantations; in 21 cases, there was no administration of prednisolone during the operation.

Correlation of Glucose Intake and Graft Function

The daily glucose intake to keep the BSL within the desired range of 120 to 200 mg/dL (6.7–11.1 mmol/L) showed a steady increase from postoperative day 0 to postoperative day 5. Preoperative levels were already exceeded on postoperative day 1 (Fig 1). Glucose intake correlated positively to Quick values ($P < .001$), coagulation factor V ($P < .001$), and bilirubin decreases ($P < .001$).

Prognostic Relevance of Hyperglycemia and Safety of Insulin Treatment

Complications occurred in 24 of 55 post-pLT periods. Infection within the first 30 days' posttransplantation was diagnosed 5 times; acute rejection within the first 6-month posttransplant period was diagnosed after 20 transplantations. In 19 of 20 cases, a liver biopsy was performed for histologic confirmation and grading of acute rejection. In 1 patient, a biopsy was not performed due to a high risk of bleeding; the patient's graft function improved significantly under steroid bolus therapy. Eight transplantations

Table 1. Indication for Pediatric Liver Transplantation

Etiology	No. of Transplantations
Biliary atresia	21
Acute liver failure due to non-A-E hepatitis	7
Progressive familial intrahepatic cholestasis	7
Alagille syndrome	4
Cystic fibrosis	5
Secondary biliary fibrosis	2
Mitochondrial disorder	2
Crigler-Najjar syndrome	1
Chronic hepatitis C	1
$Alpha_1$-antitrypsin deficiency	1
Idiopathic cirrhosis	1
Secondary sclerosing cholangitis	1
Glycogenosis (type IV)	1
Congenital cirrhosis of unknown origin	1