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Randomized control trials

The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients—A randomized-controlled clinical study

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SUMMARY

Background & aims: Rapid onset of resistance to insulin is a prominent component of stress metabolism in multiple trauma patients. Recent studies have clarified the role of amino acids (especially glutamine) in glucose transportation and the benefits of parenteral alanyl-glutamine supplementation (0.3–0.6 g/kg/day) in glucose homeostasis. The aims of this study are to evaluate the incidence of hyperglycemic episodes and the need for exogenous insulin to maintain stable glucose levels in critically ill polytrauma patients supplemented with parenteral glutamine dipeptide (Dipeptiven®) versus standard nutritional support.

Methods: This was an open-label randomized-controlled trial of 82 polytrauma patients aged 20–60 years old, randomly assigned into two equal groups independent of sex, age and Injury Severity Score. We excluded patients with diabetes mellitus, or renal or hepatic failure. One group received parenteral Dipeptiven® supplementation of 0.5 g/kg/day and the other received standard isocaloric isoproteinic nutritional support.

Results: We found that 63% of patients in the glutamine-supplemented group had no hyperglycemic episodes; only 37% required exogenous insulin (mean daily requirement of 44 units/day). In the control group, 51% of patients required insulin (mean daily requirement 63 unit/day; $p = 0.0407$).

Conclusions: The effect of glutamine supplementation on glucose homeostasis is associated with a lower incidence of hyperglycemia among critically ill polytrauma patients, and leads to a lower mean daily dose of insulin.

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1. Introduction

Critically ill patients require glutamine supplementation because levels in the plasma and cytosol levels drop significantly [1]. Skeletal muscle provides a constant supply to the circulation of 60–80 g/day. The movement of this amino acid between bloodstream and muscles and its continuous synthesis (from glutamate produced in the liver) prevent toxic build-ups of ammonia [1]. Glutamine assists in cell and organ protection through synthesizing shock proteins [2], and is crucial in critically ill patients at risk of developing post-traumatic multiple organ dysfunction syndrome (MODS) because of inflammatory changes, whereby cells are exposed to various coagulation and inflammatory factors, reactive oxygen species and free radicals.

There is intense catabolism (proteolysis) in critically ill patients. In stressful conditions, muscular efflux of glutamine increases and intracellular sources are depleted for several weeks [3]. In the intensive-care unit (ICU), plasma levels of glutamine usually drop by 20% on the first day, and stay low throughout the critical period [1]. Various studies on glutamine depletion after trauma have found that glutamine level is an independent predictor of prognosis [4–6]. In major trauma patients, with a high mortality risk, short-term prognosis depends on the cause of the trauma,

Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; BMI, body mass index; ICU, intensive care unit; ISS, Injury Severity Score; MODS, multiple organ dysfunction syndrome.

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comorbidities and age, but long-term prognosis can be improved by preventing loss of lean body mass and facilitating recovery [6]. Digestive dysfunction is common, requiring parenteral nutrition. Non-injured tissues become insulin-resistant while injured ones do not [1], thus the 80% of insulin-mediated glucose that is normally taken up by skeletal muscle becomes available to injured tissues. Delivering large amounts of exogenous glucose compromises this mechanism, but failing to administer carbohydrates enhances proteolysis and contributes lean body mass loss [7]. Current guidelines recommend supplementation with both glucose (at least 2 g/kg/day) and insulin [8].

Amino acids are involved in synthesis of acute-phase proteins and promote gluconeogenesis; the enhanced proteolysis reduces muscle mass [1] and influences glucose homeostasis by decreasing metabolic space for glucose. The resulting insulin resistance and hyperglycemia can cause complications. Under stress, both glutamine and glutamate levels influence the activity of beta-cells in the pancreas and promote glucose-stimulated insulin synthesis [9].

Recent studies have found a beneficial effect of parenteral glutamine supplementation with Dipeptiven® (0.3–0.6 g/kg/day) on glycemic homeostasis [10]. The aim of this present study was to investigate the occurrence of hyperglycemia and the insulin requirements of critically ill polytrauma patients and the effect of supplementation with parenteral glutamine (Dipeptiven®) compared to standard nutritional support.

2. Materials and methods

2.1. Patient population

This was an open-label RCT. Inclusion criteria were age of 18 years or over, multiple trauma lesions, Injury Severity Scores (ISS) of 22 or more, and a requirement for early parenteral nutritional support to achieve ESPEN (European Society for Clinical Nutrition and Metabolism) guideline targets for caloric and protein intakes in critically ill patients [8]. Patients were admitted to the ICU of the Clinical Emergency Hospital of Bucharest over a 12-month period between 1 January 2010 and 1 January 2011. Informed consent was obtained from relatives. The study protocol was reviewed by the hospital Ethics Committee, and investigations were conducted according to the Declaration of Helsinki. The number of patients required by the study, calculated by the power analysis, was 100. We excluded patients with diabetes mellitus, or renal or hepatic failure.

2.2. Study design and diet

ESPEN guidelines recommend a caloric goal of 25 kcal/kg/day for critically ill patients within 48–72 h [8]. Our protocol for ICU patients involves providing 30% of total caloric and protein intake on the first day (i.e. 550–600 kcal for a normal 70 kg adult), 60% on the second day (1100–1200 kcal), and 25 kcal/kg/day on the third day. Nutritional support was begun in the patients in this study within 24 h, via both parenteral and enteral routes, because it was not possible to achieve the nutritional target in this group of patients by the enteral route alone.

The parenteral formula comprised standard three-in-one bags containing 3.57 g protein/100 kcal (Kabiven; Fresenius Kabi). The amount given parenterally was calculated daily based on the difference between the caloric goal (for ideal bodyweight) and the energy content delivered enterally, from lipid infusions, propofol, etc. The enteral formula was Fresubin Original containing 3.8 g protein/100 kcal (Fresenius Kabi).

Our protocol requires daily monitoring of the enzymes aspartate aminotransferase and alanine aminotransferase to check for liver dysfunction (doubling in enzyme levels) in conjunction with alternate-day testing of bilirubin (>4 mg/dl), triglycerides (>400 mg/dl), gamma-glutamyltransferase (doubling in concentration) and lipase.

A computer program randomized patients independent of sex, age and ISS to receive parenteral supplementation with N(2)-L-alanyl-L-glutamine dipeptide (0.5 g/kg/day) or standard amino acid solution (0.5 g/kg/day as Aminoven 10%; Fresenius Kabi) in order to achieve the same amino acid intake of 1.3–1.5 g/kg ideal body weight (Table 1) [8].

Glutamine supplementation began alongside nutritional support and was continued for at least 7 days. Patients who were able to take at least 50% of their caloric needs enterally were excluded from the study. The primary outcome measure was blood glucose level, which was measured using the hexokinase method by a Dimension RXL Max (Siemens AG, Germany). It was checked every 4–6 h over 6 days. The desired blood level was 140–180 mg/dl [11]. For hyperglycemia (over 180 mg/dl) insulin was administered continuously via an i.v. pump. Daily insulin requirement was secondary outcome measure [11].

2.3. Statistical methods

Various statistical methods were applied in this study. We used single data point plots to compare plasma glucose levels in the two groups. Analysis of variance (ANOVA) was used to determine glutamine supplementation correlated with the amount of insulin required for glycemic control. We calculated the variance between groups, the variance within groups, the ratio of determination, and confidence intervals. We also monitored decreases in the amount of insulin needed by each patient, and were able to predict a pattern over the 6 days and reduce the amount of insulin gradually.

3. Results

Fig. 1 shows the patient selection process. A total of 506 patients were assessed, but 409 did not meet the inclusion criteria. Of these, 319 did not require early parenteral nutrition, 48 had hepatic or renal dysfunction, and 42 were in under-resuscitated shock after 24 h. The remaining 97 were randomized into two groups and 48 received glutamine supplementation (Group 1). During the 6-day study period, 8 patients died and parenteral supplementation was interrupted in 8 due to hemodynamic instability with metabolic acidosis ($n = 3$) or becoming able to be fed enterally ($n = 4$).

The remaining 41 patient per group (Table 2) provided data for the analysis (Table 2). Mean ISSs (37.22 and 36.61; $p = 0.5$), as were nutritional status on admission (similar mean body mass indexes (BMI) of 18 kg/m^2 vs 28 kg/m^2; $p = 0.5$) and albumin levels of 3.10 mg/dl (SD ± 0.22) and 3.07 mg/dl (SD ± 0.22) ($p = 0.5$). Fig. 2(A) shows mean protein intakes and Fig. 2(B) shows mean calorie intakes of each group over 6 days. We achieved target intakes from the third day by increasing nutrients delivery both the enteral and parenteral route.

Table 1
Nutritional intervention in the two groups.

Nutrient intake (per 24 h)	Group 1 ($n = 41$)	Group 2 ($n = 41$)
	Fed >7 days	Fed >7 days
	Mean (range)	Mean (range)
Amino acids (g/kg)	1.0	1.5
Dipeptiven (g/kg)	0.5	0.0
Carbohydrates (g/kg)	2.0	2.0
Lipids (g/kg)	1.4	1.4

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