Original Article

Comparison of the Efficacy and Safety of Two Different Insulin Infusion Protocols in the Medical Intensive Care Unit

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Abstract

Background: New guidelines recommend using less intensive glycemic goals in critically ill patients receiving insulin infusions.

Objective: To compare the efficacy and safety of a modified insulin infusion protocol (MIIP) with less stringent blood glucose (BG) goals to an intensive insulin infusion protocol (IIIP) in patients in a medical intensive care unit (MICU)

Methods: Retrospective review of patients receiving an insulin infusion for at least 24 hours. Patients treated for hyperglycemic emergencies were excluded. The primary endpoint of the study was mean area under the BG curve (BG-AUC) at 24 and 48 hours. Other endpoints included mean BG, hours until BG at goal, rate of BG above goal, frequency of BG measurements, and rate of hypoglycemia.

Results: BG-AUC at 24 hours was similar between the groups (MIIP = 5177.7 ± 1221.3 mg/dL $\times$ h vs IIIP = 4850.3 ± 1301.7 mg/dL $\times$ h; $P = .20$). The mean BG level at 24 hours was 225.1 ± 91.1 mg/dL in the MIIP group and 205.7 ± 89.7 mg/dL in the IIIP group ($P = .06$). In the MIIP group, 61.7% of the BG levels were above goal as compared to 87.5% in the IIIP group ($P < .0001$). Patients were able to achieve BG goals faster with the MIIP (12.58 ± 10.5 hours vs 29.37 ± 16.8 hours; $P < .001$). The rate of severe hypoglycemia was lower at 24 hours in the patients following the MIIP (0% vs 0.3%; $P = .01$).

Conclusion: The study showed that by having less intensive glycemic goals, goal BG levels can be achieved faster and the rate of severe hypoglycemia can decrease.

Key Words—insulin infusion, intensive care unit, protocol

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Hyperglycemia is common in critically ill patients and is associated with increased mortality in the intensive care unit (ICU) setting.¹ Elevated blood glucose (BG) also causes substantial increased morbidity in critical illness, including increased risk of nosocomial infections, increased infarct size with worsened outcomes in myocardial infarction, and increased protein catabolism after burn injury.^{2–5} Inpatient glucose control has become an important goal for institutions in an effort to improve quality of care. Insulin, given as a continuous infusion, has been the standard

of care in critically ill patients with hyperglycemia.⁶ However, the targeted ranges of BG have been and continue to be contested.

A study in 2001 initially demonstrated that a goal BG level of 80 to 110 mg/dL decreased in-hospital mortality by 34% in a primarily surgical ICU population compared to a goal BG level of 180 to 200 mg/dL.⁷ However, the same investigators later failed to show a significant improvement in mortality with intensive glycemic control in a medical ICU population.⁸ The Normoglycemia in Intensive Care Evaluation –

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Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial is the largest completed trial of intensive insulin therapy. This trial included mostly medical intensive care unit (MICU) patients and showed higher mortality in the intensive glycemic control group than in the conventional group (27.5% vs 24.9%; $P = .03$).⁹ This increase in mortality was thought to be due to a higher rate of hypoglycemic events. A meta-analysis of 26 studies that included the results of the NICE-SUGAR trial found a 6-fold increased risk of severe hypoglycemia in the group of patients who were receiving intensive insulin therapy.¹⁰

In response to this new evidence, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) have published revised guidelines on inpatient glycemic control.¹¹ These guidelines recommend achieving glucose control using an insulin infusion in patients in the ICU setting, with a starting threshold of no higher than 180 mg/dL and glucose levels maintained between 140 and 180 mg/dL.

At Temple University Hospital, prior to the publishing of the new recommendations, the insulin infusion protocol in the MICU had an intensive BG goal of 85 to 110 mg/dL. After the recommendations for less intensive glycemic control, the goal BG was changed to comply with the current guidelines. The modified insulin infusion protocol (MIIP) has a goal BG of 140 to 180 mg/dL. The objective of this analysis was to compare the efficacy and safety of the 2 different protocols in patients in the MICU.

METHODS

This was a retrospective chart review of adult patients who received an insulin infusion while in the MICU. The efficacy and safety of 2 different insulin infusion protocols was evaluated. Patients were identified using an inpatient pharmacy medication management system (*Horizon Meds Manager*; McKesson, Alpharetta, GA). An electronic medical record program (*Alpha ImageWorks*; Alpha Systems, Huntingdon Valley, PA) was used to collect patient data. This research was approved by the institutional review board.

Data on the intensive insulin infusion protocol (IIIP) were collected from January 2009 to December 2009. The MIIP was implemented in January 2010. We allowed for the new protocol to be in place for 6 months before evaluating its efficacy and safety in order to account for lack of knowledge or experience with the protocol. Data on the MIIP were collected between July 2010 and March 2011. Both protocols were the same

except for the goal BG level. The protocols required point-of-care testing (fingersticks/capillary blood) every hour for the first 3 hours and then every 2 hours for 24 hours. When there was a change in the insulin infusion rate, the BG level was checked 1 hour later. As part of the protocol, the use of subcutaneous insulin (standing orders or the use of correction insulin) and the use of oral antidiabetic agents were not allowed. Once the patients were started on an insulin infusion, a pre-printed copy was added to the patients' charts for nurses to follow.

Patients were included if they were 18 years of age or older, admitted to the MICU, and started on an insulin infusion for the treatment of hyperglycemia that lasted at least 24 consecutive hours. Data were collected for up to 48 hours. Patients being treated for diabetic ketoacidosis or hyperglycemic hyperosmolar state were excluded, as were all pregnant women. The goal was to include the first 50 patients who met the inclusion criteria in each time period. Data collected included demographics, history of diabetes, length of hospital stay, daily glucose measurements, creatinine clearance, nutritional status, concomitant use of corticosteroid, and concomitant use of vasopressors.

The primary endpoint of the study was area under the blood glucose curve (BG-AUC) during the first 24 and 48 hours after the start of the insulin infusion. The AUC values were calculated by integrating the BG curve 0-24 and 0-48. The trapezoidal rule was used to do the integration. The AUC for 24 and 48 hours was used to incorporate the large number of BG readings determined at various times for each patient throughout the observation period. With this endpoint, the variability in BG levels through time can taken into consideration. BG measurements were obtained from point-of-care testing data documented by nurses in the MICU flow sheets. The MICU flow sheets used were the same during the 2 periods evaluated. BG measurements were collected from fingersticks. Secondary endpoints included mean BG levels, hours until BG was at goal (BG < 110 mg/dL with the IIIP and BG < 180 mg/dL with the MIIP), rate of BG levels above goal, and frequency of BG measurements. For the safety analysis, the rate of moderate hypoglycemia (BG 40-70 mg/dL) and severe hypoglycemia (BG < 40 mg/dL) were recorded. All measurements were evaluated during the first 24 and 48 hours after the start of the insulin infusion, because in most protocols patients should achieve goals in less than 24 hours.

Descriptive statistics including mean $\pm$ SD were used to describe the results. Fisher exact tests and t tests were used to compare categorical and continuous

variables between groups, respectively. A multiple variable linear model analysis was used for BG-AUC and included group, concomitant corticosteroid use, concomitant vasopressor use, nutritional status, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. A P value $\leq .05$ was considered statistically significant. Data were analyzed using SAS V9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 968 charts were screened during the year 2009 to include 50 patients in the IIIP evaluation and 791 were screened to include 50 patients in the MIIP. Most of the patients were excluded because they were not in the MICU at the time the insulin infusion was given or because the insulin infusion was not continued for at least 24 hours. Two patients were later excluded from the IIIP evaluation because they were admitted with a hyperglycemic emergency. A total of 98 patients were included in the analysis of the first 24 hours. Of these, 36 patients in the IIIP group and 44 patients in the MIIP group received an insulin infusion for at least 48 hours, and all the endpoints were evaluated for 0 to 24 hours and 0 to 48 hours.

Table 1 summarizes baseline characteristics. Most baseline characteristics were similar between groups except for the number of patients with diagnosed type 1 and type 2 diabetes mellitus (DM) prior to admission and the use of concomitant corticosteroids. There were 8 patients (17%) with type 1 DM evaluated in the MIIP group and there were none with type 1 DM evaluated in the IIIP group ($P = .01$). Most patients were either African American or Caucasian and were receiving enteral nutrition at the time the insulin infusion was started.

Table 2 presents the results of the primary and some secondary endpoints. The BG-AUC was similar between groups for the first 24 and 48 hours. **Figure 1** shows the BG measurements from 0 to 24 hours and 0 to 48 hours in the 2 groups. The mean BG level during the first 24 hours was slightly but not statistically significantly higher in the group of patients following the MIIP (205.7 ± 89.7 mg/dL vs 225.1 ± 91.1 mg/dL, respectively; $P = .06$) compared to IIIP.

After adjusting for the baseline BG, the type of diabetes upon admission, the use of concomitant corticosteroids and vasopressors, APACHE II score, and the type of nutrition, we found that the results of the BG-AUC did not have a statistically significant difference at 0 to 24 hours ($P = .50$) or 0 to 48 hours ($P = .39$). However, we found a significant association ($P = .05$) for 0 to 48 hours between patients re-

ceiving continuous enteral nutrition and elevated BG-AUC. The most common types of enteral nutrition used were *Glucerna* (24%), *Osmolite 1.0* (16%), and *Promote With Fiber* (12%); this did not differ between groups ($P = .21$). Similarly, there was no difference in the amount of carbohydrates received per day in those patients receiving enteral nutrition. The amount of carbohydrates given during the first 24 hours was 145.8 ± 94.2 g and 168.9 ± 102.7 g in those in receiving the MIIP and IIIP, respectively ($P = .38$), and 173.1 ± 89.2 g and 169.1 ± 92.5 g during the second day in the MIIP and IIIP, respectively ($P = .87$).

The rate of hyperglycemia (BG levels above goal) was higher in the IIIP compared with the MIIP during the first 24 and 48 hours ($P < .001$). Out of 597 BG levels recorded during the first 24 hours of treatment in patients following the IIIP, 2 levels in 2 different patients were below 40 mg/dL. There were no episodes of severe hypoglycemia with the MIIP during the first 24 hours of treatment (0% vs 0.3%; $P = .01$). One patient following the MIIP (2%) and 2 patients following the IIIP (4%) presented with severe hypoglycemia during the first 48 hours after the start of the infusion. The rate of moderate hypoglycemia did not differ between groups (see **Table 2**).

The time to achieve BG goals was shorter in the MIIP group compared with the IIIP group (12.58 ± 10.5 hours vs 29.37 ± 16.8 hours; $P < .001$). In those treated with the IIIP, 52% of patients were not able to achieve a BG goal of <110 mg/dL in 24 hours. However, it took 10.48 ± 9.50 hours for the IIIP group to achieve a BG goal of <140 mg/dL.

The number of BG levels evaluated in the first 24 and 48 hours was similar in the group of patients following the MIIP and the group of patients following the IIIP. On average, there were 12.5 ± 2.6 and 12.7 ± 2.5 BG levels checked per patient in the first 24 hours ($P = .61$) and 23.1 ± 2.9 and 24.3 ± 3.8 BG levels checked per patient in the first 48 hours ($P = .13$).

DISCUSSION

Having less intensive glycemic goals for patients on insulin infusions in the MICU has been associated with a decrease in mortality and a decrease in the rate of hypoglycemic events.^{9,10} After the ADA and AACE recommended less intensive glycemic control in the ICU, the insulin infusion protocol in the MICU at our institution was changed to comply with the new recommendation. Although this evaluation was not developed to assess morbidity and mortality, the analysis showed that after making this change the rate of severe hypoglycemia initially decreased and

Table 1. Baseline characteristics of adult patients in medical intensive care unit receiving insulin protocols

Characteristic	Intensive insulin infusion protocol (n=48)	Modified insulin infusion protocol (n=50)	P*
Mean age, years $\pm$ SD	57.7 $\pm$ 14.7	59.0 $\pm$ 14.8	.67
Males, n (%)	20 (41.7)	29 (58.0)	.16
Race, n (%)			
African American	17 (35.2)	19 (38.0)	.84
Caucasian	15 (31.3)	16 (32.0)	1.0
Other	16 (33.3)	15 (30.0)	
Type of diabetes, n (%)			
Type 1	0 (0.0)	8 (17.0)	.01
Type 2	33 (70.2)	22 (46.8)	.04
No known history	14 (29.2)	17 (34.0)	.67
Unknown	1 (2.1)	3 (6.0)	.62
Mean BMI ^a $\pm$ SD	35.4 $\pm$ 11.7	32.9 $\pm$ 11.7	.29
Mean CrCl ^b , mL/min $\pm$ SD	60.3 $\pm$ 26.6	59.3 $\pm$ 36.4	.87
Reason for admission, n (%)			.76
Sepsis/ARDS	8 (16.7)	9 (18.0)	
Respiratory	23 (47.9)	21 (42)	
Cardiovascular	6 (12.5)	3 (6.0)	
Neurological	4 (8.3)	8 (16.0)	
Gastrointestinal	3 (6.3)	4 (8.0)	
Other	4 (8.3)	5 (10.0)	
Mean LOS, days $\pm$ SD	37.1 $\pm$ 33.5	27.6 $\pm$ 18.7	.09
Mean LOS ICU, days $\pm$ SD	23.3 $\pm$ 19.3	18.6 $\pm$ 13.4	.16
Mean APACHE II score $\pm$ SD	21.0 $\pm$ 7.8	19.2 $\pm$ 7.8	.26
Concomitant use of corticosteroids, n (%)	28 (58.3)	18 (36.0)	.04
Concomitant use of vasopressors, n (%)	19 (39.6)	22 (44.0)	.69
Type of nutrition, n (%)			
NPO	12 (25.0)	12 (24.0)	1.0
PO	2 (4.2)	2 (4.0)	1.0
Enteral nutrition	28 (58.3)	34 (68.0)	.40
Parenteral nutrition	6 (12.5)	2 (4.0)	.16

Note: Fisher exact tests and t tests were used to compare categorical and continuous variables between groups, respectively. APACHE II = Acute Physiology and Chronic Health Evaluation; ARDS = Acute Respiratory Distress Syndrome; BMI = body mass index; CrCl = creatinine clearance; ICU = intensive care unit; LOS = length of stay; NPO = nothing by mouth; PO = by mouth.

^aThe BMI is the actual weight in kilograms divided by the square of the height in meters.

^bCrCl was estimated using the Cockcroft-Gault equation: CrCl (mL/min) = (140 - age) $\times$ (weight in kg) $\times$ (0.85 if female) / 72 $\times$ serum creatinine.

*P value of less than .05 was considered statistically significant.

patients were able to achieve the new goals more rapidly.

The number of patients with severe hypoglycemia decreased in the MIIP group. This is similar to the results of the NICE-SUGAR trial where 0.5% of the patients following the less intensive protocol developed severe hypoglycemia compared to 6.8% undergoing

intensive insulin therapy.⁹ The similarity in the rate of hypoglycemia is of value, because what is seen in randomized, controlled, clinical trials does not always translate to what is seen in a noncontrolled setting.

The primary endpoint (BG-AUC) of this analysis was similar between groups. However, as can be seen in Figure 1 and Table 2, there were large deviations in the

Table 2. Primary and secondary endpoints in adult patients in the medical intensive care unit receiving insulin: intensive vs modified insulin infusion protocol

Endpoints	Intensive insulin infusion protocol	Modified insulin infusion protocol	<i>P</i> *
0-24 hours			
BG AUC, mg/dL x h	4850.3 ± 1301.7	5177.7 ± 1221.3	.20
Mean BG level, mg/dL ± SD	205.7 ± 89.7	225.1 ± 91.1	.06
BG levels above goal, n (%)	524 (87.5)	393 (61.7)	< .0001
Hypoglycemic events, n (%)	3 (0.5)	2 (0.3)	.60
Severe hypoglycemic events, n (%)	2 (0.3)	0 (0.0)	.01
0-48 hours			
BG AUC, mg/dL x h	9193.4 ± 2497.7	9570.4 ± 2149.4	.47
Mean BG level, mg/dL ± SD	193.9 ± 85.7	204.9 ± 82.3	.19
BG levels above goal, n (%)	734 (85.9)	596 (53.4)	<.0001
Hypoglycemic events, n (%)	4 (0.5)	6 (0.5)	.84
Severe hypoglycemic events, n (%)	2 (0.2)	1 (0.1)	.41

Note: To compare continuous variables between groups, *t* tests were used.

BG = blood glucose; BG-AUC = area under the blood glucose curve.

**P* value of less than .05 was considered statistically significant.

AUC. This shows that even when attempts are made to control BG levels, by administering insulin as a continuous infusion, we still see high variability in BG levels.

Most patients following the IIIP were not able to achieve BG goals. For those who achieved goals, it took more than 24 hours to do so. One of the reasons for the lack of protocol efficacy could be the fear of hypoglycemia by the nursing staff and/or prescribers while trying to achieve goals close to normal BG levels. Another reason could be a lack of knowledge or ex-

perience with the protocol. These are known causes for poor glycemic control in the critical care setting.¹² In the MIIP group, patients were achieving goals at an average of 12 hours after the start of the infusion. A review of different studies evaluating the efficacy and safety of different insulin infusion protocols showed that the time to achieve BG goals with the protocols ranged from 2 to 15 hours.¹³

BG levels were checked on average every 2 hours. The current recommendations are to check BG levels

Figure 1. Blood glucose measurements (A) 0-24 and (B) 0-48 hours in MICU adult patients receiving insulin: intensive vs modified insulin infusion protocol. IIIP = intensive insulin infusion protocol; MIIP = modified insulin infusion protocol.

every hour until BG is at goal and then every 2 hours thereafter.¹¹ Even though compliance with the protocol was not assessed directly, based on the number of BG levels checked in 24 and 48 hours we can make the assumption that BG was not monitored every hour during the initiation of the infusion. Delays in insulin adjustments may contribute to longer periods of hyperglycemia and longer times to achieve BG goals.

We did not find an association between the use of concomitant corticosteroids and vasopressors and the BG-AUC. The use of corticosteroids and vasopressors is known to increase gluconeogenesis and insulin resistance and therefore increase BG levels. The lack of association could have been caused by the small number of patients included in this analysis. Similarly, and probably for the same reason, we did not find an association between BG-AUC and APACHE II score. Other studies have shown an increase in glucose values with an increase in APACHE II score, which is an indicator of severity of the disease.¹⁴ However, we found an association between patients receiving continuous enteral nutrition and elevated BG-AUC during the first 48 hours of treatment.

Some of the limitations of this evaluation include the retrospective design and small patient population. When a retrospective analysis is performed, it is assumed that the documentation in the charts is appropriate; sometimes this is not the case. Because of the small sample size, we were not able to find an association between BG levels and variables known to affect BG control including type of DM, prior history of DM, severity of the condition while in the hospital, and concomitant medications. In addition, we only assessed for concomitant use of steroids and vasopressors, assuming they would have the greatest impact in BG control. Other medications that may affect BG levels, such as antipsychotics and fluoroquinolones, were not taken into account and could have contributed to changes in the efficacy and safety of the protocols. Another limitation, due to the retrospective design, was the fact that some of the baseline characteristics were not similar between groups. However, after adjusting for those variables, we did not find a difference in endpoints. Because we wanted to evaluate real-life use of the protocol, compliance with the protocols was not assessed directly. Incorrect starting doses of insulin and inappropriate changes in the rate of the infusion could have affected BG control. The study only included patients in the MICU, therefore, the results cannot be generalized to other critically ill patients. Finally, we only evaluated the efficacy and safety of the protocol up to 48 hours, so the long-term safety of the protocol is not known.

In conclusion, our analysis showed that by following the new recommendation of less intensive glycemic goals for patients on insulin infusions in the MICU, BG goals can be reached more quickly and the rate of severe hypoglycemia is lower. The conclusions from our analysis are similar to the conclusions made in randomized controlled studies that evaluated a less strict glycemic goal in critically ill patients with hyperglycemia.

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