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Provision of Balanced Nutrition Protects Against Hypoglycemia in the Critically Ill Surgical Patient

Rondi M. Kauffmann, MD, MPH*, Rachel M. Hayes, BSN, PhD**, Judith M. Jenkins, MSN*, Patrick R. Norris, PhD*, Jose J. Diaz, MD, CNS, FACS, FCCM*, Addison K. May, MD, FACS, FCCM*, and Bryan R. Collier, DO, CNSP, FACS*

*Division of Trauma and Surgical Critical Care, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

**Informatics Center, Information Integration Technology, Vanderbilt University Medical Center, Nashville, TN

Abstract

Background—Intensive insulin therapy lowers blood glucose and improves outcomes, but increases the risk of hypoglycemia. Typically, insulin protocols require a dextrose solution to prevent hypoglycemia. We hypothesized that the provision of balanced nutrition (enteral or parenteral nutrition) would be more protective against hypoglycemia (< 50 mg/dL) than carbohydrate alone.

Methods—A retrospective analysis was performed of patients treated with intensive insulin therapy and surviving > 24 hours. The computer-based insulin protocol requires infusion of D10W at 30 ml/hr if enteral or parenteral nutrition is not provided. Nutritional provision was assessed in two -hour increments, comparing periods of blood glucose control with and without balanced nutrition. The risk of hypoglycemia for each BG measurement was estimated by multivariable regression.

Results—66,592 glucose measurements were collected on 1392 patients. Hypoglycemia occurred in 11.1% patients and 0.32% of glucose measurements. Hypoglycemic events occurred in 5.8/1000 glucose tests after two hours without balanced nutrition compared to 2.2/1000 tests when balanced nutrition was given in the preceding two hours. In multivariable regression models, balanced nutrition was the strongest protective factor against hypoglycemia. Patients who did not receive balanced nutrition in the preceding two hours had a 3X increase in odds of a hypoglycemic event at their next glucose check (OR 3.6, p<0.001). Providing carbohydrate alone was not protective.

Conclusions—Balanced nutrition is associated with reduced risk of hypoglycemia. These results suggest that balanced nutrition should be given when insulin therapy is initiated. Future studies should evaluate the efficacy of enteral nutrition versus total parenteral nutrition in preventing hypoglycemia, and associations between balanced nutrition and mortality.

Corresponding Author: Rondi Kauffmann, MD, MPH, Division of Trauma and Surgical Critical Care, Vanderbilt University Medical Center, 404 MAB, 1211 21st Avenue South, Nashville, TN 37212, Phone: 615-936-0177, Fax: 615-936-0185, rondi.kauffmann@vanderbilt.edu.

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Conflict of Interest Statement

The authors do not have any conflicts of interest directly related to the writing of this manuscript.

Keywords

Parenteral Nutrition; Enteral Nutrition; Critical Care; Outcomes Research/Quality

INTRODUCTION

Hyperglycemia in the critical care setting has been shown to increase morbidity and mortality in diverse patient populations^[1–5], and intravenous insulin therapy to control hyperglycemia decreases infectious complications and mortality^[6–11]. Concerns remain, however, regarding high rates of hypoglycemia in patients treated with intensive insulin therapy (IIT) to maintain tight glucose control (80–110 mg/dL)^[12–19].

Several factors have been associated with increased risk of hypoglycemia, including time on IIT^[20], need for dialysis, history of diabetes, sepsis, need for vasopressors, and BMI^[21–23]. Although the landmark study advocating IIT by Van den Berghe et al provided a calculated glucose infusion within the first 24 hours and provided either total parenteral nutrition (TPN) or enteral nutrition (EN) by the second day^[9], little emphasis has been given to the role of nutritional provision in improving outcomes in patients treated with IIT. Differences in patient nutrition between studies confound clear conclusions regarding the benefits and risks of IIT^[24, 25]. In particular, Van den Berghe's study showing improved outcomes with IIT provided balanced nutrition (BN) very early in patients' intensive care unit (ICU) courses. We hypothesized that the provision of BN (EN or TPN) would be more protective against hypoglycemia (< 50 mg/dL) than carbohydrate alone.

MATERIALS AND METHODS

A retrospective analysis of a prospectively collected dataset was performed on a cohort of critically ill surgical patients who were admitted to the SICU of a tertiary care, academic medical center from June 2006 to September 2009 and received IIT.

Insulin Protocol and Blood Glucose Measurements

Vanderbilt University Medical Center uses a computerized, automated care provider order entry (CPOE) system to provide the recommended intravenous insulin infusion rate as previously published^[26, 27]. All critically ill, mechanically ventilated patients with serum blood glucose (BG) values above 110 mg/dL are placed on this intravenous computerized insulin protocol to direct the management of glycemic control with a glucose target range of 80–110 mg/dL. Blood glucose measurements are performed every two hours by trained nurses using the SureStep® Pro (OneTouch®) (Lifescan, Inc., Milpitas, CA) Professional Blood Glucose Monitoring System. The CPOE algorithm uses a modification to a protocol described by White et al.^[28] and Bode et al.^[29] with doses computed using the following formula:

$$\text{Insulin dose (units/hr)} = (\text{Multiplier}) * [\text{blood glucose (mg/dL)} - 60].$$

The Multiplier is a variable that is initially set at 0.03 and adapts according to a set protocol. It can never fall below zero. Blood glucose values exceeding the high target threshold on two consecutive BG measurements, or exceeding 200 mg/dL on one reading, trigger a multiplier increase of 0.01. Blood glucose values below the low target threshold decrease the multiplier by 0.01, and BG values below 60 mg/dL decrease the multiplier by 0.02. When BG values fall below the low target threshold, the protocol orders a calculated dose of intravenous 50% dextrose to correct or prevent hypoglycemia. The intravenous insulin

infusion is simultaneously withheld for two hours. Insulin is dispensed by the pharmacy as 150 units of regular insulin in 150 mL of normal saline (1U/1mL concentration). Blood glucose levels are measured at least every two hours for patients who are not hypoglycemic, and every hour for patients with a recent hypoglycemic episode. The protocol requires infusion of D10W at 30 ml/hr if the patient is not receiving either EN or TPN, to protect against hypoglycemia.

Nutrition Protocol

All patients admitted to the surgical intensive care unit (SICU) and placed on IIT receive nutritional provision of D10W @ 30 ml/hr. Enteral nutrition at ½ goal rate (as determined by ideal body weight, degree of critical illness and caloric need) is begun within 48 hours of admission, if the patient is able to tolerate EN. If full EN is not tolerated, TPN is begun by the 5th day after SICU admission. Clinical nutritionists provide daily bedside management of individual nutrition needs for all patients in the SICU.

All patients admitted to the SICU receive critical care consultation and management by a multidisciplinary critical care team including Critical Care boarded faculty, designated residents, nutritional specialists, and PharmD until discharge from the ICU. Patient care management is directed by evidence-based practice management guidelines developed and approved by the critical care faculty.

Inclusion criteria consisted of treatment with a computerized IIT protocol to maintain euglycemia (80–110 mg/dL) and remaining on protocol for at least five BG measurements and 12 hours. Patients who died within 24 hours of admission to the ICU were excluded. This study was approved by the Institutional Review Board.

Data Collection

Patient factors including gender, age, weight, date of hospital and ICU admission, mortality, Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission, and diagnosed diabetes were obtained from the electronic health record and the SICU registry. The SICU registry is an IRB-approved repository of clinical data that is prospectively collected and maintained on every patient admitted to the SICU. Patient weight was missing for 92 patients (6.6% of the study group) and was imputed to the population median (85 kg) and APACHE II score was missing for 43 patients and imputed to the population median (22). All components of the insulin protocol (BG values, test times, insulin dose, multiplier, adherence to IIT protocol, and treatment with a dose of 50% dextrose) are recorded prospectively, and each eligible patient had multiple recorded BG measurements. Blood glucose measurements during the first 12 hours (induction phase) on the IIT protocol were excluded, as were protocol interruptions >6 hours. Because BG levels are not normally distributed, BG values were transformed for analysis^[30]. Time variable data for each patient included data from the IIT protocol, current vasopressor use, and current nutritional provision.

Nutrition including dextrose, TPN, EN, and lipids (including propofol) was recorded every hour and administrations in the two hours prior to the BG test were summed. Nutrition sources included dextrose-containing intravenous fluids (IVF), propofol-containing IVF, enteral nutrition, and TPN. Oral intake, which was very rare, was excluded. Balanced nutrition (BN) was defined as either the provision of TPN (with or without lipids), or EN.

Statistical analysis

Continuous variables that were normally distributed were summarized by reporting the mean and standard deviation, and compared using a two-sample t-test. Continuous variables that

were not normally distributed were summarized by reporting the median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test. Differences in proportions were compared using the χ^2 test. Multivariable logistic regression models were fit to predict hypoglycemia at the next BG test based on nutrition over the past two hours and age, weight, time since previous BG measurement, count of previous hypoglycemic events, diagnosed diabetes, gender, current vasopressor use, hours on IIT, and baseline APACHE II score. For purpose of the analysis, a severe hypoglycemic event was defined as BG ≤ 50 mg/dL in order to maximize power (a cut point of 40 mg/dL provided too few hypoglycemic patients to allow robust modeling) while still selecting a BG level that would be expected to be clinically important. We focused on the occurrence of severe hypoglycemia, rather than the more mild form of hypoglycemia used by our IIT protocol, in which BG values of ≥ 60 mg/dL are treated with D50 to treat or prevent hypoglycemia. Measurements of BG and time between successive BG measurements were calculated using data beginning at 12 hours after insulin therapy initiation to allow for stabilization on the IIT protocol. Blood glucose values are repeated measures within patients and this correlation must be accounted for within the model to prevent overly optimistic standard errors. Therefore, robust covariance estimates using the Huber-White method to adjust the variance-covariance matrix for clustered data are presented^[31, 32]. Model terms included diagnosed diabetes, patient age (4 knot spline), gender, weight (3 knot spline), current vasopressor use in the two hours preceding the index measurement, time elapsed from the previous BG test, the cumulative count of previous “near-miss” hypoglycemic events (BG ≥ 60 mg/dL), and provision of BN (mL) in the two hours preceding the index BG measurement. The inclusion of “near-miss” hypoglycemic episodes was included in the model in order to determine the association between previous episodes of mild hypoglycemia with subsequent risk of severe hypoglycemia. Patient weight, rather than BMI, was included in the model due to missing height values for patients early in the study period. Variables were fit as restricted cubic splines where relationships were non-linear^[33]. The model was cross-validated with 40 data segments using the R RMS package^[33]. All confidence intervals (CI) are at the 95% level, and a two-sided p value of <0.05 indicated statistical significance. Analysis was performed using R version 2.11.0 (www.r-project.org).

RESULTS

During the study period, a total of 78, 136 BG measurements were collected on 1392 patients. After excluding BG measurements taken in the first 12 hours after SICU admission and following 6 hour gaps in IIT treatment, 66, 592 BG measurements (85.2%) remained for analysis and modeling. Hypoglycemia (≤ 50 mg/dL) occurred in 154/1392 patients (11.1%) and 226 (0.32%) of BG measurements. Demographics and clinical characteristics of those who experienced one or more hypoglycemic events at some point during their SICU stay compared to those who did not are displayed in Table 1. Patients who experienced a hypoglycemic episode were older, weighed less, were sicker (higher APACHE II score and had an increased length of stay (LOS)), with higher maximum glucose, and higher mortality.

Blood Glucose Control

During the study period, nearly half of the BG values recorded fell in the IIT target range of 80–110 mg/dL, indicating that the computerized tool functions well to control BG in a narrow range (Table 2). Nearly 85% of values fell between 80–150 mg/dL. Only 0.3% of values fell below 50 mg/dL for an overall hypoglycemic rate of 11.1% of patients. A total of 9.2% of values were hyperglycemic in the >150 mg/dL range.

Nutritional Provision by Patient

Nutritional provision over the course of the entire SICU stay was examined first by studying nutritional provision provided each patient. Nearly half (48.7%) of eligible patients admitted to the SICU during the study period did not receive BN during their SICU course. These patients received dextrose and/or propofol only. The remaining 51.3% received BN (either EN and/or TPN during their SICU stay, with or without dextrose and/or propofol). Of the 714 patients who received BN, 244 (34.2%) were given EN only, 135 (18.9%) were given TPN only, and 335 (46.9%) were given both EN and TPN (Figure 1, Table 3).

Demographics and clinical characteristics of patients who received BN sometime during the course of their SICU stay compared to those who did not are displayed in Table 4. Baseline demographics (including gender, race, and weight) did not differ between groups. Patients who were provided BN at some time during their overall SICU stay were sicker, as evidenced by higher APACHE II, longer length of stay, increased mortality, infections, number of ventilator days, and number of transfusions. Patients provided BN at some time during their overall SICU stay were also older, with higher rates of hypoglycemia in univariate analysis. Interestingly, fewer diabetic patients received BN during their SICU stay than non-diabetic patients.

Nutritional Provision by Blood Glucose Measurement

The relationship between hypoglycemia and nutritional provision over time was then evaluated by studying the rates of hypoglycemia based upon whether BN was provided in the two hours preceding each individual BG measurement. Hypoglycemic events occurred in 5.8/1000 BG tests after two hours without BN compared to 2.2/1000 BG tests when BN was given in the preceding two hours (Table 5). During periods when BN was not provided in the preceding two hours, patients had a more than three-fold increase in odds of experiencing a hypoglycemic event at their next BG check versus times when BN was provided (OR 3.6, p-value<0.001).

Multivariable Regression Models

A multivariable logistic regression model was fit with occurrence of hypoglycemia at the next BG measurement as the outcome of interest. Odds ratios for predictors with confidence intervals based on robust covariance estimates are presented in Table 6. The provision of balanced nutrition in the preceding two hours was the strongest protective factor against hypoglycemia. While the provision of balanced nutrition is independently protective against hypoglycemia, increasing age, lower weight, longer BG measurement intervals, and previous hypoglycemic events were all associated with higher risk. Baseline severity of illness, gender, vasopressor use, history of diabetes, hours on IIT protocol, and provision of dextrose, lipids or propofol in the preceding two hours were not independently associated with hypoglycemia when controlling for provision of balanced nutrition, weight, and time between measurements.

DISCUSSION

The use of IIT to control BG is an important component of the care of the critically ill surgical patient. Controversy remains regarding appropriate targets for glycemic control, and concern over rates of hypoglycemia and possible influence on outcome persists. We sought to determine whether the provision of BN may alter a patient's risk of hypoglycemia.

The association between nutritional provision and hypoglycemia has not been well-studied, although many IIT protocols require the concurrent provision of a dextrose-containing fluid in order to minimize the risk of hypoglycemia. Elia et al. reported no difference in overall BG control between patients provided EN vs. TPN, and that hypoglycemia usually occurred

during unplanned interruptions in EN^[25]. Although inadequate nutrition appears to increase the risk of hypoglycemia^[34, 35], previous studies have not evaluated whether the type of calories provided is associated with subsequent risk of hypoglycemia.

The analysis presented suggests that the provision of BN, to include carbohydrate and protein, is important in protecting against hypoglycemia over time. Even the provision of hypocaloric nutrition protects against hypoglycemia. Factors identified to be independently associated with subsequent hypoglycemic events include previous episodes of “near-miss” hypoglycemia (< 60 mg/dL), time since the previous BG measurement, the provision of BN in the last two hours, and patient weight. During the time that BN is not provided, patients are at a three-fold higher risk of hypoglycemia at their next BG check than periods during which BN is provided, regardless of the route of administration. Furthermore, provision of fat or carbohydrate calories alone does not afford the same protection against hypoglycemia. Although hypoglycemia’s contribution to the risk of mortality remains uncertain, with studies yielding conflicting results^[36–38], the need to minimize hypoglycemia to protect patient’s from possible adverse outcomes is well-accepted.

In multivariate analysis, the provision of BN in the preceding two hours was protective against hypoglycemia. Lipids, propofol, and a dextrose-containing fluid were not protective against hypoglycemia. Although it is possible that the protective effect of BN is due solely to the increased amount of dextrose provided relative to a dextrose-containing IVF, the combination of carbohydrate plus protein appears to be important in protecting against hypoglycemia. Additional studies should focus on elucidating the role played by the addition of protein to carbohydrate in protecting against hypoglycemia. Fat calories alone do not protect against hypoglycemia.

The univariate findings that patients who receive BN at some point during their critical illness have longer LOS, higher mortality rates, higher rates of infection, more transfusions, and more ventilator days are not surprising. This likely represents sicker patients, who are in the ICU longer, and therefore are more likely to be placed on BN at some point over the course of their stay. Furthermore, the fact that overall rates of hypoglycemia during the course of the SICU stay are higher in patients who receive BN at some point during their SICU stay in univariate analysis is also expected, as patients who stay on an IIT protocol in the ICU for longer have more opportunity to become hypoglycemic due to longer time on IIT. When controlling for hours on IIT and illness severity in multivariable logistic regression models, the provision of BN was PROTECTIVE against hypoglycemia occurring at the next BG measurement. It is certainly interesting that in univariate analysis, diabetic patients are less likely to be placed on BN over the entire course of their SICU stay. This may be due to concern that provided EN or TPN will cause further hyperglycemia in patients who are hyperglycemic at baseline, leading to a delay in initiating BN. Additional investigation is needed to elucidate these practice differences.

Table 1 shows that hyperglycemia is more pronounced in patients experiencing a hypoglycemic episode. This may be due simply to higher severity of illness, as demonstrated by a higher average APACHE II score. However, we have also previously shown that increased BG variability is associated with higher risk of hypoglycemia^[39]. Thus, it may also be that the increased hyperglycemia noted in patients who experience a hypoglycemic event reflects this overall instability of BG control. Additional studies are needed to elucidate the association between BN and hyperglycemia.

Figure 1 shows the distribution of nutritional provision over the courses of patients’ entire SICU stays. The fact that 48.7% of patients never received either EN or TPN likely represents patients who recover quickly from their surgical insult, and are either started on

oral enteral nutrition (which was not captured or analyzed in our study), or are discharged from the SICU. The remaining 51.3% of patients received either EN or TPN during the course of their SICU stay. Of note, only 17.5% of patients in the total study population received EN only, which is the current recommendation per A.S.P.E.N. guidelines. This likely reflects the high acuity of patients treated in our institution's SICU. Patients' average APACHE II score is around 20, reflecting a sick patient population requiring a high level of care. Furthermore, post-operative patients often do not tolerate enteral nutrition for several days, either due to recent gastrointestinal surgery and subsequent ileus, or do to critical illness itself. These patients have a high likelihood of requiring TPN at some point during their SICU stay, as reflected by the fact that nearly 10% of the total study population received TPN only, and nearly 25% of the total study population received both EN and TPN. In addition, it is not uncommon for patients in our SICU to be started on TPN during the period of post-operative ileus, only to be transitioned directly to oral enteral nutrition (and therefore, not the tube feed form of EN) once their ileus resolves.

The findings that time since previous BG measurement is independently associated with hypoglycemia are consistent with our previous work that demonstrated a 3% rate of BG less than 60 mg/dL if blood sample analysis extended beyond three hours and only 1% if it did not^[40]. Our protocol calls for analysis at least every two hours, regardless of glucose range and stability. A recent randomized study of nurse titration every two hours with and without the availability of every five minute glucose values also demonstrated that more frequent glucose analysis can reduce severe hypoglycemia (1.6% intervention vs. 11.5 % control, $p = 0.031$)^[41].

The strengths of this study include its large sample size, robust data collection into a centralized data warehouse, and effectiveness of the computerized IIT protocol in both bringing patients into target range. There are several important limitations however. First, as with any retrospective, uncontrolled analyses, causality cannot be inferred. The absence of BN, as an effect of increased disease severity, or a contributing cause, cannot be determined from this data. Additionally, patients who receive BN are sicker, as evidenced by longer LOS, higher infection rates, more transfusions, more ventilator days, and higher mortality. Although the multivariable model corrected for time on protocol, the potential for bias remains given that sicker patients were more likely to be provided BN. In addition, the precise caloric content of both EN and TPN are individualized, therefore, the total calories of carbohydrate, fat, and protein provided to each patient cannot be ascertained from this analysis. Furthermore, APACHE II score at SICU admission was used to control for severity of illness. However, patient condition can change, such that BN (and particularly EN) is held as patients become more severely ill. Therefore, daily severity of illness scores would likely be a better means of controlling for severity of illness in our multivariate regression model. Daily severity of illness scores are not widely utilized in our SICU however, and therefore were not available for our study population. Any future prospective study to evaluate the association between BN and hypoglycemia should include the calculation of severity of illness scores on a daily basis, as a means of controlling for severity of illness in regression models. Finally, APACHE II scores and weight were imputed for patients with missing values, thus introducing potential bias if true values differed significantly from imputed values.

CONCLUSIONS

The early provision of EN in combination with glycemic control remains the standard of care for critically ill surgical patients. When EN cannot be provided however, the provision of intravenous BN, including carbohydrate and protein, should be initiated to guard against hypoglycemia. From the standpoint of safer insulin therapy, BN, either EN or TPN, should

begin when IIT is initiated. This data supports the use of a dextrose plus protein fluid source with IIT, rather than a dextrose fluid only. Future studies should evaluate the efficacy of EN versus TPN in preventing hypoglycemia, the differential effects of dextrose, fat and protein in preventing hypoglycemia, and associations between BN and outcomes including mortality and infection risk.

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Abbreviations

BG	Blood Glucose
BN	Balanced Nutrition
CPOE	Computerized Provider Order Entry
EN	Enteral Nutrition
IIT	Intensive Insulin Therapy
LOS	Length of Stay
SICU	Surgical Intensive Care Unit
TPN	Total Parenteral Nutrition

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Clinical Relevancy Statement

Hyperglycemia in the intensive care unit increases morbidity and mortality. For this reason, intravenous insulin therapy has been used to control hyperglycemia. Concerns remain, however, regarding high rates of hypoglycemia in patients treated with intensive insulin therapy to maintain tight glucose control. Since the first study on the association between intensive insulin therapy and outcomes by Van den Berghe et al, little emphasis has been given to the role of nutritional provision in improving outcomes in patients treated with intensive insulin therapy. We have shown that the provision of balanced nutrition (enteral nutrition or total parenteral nutrition) is more protective against hypoglycemia (< 50 mg/dL) than carbohydrate alone. Furthermore, our data suggests that, from the standpoint of safer insulin therapy, balanced nutrition (either enteral nutrition or total parenteral nutrition), should begin when intensive insulin therapy is initiated.

Figure 1.
Flowchart of patients' nutritional provision over their entire SICU stay, expressed as percentage of the entire population.

Table 1**Patient demographics**

There are 1,392 eligible patients and 66,592 distinct blood glucose test results.

	Ever Hypoglycemic n= 154	Never Hypoglycemic n= 1238	p-value
Age in yrs	60.7 (14.3)	58.2 (14.5)	0.04
% Males	58.4	59.7	0.8
Patient weight in kg	81.3 (26.2)	87.4 (26.6)	0.01
% History of diabetes	26.6	33.4	0.11
APACHE II	21 (16–25)	19 (15–23)	0.001
Hospital LOS	22.6 (14.2–35.1)	12.5 (7.6–21.1)	<0.0001
ICU LOS	14.8 (8.7–24.5)	5 (2.9–9.9)	<0.0001
Average blood glucose *	109 (105–114)	108 (101–117)	0.9
Max glucose	197 (169–239)	150 (126–185)	<0.0001
% Mortality	24.7	12.5	<0.0001

* For average blood glucose, the median transformed blood glucose was determined for each patient. The values in this table represent the back-transformed median and IQR of these values by outcome.

Bold values indicate statistical significance

Table 2

Blood Glucose Control by Blood Glucose Test

Blood Glucose Category	Count of Blood Glucose Tests (%)
<=50 mg/dL	208 (0.3)
51–80 mg/dL	4,155 (6.2)
81–110 mg/dL	29,895 (45.0)
111–150 mg/dL	26,182 (39.3)
151–200 mg/dL	5,198 (7.8)
>200 mg/dL	954 (1.4)

Table 3

Nutrition provision at the patient and blood glucose test level; patients are classified by whether they received BN at any point during their SICU stay and which type of BN was provided; blood glucose tests are classified by nutrition provision in the preceding two hours

	No TPN/no EN	EN only	TPN only	TPN and EN
Patients (%)	678 (48.7)	244 (17.5)	135 (9.6)	335 (24.1)
Blood glucose tests (%)	16,682 (25.1)	18,370 (27.6)	21,672 (32.5)	9,868 (14.8)
Median (IQR) count of BG tests per patient	10 (5–18)	21 (8–48)	30 (13–58)	21 (11–37)

Table 4

Demographic and Clinical Characteristics of patients who received balanced nutrition during the course of their entire SICU stay compared to patients who did not

	Patients who <u>DID</u> Receive Balanced Nutrition During Their SICU Stay n=714	Patients who <u>DID NOT</u> Receive Balanced Nutrition During Their SICU Stay n=678	p- value
Male (%)	417 (58.4)	412 (59.0)	0.4
White (%)	601 (84.2)	551 (81.3)	0.17
Mortality (%)	155 (21.7)	38 (5.6)	<0.001
Any infection (%)	255 (35.7)	18 (2.6)	<0.001
Ventilator days	8.2 (4–15.3)	1.3 (0.9–2.2)	<0.001
Transfused (%)	583 (81.6)	427 (63.0)	<0.001
Diagnosed diabetes (%)	196 (27.4)	259 (38.2)	<0.001
Ever hypoglycemic (%)	136 (19.0)	18 (2.6)	<0.001
Patient age	61 (51–71)	58.5 (50–66)	<0.001
Patient weight (Kg)	80.2 (68.2–98.2)	82.4 (70.1–100.0)	0.12
Hospital LOS (days)	20.3 (13.6–29.8)	8.4 (6.3–12.8)	<0.001
ICU LOS (days)	11.1 (6.9–18.2)	3.2 (2.1–4.5)	<0.001
APACHE II score	20 (16–25)	18 (14–22)	<0.001
Average BG*	110 (104–115.4)	107.4 (97.7–119.13)	<0.001
Median (IQR) count of BG tests	68 (35–120)	14 (10–21)	<0.001

* For average blood glucose, the median transformed blood glucose was determined for each patient. The values in this table represent the back-transformed median and IQR of these values by outcome.

Bold values indicate statistical significance

Table 5

Association between TPN or EN administration in the preceding two hours and hypoglycemic event (BG 50 mg/dL) at the blood glucose test level

	BG > 50 mg/dL	BG 50 mg/dL	Event rate per 1000 BG tests
BG tests when patient not on EN or TPN in the preceding two hours (%)	16,919 (99.4)	98 (0.6)	5.79
BG tests when patient receiving EN or TPN in the preceding two hours (%)	49,673 (99.8)	110 (0.2)	2.21

Table 6

Model covariates with odds ratios and 95% confidence intervals based on robust covariance estimates

Predictors independently associated with hypoglycemia at next BG measurement	Exposure	OR	95% CI
Tube feeding in previous 2 hours (mL) *	IQR (0–70)	0.38	0.24–0.6
TPN in previous 2 hours (mL) *	IQR (0–104)	0.22	0.13–0.38
Patient weight (kg) *	IQR (70–103)	0.75	0.57–0.98
Patient age (yrs) *	IQR (51–70)	1.58	1.03–2.42
Minutes from last BG test *	IQR (49–247)	1.36	1.24–1.49
Count of previous “near-miss” hypoglycemic episodes (60)	0	Reference	
	1	2.12	1.42–3.15
	2	2.49	1.43–4.34
	3 or more	4.91	2.89–8.34

Predictors <u>not</u> independently associated with hypoglycemia at next BG measurement	Exposure	OR	95% CI
Volume 5% Dextrose in previous 2 hours (mL) *	IQR (0–75)	0.79	0.48–1.28
Lipids in previous 2 hours (mL) *	IQR (0–10)	0.86	0.71–1.04
Propofol in previous 2 hours (mL) *	IQR (0–162)	0.94	0.07–13.46
Diagnosed diabetes	Y/N	0.79	0.56–1.12
Female sex	Y/N	1.06	0.77–1.45
Current vasopressors	Y/N	1.0	0.73–1.37
Hours on protocol *	IQR (49–247)	1.01	0.88–1.16
Baseline APACHE II score *	IQR (17–26)	0.9	0.71–1.15

* OR for risk associated with 75th percentile compared to 25th percentile is shown (although variable was entered as a continuous variable in the regression model).