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Research Article

Safer Glycemic Control Using a Fructose-Based Enteral Formula: A Randomized Crossover Clinical Trial

Magali CC Kumbier[1], Cassiano Teixeira[2], Suzi Alves Camey[3] and Jussara Carnevale de Almeida[1,4]*

[1]*Graduate Program on Medical Sciences: Endocrinology, Hospital de Clinicas de Porto Alegre, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

[2]*Internal Medicine Department, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil*

[3]*Statistics Departament and Epidemiology Posgraduation Program. Hospital de Clinicas de Porto Alegre. Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

[4]*Nutrition Department, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*

***Corresponding Author:** Jussara Carnevale de Almeida, Graduate Program on Medical Sciences: Endocrinology, Hospital de Clinicas de Porto Alegre, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

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Abstract

Introduction: Glycemic variability during nutritional therapy in critically ill patients is associated with morbidity and mortality. A low-carbohydrate diet can be help avoid glycemic oscillation in patients under enteral nutrition; however, it is unclear whether the presence of fructose interferes with glycemic variability.

Aim: Our study aimed to evaluate the effect of two diabetes-specific diets (fructose-based versus maltodextrin-based) on the glycemic variability of critically ill patients.

Methods: This was a randomized, active-controlled, double-blinded crossover clinical trial comparing diabetes-specific enteral formula with fructose versus without fructose. Patients under enteral nutrition who developed hyperglycemia during their intensive care unit stay were included. Patients were randomized to receive one of two diets for 2 days before switching to the other diet. A capillary blood sample was taken every 4 h, and glycemic variability was defined as the difference between each time point.

Results: Twenty-five patients completed both formulas. Patients that underwent the fructose- based diet reduced their glycemic variability by 6.30 mg/dL relative to those that received the maltodextrin-based diet (95%CI -13.86 to 1.26 mg/dL, p = 0.101 for between-group differences). This effect was seen without any complications.

Conclusion: A diabetes-specific enteral formula with fructose had no difference in glycemic variability in critically ill patients versus a diabetes-specific enteral formula without fructose.

Keywords: *Enteral Nutrition; Critically Ill; Fructose; Diabetes Mellitus; Blood Glucose*

Abbreviations

ICU: Intensive Care Unit; GEE: Generalized Estimating Equations

Introduction

Hyperglycemia is an undesired adverse event and an independent risk factor for mortality and morbidity in critically ill patients [1,2]. For example, optimized blood glucose control-similar to early mobilization-might positively influence mechanical ventilation time during an Intensive Care Unit (ICU) stay [3]. However, intensive glycemic therapy, especially insulin therapy, can lead to a fatal hypoglycemic event [4]. Not only hyperglycemia, also variability of blood glucose levels and hypoglycemia has been associated with adverse outcome [1]. Thus, any improvement in patient care towards glycemic control to reduce insulin need could be of interest [5]; carbohydrate manipulation on enteral or parenteral nutrition is some of the most investigated therapies [6].

Comparisons between diabetes-specific enteral formulas and standard enteral formulas have been published. A specialized diet might result in better glycemic control [7-9] and exogenous insulin reduction than standard formulas [10,11]. Specialized formulas are typically higher in fat and lower in carbohydrates (around 34 - 45%); they may or may not have fructose in their composition [10]. Fructose is a natural nutrient found in fruits [12]. There is currently significant interest in the role of fructose in the diet because it is an additive in foods and beverages. Data suggests that replacement of either glucose or sucrose by fructose results in a significantly lowered peak postprandial blood glucose and insulin concentrations-particularly in hyperglycemic non-critical care patients. Also, the isoenergetic replacement does not result in a substantial increase in blood triglyceride concentrations [13].

Diabetes-specific enteral formulas can have various proportions of macronutrients and carbohydrate types. More interestingly, despite the apparent advantage of this type of diet for glycemic control in critically ill patients, there is limited evidence for formulations [9,14-16]; thus, there is no consensus on which is more effective for glycemic control during intensive care.

Thus, we conducted a randomized controlled crossover clinical trial comparing diabetes- specific enteral formula with and without fructose in critically ill patients.

Aim of the Study

The aim of this clinical trial was to evaluate the effect of two diabetes-specific diets on glycemic variability-the primary outcome of this study. We hypothesized that patients under a fructose-based diet would present lower glycemic variability than those on a standard diet.

Methods

Study overview

This is a randomized, double-blind, cross-over design clinical trial conducted in a mixed ICU (general, neurologic and cardiologic) in a tertiary hospital in southern Brazil. The study protocol was approved by the Institutional Review and Ethics Board and registered at the clinicaltrials.gov database (NCT03003507). All the study conception and practices were conducted based on the Declaration of Helsinki principles for the research with human beings related to ethical standards.

Eligibility criteria and recruitment patients

For our eligibility criteria, patients needed to be 20-years-old or more under an exclusive enteral diet regimen and with hyperglycemia due to diabetes history or stress-induced; this was defined by an any time capillary blood sample ≥ 180 mg/dL [6]. Exclusion criteria were: 1. counter indication for any tested diet such as those with renal or hepatic insufficiency; 2.when the enteral diet was first given via an oral diet (i.e. mixed nutritional therapy); and 3. a partial or total parenteral diet initially complemented the enteral supply. If the patient could not provide consent (e.g. because they were unconsciousness or in a coma), then the family members were contacted and asked to complete an informed consent form to enroll the subject.

To calculate the sample size for this trial, we considered a 35 mg/dL reduction in mean blood glucose concentrations during 48h of feeding to be clinically meaningful. Assuming a standard deviation of 23 mg/dL observed for Egi., *et al*. [14], 80% power at an α level of 0.05, 25 patients were required.

Intervention

The two enteral formulas were iso-caloric and had a similar distribution of carbohydrates comprising about 35% of the total energy. According to manufacturer, the nutritional compositions (per 100 mL) of formula with fructose was 100 kcal of energy, 17% of total energy from protein, 48% of total energy from fat and 35% of total energy from carbohydrates (5.34g of maltodextrin, 1.80g of fructose, and 1.73g of soy polysaccharides), with 1.40g of total fiber. The formula without fructose (maltodextrin-based) composition (per 100 mL) was 100 kcal of energy, 22% of total energy from protein, 42% of total energy from fat, and 36% of total energy from carbohydrates (maltodextrin) with 1.20g of total fiber.

Twenty-five patients received two different diets: an enteral feeding with or without a fructose-based diet. The order of the diets was randomly assigned by an independent investigator blinded to the outcomes of the study and was performed manually via two opaque envelopes with the same sorting probability. At the time of the draw, there were two opaque envelopes with the starting diet described (maltodextrin-based or fructose-based). The blinded collaborator randomly selected one envelope or another when the patient was included in the study. The patients were observed for four days (based on the average days of hospitalization of patients with enteral diet), and the first diet was offered for two days; the second diet was infused over the following two days.

All patients underwent a standard insulin protocol with blood glucose monitoring every hour. Briefly, patients with blood glucose values > 180 mg/dL received 1.2 IU/hr. The increment of every 20 - 25 mg/dL of blood glucose was adjusted with increasing insulin dose to 0.1 IU/hr. Patients with blood glucose values below 110 mg/dL had a 25 - 50% reduction in insulin dose. In addition, the protocol provided for the suspension of insulin infusion for patients with hypoglycemia < 60 mg/dL (3.3 mmol/L) and more frequent blood glucose monitoring (15 - 30-minute intervals).

We considered that the diet change was unlikely to cause any risks to the patients once they were formulated specifically for glycemic control and individualized according to their proper nutritional demands. No wash-out period was used once patients were under intensive insulin therapy; the patients received both diets sequentially to avoid hypoglycemic events.

The diets were provided by the institution and were previously approved by the hospital internal drug-quality committee; they were already administrated as a routine practice. The researchers involved in the study were blinded to the patient allocation and data analysis. The prescription and dispensation were done by personnel not involved with the study. The nutritional prescription was made by two nutritionists uninvolved with the study, and the formula was dispensed by an uninvolved pharmacist from the hospital. The nursing technician was blinded to the diets by covering the formula and thus avoiding visual identification. There were no accidental unblinding and no protocol deviation (i.e., interruption or diet change) throughout the study.

At the end of the study, patients followed the usual hospital practice according to the internal routing protocol. Enteral feeding was with nasoenteral tube, gastrostomy, or jejunostomy; it was administered at 100% of basal energy expenditure calculated by the simplistic weight-based equation (25 - 30 kcal/kg/d) [17].

Outcomes

The primary outcome was the two days overall glycemic variability defined as the mean of time-by-time variability on capillary blood glucose concentrations obtained by capillary blood sample (i.e. 24 measures along 4 days, ACCU-CHEK Advantage® glucometers).

We collected the samples in the 4-h time frame, and the values were recorded in a specific worksheet on all study days. Insulin and other medications and care were maintained as directed by the attending physician. Serum creatinine, total hemoglobin, hematocrit, and total lymphocyte were also collected at the start and the finish of each diet regimen. Serum creatinine was analyzed by a colorimetric-kinetic assay method. Total hemoglobin, hematocrit, and total lymphocyte were quantitatively analyzed by impedance pulse and flow cytometry in an automatized system; morphological analysis was performed by color smearing (SP1000i, SP10) at the central ICU laboratory.

Statistical analyses

Demographic variables were described by a mean ± standard deviation for continuous variables and by binary frequencies for categorical variables. The treatment effect size data is presented by mean ± 95% CI. The data normality was tested with a Shapiro-Wilk test. Blood glucose variability was calculated by the difference between two consecutive measurements, as follow:

$delta_i = m_{i,j} + m_{i,j+1}$, where $m_{i,j}$ is a measure for diet i at time j, i= 1,2 and j=1, ...,11.Thus, for each diet we get 11 measures and were the variable used in our analysis. The comparison of the delta between the groups and over time was made by the generalized estimating equations (GEE) marginal model technique before all pairwise comparisons of least-squares means. Our fitting was based on a model considering diet, time, and its interaction as candidate factors to modify glycemic variability as performed by the Wald Test. The pre-post comparison for serum markers was performed by the two-tailed paired t-test. All patients were included in all analysis (no missing data). All analyses were performed by the SAS 9.4 program. The level of statistical significance was 5% in a two-tailed manner.

Results

We assessed 360 patients for eligibility; 334 patients were excluded due to total/supplementary parenteral nutrition or supplementary oral nutrition. One patient refused to provide consent (Figure 1). All patients underwent both diets, and no patient was excluded after randomization. The baseline characteristics of the patients are described in table 1.

Variables	Fructose based diet	Maltodextrin based diet	P
n	25 (100%)	25 (100%)	-
Age (years)	77.0 ± 9.8		-
Gender (male)	15 (60.0)		-
Previous Diabetes (yes)	7 (28.0%)		-
Reason for hospitalization			
Infection and/or Respiratory insufficiency	8 (32.0%)		-
Acute Respiratory Distress Syndrome	1 (4.0%)		-
Bronchopneumonia	2 (8.0%)		-
Cardiorespiratory Arrest	2 (8.0%)		-
Sensory depression	2 (8.0%)		-
Stroke	2 (8.0%)		-
Sepsis	1 (4.0%)		-
Traumatic Brain Injury	1 (4.0%)		-
Multiple Myelomas	1 (4.0%)		-
Subarachnoid Hemorrhage	1 (4.0%)		-
Chronic Obstructive Pulmonary Disease	1 (4.0%)		-
Hydrocephalus	1 (4.0%)		-
Polyneuropathy	1 (4.0%)		-
Intestinal Sub-occlusion	1 (4.0%)		-
Death (yes)	12 (48.0%)		-
Actual body weight (kg)	69.8 ± 20.2		
Basal glucose (mg/dL)	227 ± 104	194 ± 72	0.398
Mean blood glucose values (mg/dL)	167 ± 49	170 ± 57	0.500
Serum creatinine (mg/dL)	1.3 ± 0.5	1.4 ± 0.7	0.386

Table 1: *Demographic data and subject characteristics at baseline.*
Data were described as mean ± DP, number (% of total cases) or median and interquartile range.

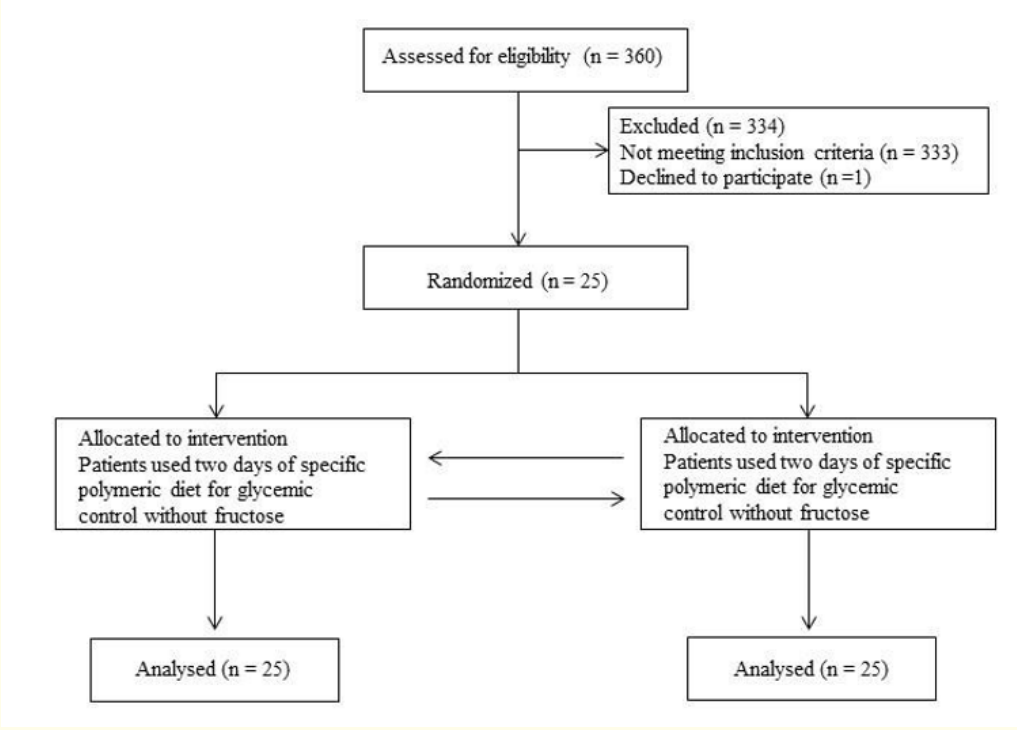

Figure 1: *Study flow chart. Enrollment, randomization, follow-up and analysis of the study participants.*

The mean age of the patients was 77.0 ± 9.8 years, and body mass index was 25.0 ± 5.8 kg/m^2: (60% of them were male, and 72% patients did not have previous diabetes). The main reason for admission to the ICU was the diagnosis of respiratory failure (32%); 12 patients (48%) died during the study regardless of diet regimen. All patients used mechanical ventilation.

In relation to drug use, 13 patients (52%) were administered corticosteroids, and five patients (20%) underwent hemodialysis therapy. All patients who used steroids (52%) and hemodialysis (5%) maintained their use during the infusions of both diets. There was no initiation or discontinuation at any time during the four days. The daily caloric intake of patients was not different between fructose-based diet period as compared to the maltodextrin-based diet period (1,345 ± 255 *vs.* 1,314 ± 189 kcal/day; P = 0.981).

The mean blood glucose of the patients during the fructose diet was 167 ± 49 mg/dL and 170 ± 57 mg/dL during the maltodextrin diet (P = 0.500). Also, basal glucose values were not different between fructose diet (227 ± 104 mg/dL) and maltodextrin diet (194 ± 72 mg/dL; P = 0.398). The marginal fitting model was used to detect an effect on time ($p < 0.001$) but no independent effect for diet ($p = 0.1$) and no interaction effect between diet and time ($p = 0.11$). The mean glycemic variability observed in patients fed the fructose-based diet was 33.5mg/dL (minimum of 1.0 to 177.0 mg/dL). This was 40.1 mg/dL (minimum of 1.0 to 298.0 mg/dL) in patients fed maltodextrin-based diet (Figure 2). All patients tolerated the protocol feeding- there were no adverse effects such as diarrhea, regurgitation, vomiting, or hypoglycemic episodes. [The hypoglycemia alert value in hospitalized patients is defined as blood glucose < 60 mg/dL (3.3 mmol/L)]. There were no complications related to feeding or blood glucose monitoring. The diets were administered as a continuous infusion throughout the study period.

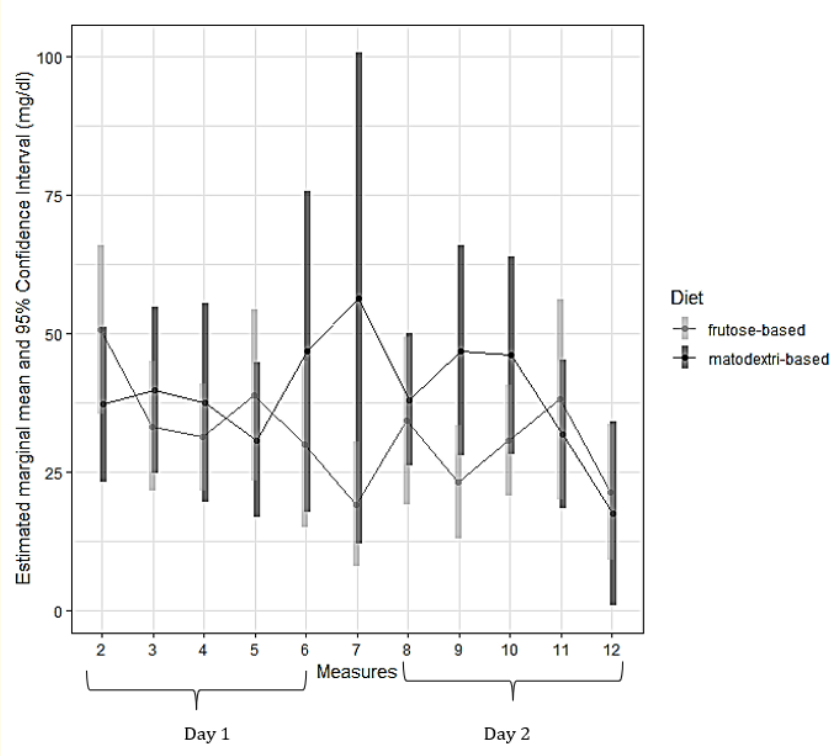

Figure 2: *Glycemic variability- The blood glucose variability was calculated by the difference between two consecutive measurements (delta$_j$) in 25 patients given a diabetes-specific enteral formula fructose-based diet (grey line) or a maltodextrin-based diet for two days (black line). A reduction in glycemic variability for the fructose diet of 6.30 mg/dL relative to those that received the maltodextrin-based diet (95%CI -13.86 to 1.26 mg/dL, p = 0.101 for between-group differences).*

Discussion and Conclusion

This randomized controlled crossover study demonstrated that the fructose-based diet by enteral feeding no significantly reduced the glycemic variability of critically ill patients relative to a maltodextrin-based diet. To our knowledge, no previous study has evaluated glycemic control via a fructose-based enteral diet versus a maltodextrin-based control in critically ill patients. Around 75% of critically ill patients have used exclusive enteral feeding according to the international multicenter study [18]; therefore, this study has high clinical applicability because our study only included patients with enteral nutrition.

Specialized enteral formulas (with fructose) for glycemic control seem to show better effect in glycemic control versus standard diets [15,19]. However, the null effect between the two specific diets (with and without fructose) in glycemic variability of critically ill patients has been demonstrated in the only one randomized clinical trial [10].

We found no adverse events regarding blood glucose homeostasis unlike other studies [5,15,19]. Hypoglycemic events are undesired in the ICU-especially in patients under continuous sedation where the symptoms become difficult to recognize; an extensive episode could lead to a permanent cerebral lesion [17]. In this context, both diets are considered safe.

A potential limitation of the present study is that it does not include a washout period. Although this effect is not likely to last for more than a few hours, it may still bias/alter the early glucose measurements immediately after crossover and the short-term follow-up. However,

a 48- h period can be considered an adequate time in the ICU because the changes are immediate in these patients. Another limitation is glucose measurement error-especially with capillary measurements performed by glucometers. The lack of daily insulin dose information per patient is a limitation too. Finally, there is a limitation on the external validity of the study because this was a single center randomized clinical trial in a very specific population.

In summary, we conclude no difference in glycemic variability in critically ill patients as a function of diabetes-specific enteral formula (with and without fructose). Another randomized clinical trial needs to be performed considering the possible reduction of insulin use and hard outcomes such as mortality or length of hospital stay. Also, the analysis of cost-effectiveness is needed to support a possible recommendation from the use of this nutritional therapy in the management of critically ill patients.

Financial Disclosure

None declared.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

Clinical Trial Registry

www.clinicaltrials.gov: NCT03003507.

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