Postoperative Effects of Intraoperative Hyperglycemia in Liver Transplant Patients

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Abstract

Objectives: The aim of this study was to determine the effects of intraoperative hyperglycemia on postoperative outcomes in orthotopic liver transplant recipients.

Materials and Methods: After ethics committee approval was obtained, we retrospectively analyzed the records of patients who underwent orthotopic liver transplant from January 2000 to December 2013. A total 389 orthotopic liver transplants were performed in our center, but patients aged < 15 years (179 patients) were not included in the analyses. Patients were divided into 2 groups based on their maximum intraoperative blood glucose level: group 1 (patients with intraoperative blood glucose level < 200 mg/dL) and group 2 (patients with intraoperative blood glucose level > 200 mg/dL). Postoperative complications between the 2 groups were compared.

Results: There were 58 patients (37.6%; group 1, blood glucose < 200 mg/dL) who had controlled blood glucose and 96 patients (62.3%; group 2, blood glucose > 200 mg/dL) who had uncontrolled blood glucose. The mean age and weight for groups 1 and 2 were similar. There were no differences between the 2 groups regarding the duration of anhepatic phase (\(P = .20\)), operation time (\(P = .41\)), frequency of immediate intraoperative extubation (\(P = .14\)), and postoperative duration of mechanical ventilation (\(P = .06\)). There were no significant differences in frequency of patients who had postoperative infectious complications, acute kidney injury, or need for hemodialysis. Mortality rates after liver transplant were similar between the 2 groups (\(P = .81\)).

Conclusions: Intraoperative hyperglycemia during orthotopic liver transplant was not associated with an increased risk of postoperative infection, acute renal failure, or mortality.

Key words: Complications, End-stage liver disease, Glucose, Infection

Introduction

Perioperative high blood glucose level is a risk factor for serious intraoperative and postoperative complications.1 Uncontrolled blood glucose levels in diabetic patients may lead to serious organ damage, depending on the duration of diabetes.2 Surgery-related stress response also has been associated with various postoperative complications because administered pharmacologic agents may cause high perioperative blood glucose.3

Liver transplant is a complex process in terms of surgery, anesthetic approach, and metabolic changes. These patients may have failure of different organ systems, depending on duration of liver failure. Various abnormalities might be observed in the endocrine system in patients with liver failure associated with low or high blood levels of hormones that are synthesized and catabolized in the liver.4 Hypoglycemia or hyperglycemia may affect all systems negatively and may be observed in these patients.5

Intraoperative blood glucose regulation is important. High blood glucose levels that may be
observed for various reasons during liver transplant may negatively affect postoperative morbidity and mortality. Many treatments such as immunosuppressive drugs used after liver transplant, blood and blood product replacements, mechanical ventilation, invasive procedures for diagnosis and treatment, and catheterizations are risk factors for various infections.

In this study, we aimed to determine the effects of intraoperative hyperglycemia on postoperative outcomes in orthotopic liver transplant recipients.

Materials and Methods

Our study included patients having elective orthotopic liver transplant due to liver failure between January 2001 and December 2013 at Başkent University Faculty of Medicine. A total of 389 patients had liver transplant in our center. Patients aged < 15 years were excluded (179 patients). Patients were divided into 2 groups according to their maximum intraoperative blood glucose level: group 1 included patients with maximum intraoperative blood glucose < 200 mg/dL and group 2 included patients with maximum intraoperative blood glucose > 200 mg/dL. Postoperative complications were compared between the 2 groups.

The same anesthetic and surgical techniques were used in all patients. They were admitted to the intensive care unit at the end of surgery. The same surgical and anesthesia team performed all liver transplants. After operation, the patients were routinely maintained on mechanical ventilation until spontaneous breathing effort was evident and hemodynamic stability had been achieved. Patients were assessed in detail 1 day before the operation and informed about the anesthesia. Patients were premedicated with midazolam (0.1 mg/kg oral) and hydroxyzine hydrochloride (1 mg/kg oral) 1 hour before the operation. All patients were taken to the operating room and routinely monitored with a 5-channel electrocardiogram, pulse oximeter, heat probe, and invasive blood pressure measurement.

Thiopental (3-6 mg/kg intravenous) and fentanyl citrate (1-2 μg/kg intravenous) were administered for induction of general anesthesia, and vecuronium bromide (0.1 mg/kg intravenous) was administered to attain sufficient muscle relaxation before intubation. Isoflurane (0.5%-1%) was administered in a mixture of 50% oxygen and 50% air for maintenance of anesthesia. Calcium, dopamine, and remifentanil hydrochloride infusion were initiated for controlled hypotension. Vascular access was established with a double-lumen hemodialysis catheter with suitable diameter and length, and the widest intravenous cannula possible was used to provide rapid fluid resuscitation. Radial artery cannulation was performed for invasive blood pressure follow-up and femoral artery cannulation for monitoring of pulse-induced contour cardiac output (PiCCO, Philips, Amsterdam, Netherlands).

Measurements were performed with pulse-induced contour cardiac output at the beginning of operation, 2 hours later, before, during, and after and the anhepatic phase, and before intubation. Fluid and blood replacement decisions were made according to pulse-induced contour cardiac output. Thromboelastogram was used in patients for whom intraoperative hemostasis could not be ensured or coagulopathy was considered.

Hemodynamic parameters (systolic and diastolic arterial blood pressure, heart rate, and oxygen saturation) were recorded in the anesthesia record at 5-minute intervals. Postoperative pain control was ensured with intravenous morphine (0.3 mg/h basal infusion; 15 minutes locking time) using a patient-controlled analgesia machine.

Hemodynamic stability (absence of hypotension) and normothermia were the primary criteria required for extubation following liver transplant. Other criteria were an awake patient obeying verbal commands, sufficient ventilation (respiratory rate < 30 breaths/min with a good respiration pattern; oxygen saturation > 95% at room air; end-tidal carbon dioxide pressure, 30-40 mm Hg), complete resolution of neuromuscular blockade, normal arterial blood gas results, and sufficient hemostasis. All patients were taken to intensive care following extubation in the operating room, and monitoring included electrocardiogram, oxygen saturation, respiratory rate, urination, radial artery pressure, and central venous pressure. Respiratory physiotherapy, prophylactic antibiotics, nutritional support, fluid infusion, and supportive oxygen to keep oxygen saturation > 94% were administered in the intensive care unit.

Preoperative data collected included age (mo), sex, height (cm), weight (kg), liver failure (including
duration and etiology), abdominal acid, hepatopulmonary syndrome, hepatorenal syndrome, concomitant systemic diseases, donor degree of kinship, and Child-Pugh classification. Preoperative laboratory parameters included complete blood count, aspartate aminotransferase, alanine aminotransferase, total and indirect bilirubin, blood urea nitrogen, creatinine, electrolytes, activated partial thromboplastin time, prothrombin time, international normalized ratio, blood glucose levels, hepatitis markers, and preoperative biopsy. Intraoperative data included fluids, blood, and blood products administered; maximum and minimum systolic, diastolic, and mean blood pressure, heart rate, and central venous pressure; oxygen saturation; the worst blood gas pH, partial pressure of oxygen, carbon dioxide, and lactate levels recorded; the frequency of hypotension and bradycardia; vasopressor or antihypertensive therapy (20% of baseline values that require 6 or vasopressor support of blood pressure values as hypotension; 50 beats/min or below the required atropine for bradycardia was defined as heart rate values) (Hypotension was defined as a mean blood pressure less than 60 mm Hg or vasopressor requirement or mean blood pressure less than 20% of the baseline value; bradycardia was defined as a heart rate less than 50 beats/min or use of atropine); graft weight; intraoperative urine output; duration of anesthesia; and intraoperative blood glucose measurements. Postoperative data included intensive care unit stay, postoperative mechanical ventilation required, duration of mechanical ventilation, postoperative renal injury, lung injury, graft loss, revision surgery and indications, postoperative blood and blood products administered, postoperative pulse steroid therapy, number of rejection episodes, postoperative white blood cell count and C-reactive protein level, culture results, and mortality.

**Statistical analyses**

All data were analyzed with statistical software (Statistical Package for the Social Sciences, Version 17.0, SSPS Inc., Chicago, IL, USA). The 2 groups were compared using chi-square and Mann-Whitney tests. Logistic regression analysis was performed with variables of clinical and statistical significance for postoperative infection. The data were expressed as mean ± standard deviation (SD). Statistical significance was defined by $P \leq .05$.

**Results**

There were 58 patients (37.6%) (group 1, blood glucose $< 200$ mg/dL) who had controlled blood glucose and 96 patients (62.3%) (group 2, blood glucose $>200$ mg/dL) who had uncontrolled blood glucose (Table 1). The mean age and weight were similar for groups 1 and 2 (Table 1). There were more diabetic patients in group 1 (27 patients) than group 2 (3 patients; $P \leq .001$). There were no differences between the 2 groups in the duration of anhepatic phase, operation time, frequency of early (immediate) intraoperative extubation, or postoperative duration of mechanical ventilation (Table 1).

There were 60 (50) of the 154 patients (38.9%) who had postoperative infectious complications. The most frequent infectious complications for the 2 groups were pneumonia, followed by urinary tract infection, surgical site infection, and cholangitis (Table 2). Mortality rates after liver transplant were similar between the 2 groups (Table 2). There were no significant differences in frequency of acute kidney injury between group 1 (31 patients [53.4%]) and group 2 (45 patients [46.9%]; $P = .43$) or need for postoperative hemodialysis between group 1 (13 patients [22.4%]) and group 2 (25 patients [26%]; $P = .61$).

**Discussion**

We analyzed the effects of intraoperative hyperglycemia on postoperative outcomes in orthotopic
liver transplant recipients. Our results for 154 patients suggest that intraoperative hyperglycemia during liver transplant was not associated with an increased risk of postoperative infection, acute renal failure, or mortality. Previous studies showed different results about perioperative outcomes in diabetic patients who underwent liver transplant. Many factors may contribute to infection in liver transplant patients. A previous study of 680 patients demonstrated that major intraoperative hyperglycemia was an independent risk factor for postoperative surgical site infection, and it is possible that our study did not have sufficient power to determine such a difference.8

Glycemic control is of great interest in recent years. Significant improvements in morbidity and mortality were demonstrated in various studies with intensive care patients.1,9,10 Postoperative hyperglycemia after solid-organ transplant is associated with increased infection rate, graft dysfunction, and mortality.11,12 Positive effects on cerebral and cardiac function were shown in patients with glycemic control.13-15 Infection is 1 of the important factors associated with morbidity and mortality in liver transplant recipients. In addition, wound site healing and wound site infections were more frequent in diabetic patients in various studies. In another study, heart surgery patients with high blood glucose levels had more complications following surgery despite that absence of any other risk factors.16 In our study, infection and mortality rates were similar between the 2 groups.

Hyperglycemia may have negative effects on the immune system. Hyperglycemia negatively affects bactericidal functions of macrophages, granulocytes, and neutrophils.17 Additionally, hyperglycemia impairs the functions of immunoglobulins as a result of negative effects on proteins.18 In addition, wound site healing may be delayed because of increased collagenase activity and decreased wound collagen.19 These factors may help explain the association between infections and hyperglycemia. Hyperglycemia increases reactive oxygen production in bovine aortic endothelial cells. Inducible nitric oxide synthase gene synthesis associated with vasodilation may be impaired due to hyperglycemia.20 (Vasodilation might be due to the activation of inducible nitric oxide synthase gene synthesis due to hyperglycemia.) Reperfusion damage following liver transplant in hyperglycemic patients might be aggravated with impaired nitric oxide synthase activity.21

Adult liver transplant patients in the postoperative period of intraoperative blood glucose high mortality and morbidity in our study we examined the effect on blood glucose during surgery height did not show adverse effects on the development of the infection. (Intraoperative blood glucose in adult liver transplant patients is associated with high mortality and morbidity in the postoperative period. In our study, elevation of blood glucose during surgery not shown adverse effects on the development of infection in the postoperative period.) There are no guidelines for treatment of glucose levels during the perioperative period.

There were some limitations to our study. There are many factors that may facilitate transplant in patients with postoperative infection. Considering all these factors, we did not standardize the 2 groups completely. Other limitations of the study included the possibly limited clinical data, retrospective design, analysis of registry data, frequent missing data, and misclassification of important exposures.

In conclusion, according to this study, intraoperative hyperglycemia during liver transplant was not associated with an increased risk of postoperative infection, acute renal failure, or mortality.

References