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Research Article

Studying the effect of parenterally administered L-alanyl L-glutamine dipeptide in diabetes and new onset diabetes in liver transplantation

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KEYWORDS

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Abstract *Objective:* The objective of this study was to evaluate the efficacy of using alanine–glutamine (Aln–Gln) dipeptide as a supplement to control diabetes in liver transplanted patients.
Patients and methods: Eighty patients aged >18 yr admitted to ICU after receiving right lobe living donor liver transplantation (LDLT), had a previous history of diabetes or had a new onset diabetes (NODM) were enrolled in this prospective randomized double blind study. Patients were randomized into two groups and assigned to receive parenterally an equal dose of amino acids either with alanyl-glutamine dipeptide in the dose of 0.5 g/kg/d (group AG) or without alanyl-glutamine dipeptide (control group C). This regimen started at day 1 postoperative in diabetic patients or when new onset diabetes has been diagnosed in non-diabetic and continued till day 9 with measuring the incidence of hyperglycemia, hyperglycemic episodes, total insulin requirements/day, infectious episodes, ICU and hospital length of stay, and 6 month mortality rate.
Results: The hyperglycemic episodes were significantly less in AG group patients than in control group patients (29 vs 38). Hyperglycemia requiring insulin therapy in AG group was significantly less (22 vs 28 patients). Also those who required decreasing TPN requirements were significantly lesser in the AG group (7 vs 11 patients). Insulin requirements per day in the AG group were significantly lower (53 ± 11 vs 78 ± 9 IU). The number of episodes of nosocomial infection per patient was lower in the AG group than in the control group (20 vs 28). The decrease in nosocomial infections in patients receiving AG was related mainly to a decrease in the incidence of pneumonia (7 vs 11). The ICU length of stay (LOS) was significantly lower in the AG group than in the control group (7.81 ± 2.98 vs 10.43 ± 4.67 day)
Conclusion: Our study showed that using AG supplementation in liver transplanted patients who have either a history of diabetes or NODM, reduces the insulin requirements, hyperglycemic episodes, infectious events and ICU stay.

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1. Introduction

Diabetes is a common complication of liver transplantation increasing the risk of infection and mortality. New onset diabetes (NODM) accounts for nearly 15% of liver transplant recipients and a similar proportion of patients have diabetes prior to transplant thus increasing the magnitude of the problem [1]. Diabetes may develop from either impaired glucose tolerance, insulin resistance associated with impaired liver function, or a result of corticosteroids treatment post transplant [2]. A proper tight glycemic control reduces morbidity and mortality and requires multiple therapies.

Glutamine (Gln) is the most abundant free amino acid in the extracellular and intracellular compartments, accounts for approximately 6% of bound amino acids [3], and plays an important role as immune function regulator and modulation of cell metabolism [4]. Gln enhances glucose-stimulated insulin secretion via the metabolism of the gamma-glutamyl cycle, glutathione synthesis and mitochondrial function [5]. In conditions of excessive organ or tissue demand of glutamine during episodes of sepsis, after trauma, major surgery, and other catabolic stress situations, endogenous glutamine production may not be sufficient to meet the increased requirements.

Several studies have shown that alanine–glutamine (Aln–Gln) dipeptide added to parenteral formulas improves nitrogen balance; increases protein synthesis; ameliorates immune function; preserves intestinal barrier permeability; and can reduce morbidity, length of stay, and mortality in critically ill patients [6–8]. Furthermore, glutamine can modify fatty acid oxidation and attenuates hyperglycemia and insulin resistance [9].

The aim of this study was to evaluate the efficacy of using Aln–Gln as a supplement to control diabetes in liver transplanted patients.

2. Patients and methods

After obtaining institution ethical board approval and written informed consent from patients, eighty patients were enrolled to this randomized double blind prospective, controlled study conducted between February 2012 and August 2015 in liver transplant unit in Ain Shams University Specialized Hospital. Patients included in the study were adults >18 years, admitted to ICU after performing right lobe living donor liver transplantation (LDLT), had a previous history of diabetes or had a new onset diabetes (defined as symptoms of diabetes plus casual plasma glucose $\geqslant 200$ mg/dl or fasting plasma glucose $\geqslant 126$ mg/dl on more than 2 occasions) [10].

Preoperative exclusion criteria were persistent hemodynamic failure (systolic blood pressure <80 mmHg), severe renal insufficiency (serum creatinine level $\geqslant 2.8$ mg/dl and (or) creatinine clearance <40 ml/min), and severe or uncontrolled sepsis. The following criteria may lead to the exclusion of a patient even after inclusion in the study period: necessity to perform major non-scheduled procedures within the study with subsequent total parenteral nutrition (TPN) discontinuation for more than 24 h, intolerable or serious adverse event, any inter-current disease likely to interfere with the study, or withdrawal of patient's consent.

All patients were assessed and received the standard preoperative care for patients undergoing liver transplantation according to our unit protocol. Standard anesthetic and surgical techniques for hepatic transplantation were performed by the same anesthesia and surgical team who were blinded to study medication. At the end of surgery patients were transferred to the ICU intubated and mechanically ventilated until fully conscious, good muscle power together with the standard acceptable ventilatory and hemodynamic parameters of weaning. Demographic data were obtained including age, sex, BMI, history of diabetes and APACHE Π score [11]. Fluid administration in intensive care unit was adjusted to maintain central venous pressure approximately 5–8 cmH_2O, mean arterial pressure >70 mmHg, urine output >1 ml/kg per hour. All patients received similar postoperative intensive care with a routine double immunosuppressive regimen including corticosteroids, and FK506 (tacrolimus) or cyclosporine. Mycophenolate with basiliximab are used instead of using tacrolimus or cyclosporine if serum creatinine rise after 48 hours.

Intravenous methyl-prednisolone 500 mg was given intraoperative after declamping. Maintenance dosage of methylprednisolone was 1 mg/kg, to be tapered rapidly over the next 7–10 days. Maintenance prednisone 0.25 mg/kg/d was continued for 3 months then steroid therapy was stopped. Cyclosporine was used for immunosuppressive therapy for all patients except hepato-cellular carcinoma (HCC) patients, and starting dose tacrolimus 0.5 mg was used instead. Maintenance dosages of tacrolimus were adjusted to maintain a level of 10–12 ng/mL during the first 2 months. For cyclosporine maintenance dosages to achieve trough levels of 150–250 ng/mL were prescribed in the first 2 months. Mycophenolate was used postoperative in the presence of preoperative renal impairment (cr.cl. 40–60) or postoperative renal dysfunction (rise in serum creatinine level >0.3 mg/dl in less than 48 h) instead of calcineurin inhibitors. Basiliximab was also used (day 0 and day 4) in the presence of preoperative renal impairment.

Postoperative prophylactic antibiotic treatment included piperacillin-tazobactam and Metronidazole for 10 days. All patients received sulfamethoxazole/trimethoprim for prophylaxis against Pneumocystis carinii on day five for 6 months. Fluconazole for prophylaxis of fungal infection was used for specific cases such as severely malnourished patients, prolonged treatment with antibiotic, fulminant hepatic failure, preoperative diabetic patients, re-exploration for surgical causes, biliary leak and small for size liver transplant.

This study began at day 1 postoperative in diabetic patients or when new onset diabetes has been diagnosed in non-diabetic patients. Partial TPN was started at day one as the standard protocol in our ICU. Non-protein energy requirements were calculated using the usual body weight and set at 25 kcal/kg/d. Protein requirements were set at 0.25 g N/kg/d. Patients were randomly assigned on a basis of 1:1 by means of a computer program into two groups AG group and control group. Protein + Ala–Gln and Protein containing TPN were labeled identically and the two solutions were indistinguishable. All patients, investigators, and coworkers were unaware of treatment allocation and remained blinded to the treatment allocation until the final statistical evaluation was completed. Patients in the Ala–Gln AG group (40 patients) received 0.5 g/kg/d of Ala–Gln dipeptide (AG) (Dipeptiven, Fresenius Kabi Spain, SA) plus 1.0 g/kg/d of a standard admixture of