Effectiveness of Regular Versus Glargine Insulin in Stable Critical Care Patients Receiving Parenteral Nutrition: A Randomized Controlled Trial

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Study Objective To compare the effectiveness and safety of two glycemic control regimens in stable critical care patients receiving parenteral nutrition (PN).

Design Prospective, randomized open-label clinical trial.

Methods Eligible postoperative critical care patients in the ICU began PN on the first to the seventh day of ICU admission. The PN admixture included regular insulin, in doses sufficient to maintain 3 or more goal blood glucose (BG) levels between 110 and 180 mg/dl. After 3 to 5 days of PN containing regular insulin, patients were randomized to 3 more days of regular insulin at the same dose or 80% of their total daily regular insulin dose provided in PN solution as glargine insulin. Capillary BG monitoring was performed every 6 hours.

Results Twenty one patients were randomized to each treatment group. Median APACHE II scores were not significantly different between the two groups within the first 24-hour of ICU admission. There were no significant differences between the two groups at day 3 for mean daily dextrose (306.9 ± 46.2 vs. 305.2 ± 52.2 g; p=0.913) or insulin (18.3 ± 8.8 vs. 19.5 ± 10.0 units; p=0.696) doses. The percentage of BG values in the goal (110–180 mg/dl), hyperglycemic (> 180 mg/dl), and hypoglycemic (< 70 mg/dl) BG levels were similar between the two groups (69.0% vs. 66.7%, p=0.567; 11.9% vs. 11.1%, p=0.780; 0% vs. 1.6%, p=0.124, respectively). Mean daily BG levels were not significantly different between the two groups on each of the 3 study days (day 1: 140 ± 20 vs. 131 ± 25 mg/dl, p=0.194; day 2: 136 ± 20 vs. 140 ± 18 mg/dl, p=0.498; day 3: 142 ± 15 vs. 140 ± 19 mg/dl; p=0.741).

Conclusion These data suggest that, compared with regular insulin added to PN, glargine insulin results in similar glycemic control and rates of hyperglycemia and hypoglycemia in stable critical care patients.

Key Words parenteral nutrition, glycemic control, glargine insulin, regular insulin.

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Hyperglycemia is one of the most common complications of parenteral nutrition (PN).[1] A joint consensus statement from the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA)

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considers hyperglycemia, regardless of its cause, to be associated with poor clinical outcomes and increased mortality risk in hospitalized patients.[2] Based on previous studies, the prevalence of hyperglycemia in patients receiving PN is variable and ranges between 10% and 88%.[3–5] A systematic review[6] with the focus on four retrospective studies[7–10] and a recent prospective, multicenter study[11] demonstrated a relationship between PN-related hyperglycemia and clinical outcomes in both critically and noncritically ill patients. Prevention of hyperglycemia and aggressive intervention to correct it may be effective in ameliorating untoward clinical consequences of patients receiving PN.

The pharmacokinetic profile of regular insulin is well-suited to concomitant use with PN. Traditional administration techniques for regular insulin include a separate insulin drip with simultaneous infusion of PN solution,[12] inclusion of insulin in the PN admixture,[13] subcutaneous (SC) insulin injection using a correctional insulin dosing protocol,[14] or a combination of techniques. Continuous intravenous insulin infusion (CII) is the most effective method for controlling pre- and/or postsurgical hyperglycemia in critical care patients.[15] However, patients receiving CII need to be converted to a SC insulin regimen before transferring out of the ICU.[16] Correctional insulin dosing as the sole regimen is very commonly used, but often ineffective.[2] Some well-designed studies have demonstrated that a basal/bolus regimen along with a correctional dose is more effective than the correctional insulin dosing monotherapy in surgical and medical patients.[17–19] The addition of insulin to PN admixtures could be a practical alternative method to CII. One key drawback is the lack of consensus on a defined protocol for insulin dosing and variable availability of insulin in PN containers,[20] which have raised some concern about the safety and effectiveness of this method.

To date, several studies have evaluated the process of transitioning patients from intravenous to SC insulin.[21–23] Established protocols for using this method in hospitalized patients are available,[24, 25] but they are not necessarily applicable to patients receiving PN. There is a paucity of studies that assess different methods of hyperglycemia management and an unmet need for data that will inform clinicians about the best available technique in this patient population.

In an attempt to address this gap in the literature, we conducted a prospective, randomized trial comparing the effectiveness and safety of transitioning from regular insulin included in PN admixtures to subcutaneously administered glargine insulin. Glargine insulin has a 24-hour time-action profile without a significant peak and can be administered simultaneously with PN infusion. Concomitant glargine insulin and PN infusion would be a convenient option for transitioning patients from the ICU to general medical/surgical units. The objective of this study was to determine if once-daily insulin glargine provides effective and safe glycemic control comparable to regular insulin in stable critical care patients receiving PN.

Methods

This was a prospective, randomized, open-label, controlled trial (ID: IRCT2013072314121 N1 registered on www.irct.ir) at Shariati Teaching Hospital, affiliated with Tehran University of Medical Sciences (TUMS). The study protocol was approved by the Institutional Review Board and the Medical Ethics committee of the university. Written informed consent was obtained from all patients or their first-degree family members. This study was conducted in accordance with the revised version of the Helsinki Declaration guideline, 2008.

Patients

Postoperative patients admitted to the neurosurgery intensive care unit (ICU), surgery ICU, or open-heart ICU who were receiving PN were screened for enrollment. Patients who met inclusion criteria (age > 18 years, and nil per os [NPO] status for ≥ 7 days) were eligible for participation in this study. Patients were excluded if they had any of the following criteria: autoimmune diseases, HIV infection or sepsis, diabetes mellitus, pregnancy, significant renal impairment (on dialysis or estimated GFR < 10 ml/min), any hypersensitivity to PN components or glargine insulin, treatment with corticosteroids or vasopressors, or receiving oral or enteral nutrition (EN).

PN Administration

At Shariati Hospital, the PN calculations, ordering, sterile admixture, and monitoring are all done through Inpatient Pharmaceutical Care Unit by a service of trained clinical and hospital pharmacists on a routine daily basis. PN formulations are designed to meet individualized caloric and

Table 1. Insulin Dosing Protocol

BG values (mg/dl)		Regular insulin dose (units)
BG values on the day before starting PN		*Initial dose per 100 g dextrose*
151–199		15
121–150		10
100–120		5
< 100		PN with no insulin
Daily insulin correction by two BG values		**Modification in regular insulin or glargine insulin dose**
BG value category		
< 70[a]	Hypoglycemia	Decrease by 50%
70–109	Borderline	Decrease by 25%
Daily insulin correction by BG values		
110–180	Desired range	No change
> 180	Hyperglycemia	Perform correctional insulin dosing protocol[b]

[a]Single value would be corrected by 12.5 g dextrose administration intravenously as soon as possible.
[b]Subcutaneous correctional insulin dosing scale: BG 150-200 mg/dl: 2 units; 201–250 mg/dl: 4 units; 251–300 mg/dl: 6 units.

nutritional requirements.[13] The PN administration provides approximately 40–60% of calculated daily carbohydrate caloric requirements during the first 24 hours, which ranges from 150 to 250 g dextrose, and is then promoted to the desired goal during the next 24 hours. Intravenous amino acid and fat emulsion are started from day 1 based on individualized requirements.[13] Calculations for micronutrients, including electrolytes, vitamins, and trace elements, on the first day are based on recommended daily requirements[13] and subsequently on individualized laboratory tests. To control blood glucose (BG) within the desired range (110–180 mg/dl), insulin is generally added to PN bags based on an insulin-dosing protocol (Table 1). Capillary BG monitoring is performed every 6 hours with Accu-Chek Inform, Roche Diagnostics (F. Hoffmann-La Roche AG, Basel, Switzerland) according to the manufacturer's instructions. New PN bags are hung daily at midnight.

Insulin Administration

As shown in Table 1, the insulin-to-dextrose ratio (IDR) on the first day was determined from BG values measured on the day before starting PN. The IDR was based on reports in the literature [13, 26, 27] and clinical practice in the hospital. If BG values were already in 151 to 199 mg/dl range, 0.15 units of insulin per gram of dextrose were added on the first day. As well, for patients with BGs 121–150, 100–120, and < 100 mg/dl measured on the day before starting PN, 10, 5, and 0 units of insulin per gram of dextrose were added in PN bag, respectively. If needed, regular insulin was also administered subcutaneously to correct any BG values above 150 mg/dl according to a correctional insulin dosing protocol. The correctional protocol provides 2 units of regular insulin for every 50 mg/dl of BG over 150 mg/dl. Subsequently, 70–100% of the correctional insulin dose is added to the next day PN solution.[28]

On the second day, dextrose was increased to meet all individualized carbohydrate calorie requirements. However, if two measured BG levels were higher than 250 mg/dl on the first day, the achievement of dextrose requirement goal would be delayed until the third day. The insulin dose provided in the PN solution was adjusted daily based on the doses of SC insulin by correctional insulin dosing protocol and recorded BG values (Table 1). The total insulin requirement on the first day (i.e., sum of correctional insulin and the amount included in PN solution) would determine the new IDR for the second day. If at least two of BG values were between 70 and 109 mg/dl, IDR was decreased by 25%. If two values were less than 70 mg/dl, IDR was decreased by 50%.

Randomization

After the second or third day of PN, the dextrose quantity was maintained, and the insulin dose adjustment was solely based on BG levels and SC insulin doses. Before randomization, individualized dextrose and calorie requirement goals were met. The insulin dosing protocol was continued for 3 to 5 days. When 3 or more BG levels remained within the goal range (110–180 mg/dl) for 24 hours,[6, 29] patients were randomly allocated (in a 1:1 ratio using a permuted-block randomization method) to an additional 3 days of either subcutaneous glargine insulin or continuation of insulin/PN (Figure 1). The insulin dose for the glargine insulin group was 80% of the total daily regular insulin dose in the PN solution on the day prior to randomization. To determine the appropriate dose of glargine insulin, we used the results of one group's study.[22] According to the results of their study, patients in the 80% conversion group had the highest percentage of BG values in the glycemic target range (80–140 mg/dl). Glargine insulin was administered 2 hours before starting the next PN infusion. In order to keep BG levels

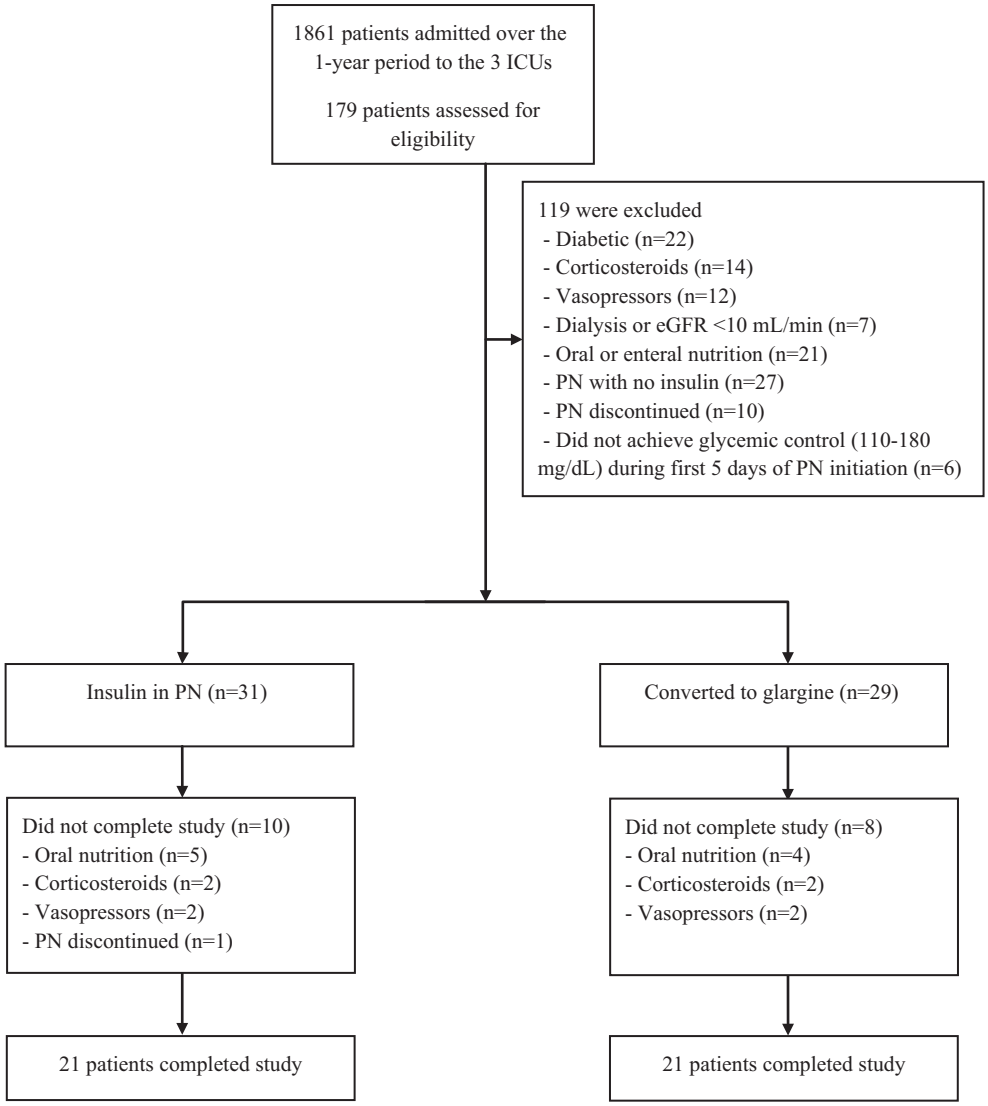

Figure 1. Study flow diagram.

within the desired range, the daily insulin dose was corrected according to insulin dosing protocol (Table 1).

Outcomes

The primary endpoint was the mean daily BG level on day 3 after randomization. Secondary endpoints were rates of severe hypoglycemia (BG < 40 mg/dl), hypoglycemia (BG < 70 mg/dl), hyperglycemia (BG > 180 mg/dl) and euglycemia (BG between 110 and 180 mg/dl) during the 3-day postrandomization period.[30] Glycemic variability (GV) (Δ) was defined as the mean difference between the highest and lowest BG level each day.[31] Glycemic control over the 3-day period was assessed using the hyperglycemic index (HGI), defined as the area under the BG concentration curve (AUC) for BG levels > 180 mg/dl divided by the study duration.[32] The AUC above the desired BG range was calculated for each patient using the trapezoidal calculation for two points over time.[33]

Statistical Analysis

A sample size of 21 patients per group was needed to detect at least an 18-mg/dl difference in mean daily BG between the two groups at an α (2-sided) of 0.05 with 80% power, assuming that mean daily BG levels on the last day was in the target glycemic range. Statistical analysis for normality and homogeneity of variances was performed using the Kolmogorov–Smirnov test. Parametric distributed data were analyzed using the independent-samples t-test and were

reported as mean ± standard deviation (SD). Nonparametric distributed data were analyzed using Mann–Whitney *U* test and were reported as medians (interquartile range [IQR]). Probable associations between categorical variables were assessed by using χ^2 test or Fisher exact test (> 20% of the categories have expected frequencies < 5). A one-way ANOVA with repeated measures test was used to assess BG variability changes over the 3-day period. All analyses were 2-sided and p values less than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 20.0, IBM Corp., Armonk, New York).

Results

Patient Characteristics

From December 2012 to January 2014, 179 patients were screened, and 119 were excluded from the study (Figure 1). Of the 60 remaining patients who provided informed consent and were randomized, 18 patients were withdrawn from the study (Figure 1). The demographic and clinical characteristics of the 42 patients were well balanced at baseline (Table 2).

Effectiveness and safety

The proportion of BG values goal (110–180 mg/dl), hyperglycemic (> 180 mg/dl), and hypoglycemic (< 70 mg/dl) BG levels were similar between the two groups (See Table 3). No patient in the regular insulin group experienced hypoglycemic episodes (BG < 70 mg/dl). However, hypoglycemia occurred in 19% (n=4) of patients randomized to glargine insulin. Despite this, there was no statistical difference between the two groups in the percentage of patients who had experienced hypoglycemia (p=0.107). Mean daily BG levels were not significantly different between the two groups on each of the 3 study days. There were no episodes of severe hypoglycemia in either study group.

Of the patients in the regular insulin group, 43% (n=9) did not require any correctional insulin dose, 43% (n=9) received one dose, and 14% (n=3) received two doses. In glargine insulin group, 43% (n=9) did not require any correctional insulin dose, 24% (n=5) required one dose, and 33% (n=7) required two doses. The percentage of patients with a single reduction in insulin dose was similar between regular insulin and glargine insulin groups (52.4% vs. 47.6% [n=11 vs. 10]; p=0.758). Moreover, the mean decrease in insulin dose was not significantly different between regular insulin and glargine insulin groups (3.57 ± 4.01 vs. 2.24 ± 2.77; p=0.218).

Blood Glucose Variability Changes

The mean change in Δ (maximum – minimum BG) over time using a repeated measures ANOVA test demonstrated a significant difference between time points (F=4.978, p=0.012) within the glargine insulin group but not the regular insulin group. A significant decrease in mean Δ from day 1–3 and day 2–3 was observed in the glargine insulin group (See Figure 2). There was no difference with regard to mean change in Δ between regular insulin and glargine insulin groups (mean difference: −2.254; 95% confidence interval: −15.373 to 10.865; p=0.730).

Discussion

To our knowledge, this is the first randomized study comparing the effectiveness and safety of two methods of insulin administration for patients receiving PN. We found no significant difference in mean daily BG levels or percentage of BG values in defined ranges between regular insulin and glargine insulin groups. Therefore, administration of glargine insulin could be an alternative method to adding regular insulin to PN in stable critical care patients. The glargine insulin dose was 80% of the total daily regular insulin dose added to PN. Also, there were at least 3 days between ICU admission and study entry.

In parallel to recent ADA/ACE guideline recommendations,[2] CII should be implemented to control hyperglycemia in critically ill patients with a trigger value > 180 mg/dl. Although regular insulin added to PN in combination with subcutaneous correction-dose insulin is often used for patients receiving PN, the conversion can be implemented in clinically stable patients with basal insulin administered as the percentage of the total IV requirement in combination with correction doses of a rapid insulin analog or regular insulin every 4- to 6-h as needed.[16] In a nonrandomized study,[34] the effectiveness and safety of a prospective protocol (i.e., addition of regular insulin to PN with concurrent subcutaneous insulin NPH) was compared with a retrospective conventional management, primarily correctional insulin. The study found that a prospective protocol using insulin to carbohydrate

Table 2. Demographic and Clinical Characteristics of the Study Population in the Regular Insulin and Glargine Insulin Groups

	Regular insulin (n=21)	Glargine insulin (n=21)	p value
Patient demographic			
Age (years)			
Mean ± SD	55.1 ± 17.8	57.1 ± 17.1	0.725
Range	25–83	27–85	
Sex, n (%)			
Female	9 (42.9)	7 (33.3)	0.525[a]
BMI (kg/m^2) on day 1 ICU			
Mean ± SD	23.7 ± 2.9	23.2 ± 3.4	0.650
Range	18.3–28.4	15.2–28.7	
Weight (kg) on day 1 ICU			
Mean ± SD	65.7 ± 11.4	65.2 ± 12.2	0.887
Range	48–82	39–85	
Type of surgery[c] (n)			
Gastrointestinal	13	16	0.317[a]
Others[b]	8	5	
Serum creatinine (mg/dl) on day 1 ICU			
Mean ± SD	0.9 ± 0.3	0.8 ± 0.3	0.638
Range	0.5–1.5	0.5–1.4	
Albumin (g/dl) on day 1 ICU			
Mean ± SD	2.9 ± 0.6	2.8 ± 0.6	0.604
Range	1.8–4.0	1.8–3.9	
Total hospital length of stay (days)			
Median (IQR)	37 (27–45.5)	37 (29–54)	0.642
Range	17–83	15–75	
Total ICU length of stay (days)			
Median (IQR)	16 (9–29)	17 (11.5–32)	0.442
Range	8–59	8–67	
Time elapsed from PN initiation to randomization (days)			
Median (IQR)	4 (3–4)	4 (3–4)	0.818
Range	3–5	3–5	
Duration of PN (days)			
Mean ± SD	20.28 ± 13.40	18.57 ± 11.50	0.659
Range	7–56	6–51	
APACHE II score day 1 ICU			
Median (IQR)	14 (10–18)	16 (13–21)	0.212
Range	6–24	8–27	
Patient characteristics at the time of randomization			
SOFA score day 1 randomization			
Median (IQR)	1.0 (0.5–3.0)	2.0 (1.0–4.0)	0.572
Range	0–6	0–6	
SOFA score day 3 randomization			
Median (IQR)	1.0 (0.5–2.5)	1.0 (0–3.5)	0.979
Range	0–6	0–8	
Total daily energy intake (mean ± SD)			
kcal/day	1998.2 ± 234.0	1995.0 ± 270.4	0.967
kcal/kg/day	30.9 ± 3.7	31.1 ± 3.2	0.877
Total protein calorie intake			
kcal/day (median [IQR])	400 (400–500)	400 (300–550)	0.702
g/kg/day (mean ± SD)	1.7 ± 0.3	1.7 ± 0.3	0.750

BMI = body mass index; APACHE = Acute Physiologic and Chronic Health Evaluation; SOFA = Sequential Organ Failure Assessment; ICU = intensive care unit; IQR = interquartile range.

[a]χ^2 test.

[b]Cardiovascular and Neurosurgery.

[c]Surgical procedures: Whipple procedure, Gastrectomy, Esophagectomy, Sigmoidectomy, Colectomy, Enterocutaneous fistula, Small bowel resection, Proctocolectomy, Duodenectomy, Mitral valve and aortic valve replacement, Coronary artery bypass graft, Coronary artery bypass graft and tricuspid valve replacement, Orbitozygomatic craniotomy, Extended bifrontal craniotomy, Retro-sigmoid craniotomy.

ratio resulted in superior glycemic control than a retrospective conventional management.

In order to achieve glycemic control in our critical care population, we considered several substantial aspects of implementation that permit safe and effective conversion compared to earlier studies.[21, 22, 35] First, in our study, a time interval of at least 3 days elapsed between

Table 3. Blood Glucose and Insulin Characteristics

	Regular insulin (n=252 BG readings)[c]	Glargine insulin (n=252 BG readings)[c]	p value
Percentage of BG values in 110–180 mg/dl range (n)	69 (174)	66.7 (168)	0.567[a]
Percentage of BG values < 40 mg/dl throughout study	0	0	1.000
Percentage of BG values < 70 mg/dl (n)	0	1.6 (4)	0.124[b]
Percentage of BG values in 70–109 mg/dl range (n)	19 (48)	20.6 (52)	0.655[a]
Percentage of BG values > 180 mg/dl (n)	11.9 (30)	11.1 (28)	0.780[a]
Mean daily BG on the day before PN initiation (mg/dl)			
Mean ± SD	118 ± 18	119 ± 19	0.796
Range	83–158	94–163	
Mean daily BG on the day before randomization (mg/dl)			
Mean ± SD	147 ± 15	148 ± 19	0.807
Range	120–176	113–175	
Mean daily BG on day 1 (mg/dl)			
Mean ± SD	140 ± 20	131 ± 25	0.194
Range	102–188	92–181	
Mean daily BG on day 2 (mg/dl)			
Mean ± SD	136 ± 20	140 ± 18	0.498
Range	96–188	107–182	
Mean daily BG on day 3 (mg/dl)			
Mean ± SD	142 ± 15	140 ± 19	0.741
Range	113–164	106–169	
Percentage of mean daily BG values in 110–180 mg/dl range (n)	92.1 (58)	84.1 (53)	0.169[a]
Insulin to dextrose ratio day 3 (unit/g)			
Mean ± SD	0.062 ± 0.034	0.065 ± 0.035	0.820
Range	0.014–0.14	0.011–0.16	
Total daily insulin dose at day 3 (units)			
Mean ± SD[d]	18.3 ± 8.8	19.5 ± 10.0	0.696
Range	5–37	4–41	
Total daily dextrose at day 3 (gram)			
Mean ± SD	306.9 ± 46.2	305.2 ± 52.2	0.913
Range	250–400	200–380	
Correctional insulin			
Number of doses	15	18	0.254[a]
Total dose (units)	35	49	0.411
Median (IQR)	2 (5)	2 (5)	
Range	0–7	0–8	
Hyperglycemic Index (mg/dl)			
Median (IQR)	13.34 (3.61–37.05)	21.51 (0–58.30)	0.909
Hypoglycemia rate per 100 hours insulin therapy	0	5.56	0.124[b]

[a]χ^2 test.
[b]Fisher exact test.
[c]BG measurements after treatment of a hypoglycemic episode were not analyzed.
[d]Regular insulin added in PN solutions or subcutaneously administered glargine insulin.

ICU admission and transition.[36] This may provide sufficient time for stabilizing patients' physiological status and, consequently, decreasing the levels of counter-regulatory hormones, especially epinephrine. In contrast, another group[35] converted cardiac surgery patients with a history of diabetes from CII to different doses of glargine insulin within one day of surgery. That study concluded that earlier transition may account in part for the lower number of patients with controlled BG values. Second, unlike other studies,[34, 35] we considered all plausible confounding factors of glycemic control and excluded patients with diabetes and those receiving corticosteroids, vasopressors or enteral feeding. Thus, our study population appears to be relatively homogeneous.

The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend a target BG range of 140–180 mg/dl for hospitalized adults receiving nutrition support.[29] In contrast, the findings of one systematic review suggest that a lower target range (i.e., 113–164 mg/dl) may be more appropriate.[6] However, the lower threshold of desired range is not entirely clear, and no trial has yet compared intensive insulin therapy (80–110 mg/dl) with a range of 110–180 mg/dl.[37] Altogether, we took into account a target BG range of 110–180 mg/dl.

Several large randomized studies compared the effects of intensive insulin therapy (IIT; BG 80–110 mg/dl) with higher BG ranges and suggested different optimal target ranges.[30, 38, 39]

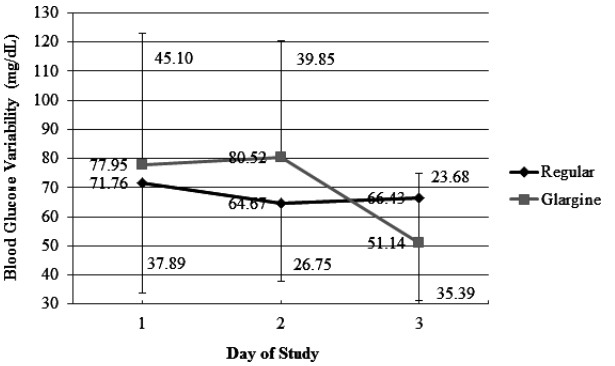

Figure 2. Variability in blood glucose values defined as mean daily Δ (average of daily difference between the highest and lowest blood glucose) ± standard deviation: Regular insulin group vs. glargine insulin group.

Hypoglycemia predicts mortality and poor clinical outcomes.[39, 40] In a post hoc analysis of the NICE-SUGAR study,[41] patients with hypoglycemia or severe hypoglycemia had a higher risk of death compared with those without hypoglycemia. In addition, increase in the risk of death was higher in patients with severe hypoglycemia than those with hypoglycemia.[41] Following transition in our study, 1.6% (n=4) of BG values were in the hypoglycemic range, and 19% (n=4) of our patients in the insulin glargine group during the 3-days period of study. Despite this, we did not detect any episode of severe hypoglycemia. Our study was not adequately powered to show a significant difference in percentage of BG values in the hypoglycemic range and percentage of patients having hypoglycemia between the study groups. They might be significantly different if the study was designed based on secondary outcomes with adequate power. Conversion to a dose of glargine lower than 80% of the total daily dose might have reduced the frequency of hypoglycemia. However, its impact on achievement of glycemic goals is yet unknown. Similarly, use of more frequent BG measurements could be studied to assess its impact on safety and effectiveness of such a protocol. Nevertheless, conversion from regular insulin in PN to SC glargine insulin may facilitate glycemic control in stable critical care patients who are in transitioning from ICU to general medical/surgical units.

A meta-analysis concluded that tight glycemic control (TGC; BG 80–110 mg/dl) is more beneficial in ICU patients receiving PN compared with enteral feeding.[42] However, findings of the prior study were not authenticated in a randomized prospective trial comparing early vs. late PN.[43] The patients receiving early PN (initiation of EN plus PN on ICU day 2) experienced the same BG levels (averaging 102–107 mg/dl) compared with late PN (initiation of EN on ICU day 2 and PN on ICU day 8). Nevertheless, the patients receiving late PN had better overall outcomes. Therefore, insulin infusion seems to be appropriate for patients regardless of the source of carbohydrate. In addition, glycemic control alone is not sufficient to decrease the apparent risks associated with PN.

The association between different GV metrics and clinical outcomes has been determined in hospitalized patients.[31] Nevertheless, the most appropriate metric to describe GV has not yet been defined.[30, 31] Recently, a study[44] demonstrated that high GV measured by the mean SD of all BG values and by the mean BG daily Δ change was associated with increased mortality and poor clinical outcome in hospitalized patients receiving PN. In our study we assessed mean daily Δ changes both between and within the study groups. These changes were not significantly different between the two groups. However, mean daily Δ changes differed significantly within glargine insulin group presumably owing to glargine administration itself. As shown in Figure 2, significant difference between time points 1 and 2 and time point 3 within glargine insulin group explained that by implementation of study protocol, variability in blood glucose was decreased by day 3 study.

Our study has four major limitations. First, significant exclusion criteria in stable critical care population limit generalizability. Second, despite that the sample size appears to be sufficiently large to detect any differences in mean daily BG, but it might be too small to identify the real differences of hypoglycemic or hyperglycemic episodes between two the study groups. Third, finger-stick capillary glucose monitoring may provide different results compared with a reference laboratory methodology using arterial or venous site samples in critically ill patients. However, owing to availability and reporting rapid results, we chose this blood glucose meter.[30] Forth, this study was designed only to assess impacts of regular insulin and glargine insulin on glycemic control (surrogate endpoint), not patient-level outcomes.

Conclusion

The data of the current study suggest that glargine insulin appears to be at least as effective and

safe as regular insulin in PN solution for glycemic control in stable critical care patients receiving PN. Based on the results of our study, successful transition from insulin infusion to basal SC insulin occurs when the patients receive insulin infusion for 3 or more days to achieve a level of glycemic control. Studies with more follow-up duration will include patients requiring vasopressors, enteral nutrition, corticosteroids and those with pre-existing diabetes mellitus to assess the current study protocol in both critical care and noncritical care populations receiving PN with especial focus on clinical outcome.

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References

1. **Maroulis J, Kalfarentzos F.** Complications of parenteral nutrition at the end of the century. Clin Nutr 2000;19:295–304.
2. **Moghissi ES, Korytkowski MT, DiNardo M, et al.** American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009;32:1119–31.
3. **der Voort PH, Feenstra RA, Bakker AJ, et al.** Intravenous glucose intake independently related to intensive care unit and hospital mortality: an argument for glucose toxicity in critically ill patients. Clin Endocrinol (Oxf) 2006;64:141–5.
4. **Schloerb PR.** Glucose in parenteral nutrition: a survey of U.S. medical centers. JPEN J Parenter Enteral Nutr 2004;28:447–52.
5. **Rosmarin DK, Wardlaw GM, Mirtallo J.** Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. Nutr Clin Pract 1996;11:151–6.
6. **Kumar PR, Crotty P, Raman M.** Hyperglycemia in hospitalized patients receiving parenteral nutrition is associated with increased morbidity and mortality: a review. Gastroenterol Res Pract 2011;2011:760720. doi: 10.1155/2011/760720.
7. **Cheung NW, Napier B, Zaccaria C, Fletcher JP.** Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. Diabetes Care 2005;28:2367–71.
8. **Lin LY, Lin HC, Lee PC, Ma WY, Lin HD.** Hyperglycemia correlates with outcomes in patients receiving total parenteral nutrition. Am J Med Sci 2007;333:261–5.
9. **Pasquel FJ, Spiegelman R, McCauley M, et al.** Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. Diabetes Care 2010;33:739–41.
10. **Sarkisian S, Fenton TR, Shaheen AA, Raman M.** Parenteral nutrition-associated hyperglycemia in noncritically ill inpatients is associated with higher mortality. Can J Gastroenterol 2010;24:453–7.
11. **Olveira G, Tapia MJ, Ocón J, et al.** Parenteral nutrition-associated hyperglycemia in non-critically ill inpatients increases the risk of in-hospital mortality (multicenter study). Diabetes Care 2013;36:1061–6.
12. **Sajbel TA, Dutro MP, Radway PR.** Use of separate insulin infusions with total parenteral nutrition. JPEN J Parenter Enteral Nutr 1987;11:97–9.
13. **Mirtallo J, Canada T, Johnson D, et al.** Safe practices for parenteral nutrition. JPEN J Parenter Enteral Nutr 2004;28:S39–70.
14. **McMahon MM.** Management of hyperglycemia in hospitalized patients receiving parenteral nutrition. Nutr Clin Pract 1997;12:35–8.
15. **Moghissi ES.** Addressing hyperglycemia from hospital admission to discharge. Curr Med Res Opin 2010;26:589–98.
16. **Umpierrez GE, Hellman R, Korytkowski MT, et al.** Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:16–38.
17. **Umpierrez GE, Smiley D, Zisman A, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diabetes Care 2007;30:2181–6.
18. **Umpierrez GE, Smiley D, Jacobs S, et al.** Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 Surgery). Diabetes Care 2011;34:256–61.
19. **Korytkowski MT, Salata RJ, Koerbel GL, et al.** Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. Diabetes Care 2009;32:594–6.
20. **Christianson MA, Schwartz MW, Suzuki N.** Determinants of insulin availability in parenteral nutrition solutions. JPEN J Parenter Enteral Nutr 2006;30:6–9.
21. **Weant KA, Ladha A.** Conversion from continuous insulin infusions to subcutaneous insulin in critically Ill patients. Ann Pharmacother 2009;43:629–34.
22. **Schmeltz LR, DeSantis AJ, Schmidt K, et al.** Conversion of intravenous insulin infusions to subcutaneously administered insulin glargine in patients with hyperglycemia. Endocr Pract 2006;12:641–50.
23. **Silinskie KM, Kirshner R, Hite MS.** Converting continuous insulin infusion to subcutaneous insulin glargine after cardiac surgery using percentage-based versus weight-based dosing: a pilot trial. Ann Pharmacother 2013;47:20–8.
24. **Donaldson S, Villanueva G, Rondinelli L, Baldwin D.** Rush University guidelines and protocols for the management of hyperglycemia in hospitalized patients: elimination of the sliding scale and improvement of glycemic control throughout the hospital. Diabetes Educ 2006;32:954–62.
25. **O'Malley CW, Emanuele M, Halasyamani L, Amin AN, Society of Hospital Medicine Glycemic Control Task Force.** Bridge over troubled waters: safe and effective transitions of the inpatient with hyperglycemia. J Hosp Med 2008;3(5 Suppl):55–65.
26. **Mattox TW, Catherine MC.** Parenteral Nutrition. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: a pathophysiologic approach, 8th ed. New York, NY: McGraw-Hill, 2011:2505–22.
27. **Roehl KA, Lach K, Coltman AE, et al.** Predictors of insulin requirements among hospitalized adults receiving parenteral nutrition. JPEN J Parenter Enteral Nutr 2013;37:755–62.
28. **Madsen H, Frankel EH.** The Hitchhiker's Guide to Parenteral Nutrition Management for Adult Patients. Pract Gastroenterol 2006;30:46–68.
29. **McMahon MM, Nystrom E, Braunschweig C, Miles J, Compher C, American Society for Parenteral and Enteral Nutrition** (A.S.P.E.N.) Board of Directors, **American Society for Parenteral and Enteral Nutrition.** A.S.P.E.N. clinical guidelines: nutrition support of adult patients with hyperglycemia. JPEN J Parenter Enteral Nutr 2013;37:23–36.
30. **Jacobi J, Bircher N, Krinsley J, et al.** Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012;40:3251–76.
31. **Braithwaite SS.** Glycemic variability in hospitalized patients: choosing metrics while awaiting the evidence. Curr Diab Rep 2013;13:138–54.

32. **Badawi O, Yeung SY, Rosenfeld BA.** Evaluation of glycemic control metrics for intensive care unit populations. Am J Med Qual 2009;24:310–20.
33. **Brown G, Dodek P.** Intravenous insulin nomogram improves blood glucose control in the critically ill. Crit Care Med 2001;29:1714–9.
34. **Jakoby MG, Nannapaneni N.** An insulin protocol for management of hyperglycemia in patients receiving parenteral nutrition is superior to ad hoc management. JPEN J Parenter Enteral Nutr 2012;36:183–8.
35. **Shomali ME, Herr DL, Hill PC, Pehilvanova BS, Sharretts JM, Magee MF.** Conversion from intravenous insulin to subcutaneous insulin after cardiovascular surgery: transition to target study. Diabetes Technol Ther 2011;13:121–6.
36. **Furnary AP, Braithwaite SS.** Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. Am J Cardiol 2006;98:557–64.
37. **Ichai C, Preiser JC, Société Française d'Anesthésie-Réanimation, Société de Réanimation de langue Française, Experts group.** International recommendations for glucose control in adult non diabetic critically ill patients. Crit Care 2010;14:R166.
38. **van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
39. **Preiser JC, Devos P, Ruiz-Santana S, et al.** A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 2009; 35:1738–48.
40. **NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al.** Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.
41. **NICE-SUGAR Study Investigators, Finfer S, Liu B, et al.** Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–18.
42. **Marik PE, Preiser JC.** Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest 2010;137:544–51.
43. **Casaer MP, Mesotten D, Hermans G, et al.** Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–17.
44. **Farrokhi F, Chandra P, Smiley D, et al.** Glucose variability is an independent predictor of mortality in hospitalized patients treated with total parenteral nutrition. Endocr Pract 2014;20:41–5.