

# Safety and Efficacy of Continuous Insulin Infusion in Noncritical Care Settings

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**BACKGROUND:** Continuous insulin infusion (CII) to manage hyperglycemia is the accepted standard of care in the intensive care unit (ICU); however, the safety and efficacy of CII in the non-ICU setting has not been determined.

**RESEARCH DESIGN AND METHODS:** This is a retrospective analysis of 200 consecutive patients receiving CII while admitted to general medical-surgical units at Emory University Hospital. We evaluated clinical outcomes and rates of hyperglycemia (blood glucose [BG] >200 mg/dL) and hypoglycemia (BG <60 mg/dL) events during CII.

**RESULTS:** A total of 200 patients (age  $52 \pm 16$  years; male/female [M/F] 108/92) were admitted to general medicine (45%) or surgery (55%) services, 88.5% with history of diabetes and 41% treated with corticosteroids. The mean BG prior to and during the CII was 323 mg/dL and 170 mg/dL, respectively. Blood glucose of  $\leq 150$  mg/dL was the targeted goal in 85% of patients and 67% achieved a BG  $\leq 150$  mg/dL by hospital day 2. Hypoglycemia (BG <60 mg/dL) occurred at least once in 22% of patients, and severe hypoglycemia (BG <40 mg/dL) occurred in 5% of patients. Multivariate regression analyses showed that nutrition status during CII was associated with increased frequency of hyperglycemia and hypoglycemia. Compared to patients kept nil per os (NPO), oral intake during CII increased rates of hyperglycemic ( $P = 0.012$ ) and hypoglycemic events ( $P = 0.035$ ).

**CONCLUSIONS:** CII resulted in rapid and sustained glycemic control and a rate of hypoglycemic events similar to that reported in recent ICU trials. The rates of hypoglycemic and hyperglycemic events are significantly higher in patients allowed to eat during CII. *Journal of Hospital Medicine* 2010;5:212–217. © 2010 Society of Hospital Medicine.

**KEYWORDS:** general wards, hypoglycemia, inpatient hyperglycemia, insulin drips.

Increasing evidence suggests that in hospitalized adult patients with and without diabetes, hyperglycemia is associated with increased risk of complications, prolonged length of hospitalization, and death.<sup>1–5</sup> Past studies have shown that intensive glucose control in the intensive care unit (ICU) with continuous insulin infusion (CII) improves clinical outcomes by reducing the risk of multiorgan failure, systemic infection, and mortality. Effective management of hyperglycemia, an independent marker of poor outcome,<sup>1,3,6</sup> is also associated with a decreased length of ICU and hospital stay<sup>7–9</sup> and decreased total hospitalization cost.<sup>10</sup> Based on several observational and interventional studies, improved control of blood glucose (BG) has been recommended for most adult patients with critical illness.<sup>2,6,11</sup>

Detrimental effects of hyperglycemia on outcome are not limited to patients in the ICU setting and CII has increasingly been used in non-ICU settings. In such patients, the presence of hyperglycemia has been associated with prolonged hospital stay, infection, disability after hospital discharge, and death.<sup>1,3,6</sup> In general medicine and surgery services, however, hyperglycemia is frequently overlooked and

inadequately addressed. Numerous reports have shown that sliding scale regular insulin (SSRI) continues to be the most common insulin prescribed regimen in the non-ICU setting.<sup>12</sup> This regimen is challenged by limited and variable efficacy and continued concern for hypoglycemia<sup>13</sup>; thus, a more structured, target-driven protocol such as scheduled SC insulin or a CII protocol could facilitate glycemic control in the non-ICU setting. Recently, we reported that a scheduled regimen using basal-bolus insulin subcutaneously was safe, effective, and superior to SSRI in controlling BG levels in hospitalized subjects with type 2 diabetes. As in many institutions in the United States, we have used CII protocols as an alternative to subcutaneous (SC) insulin for the management of persistent hyperglycemia in non-ICU areas during the past 10 years, particularly during the postoperative period, transplant recipients, or patients transferred from the ICU. There is, however, no clinical evidence regarding the safety, efficacy, or outcomes with the use of CII in the non-ICU setting. Accordingly, we analyzed our experience on the efficacy and safety of CII in the management of hyperglycemia in general medicine and surgical services.

**TABLE 1. CII Orders**

Date (mm/dd/yyyy):	Time:	Allergies: NKA
1. Begin this protocol and IV fluids on ___/___/___ at _____ (time). Discontinue previous insulin orders when this protocol is started.		
2. Bedside BG monitoring q 1 h until patient is within target range × two consecutive readings, and then obtain BG q 2 h. If the BG falls above or below the targeted range, resume q 1 h readings. (If using A-line specimen, please use consistently while patient on drip).		
3. If initial BG >150 mg/dL give Regular Insulin bolus: Dose ___ units. (Dose 0.1 units/kg body weight)		
4. Insulin drip: 125 units of Regular Insulin in 250 mL 0.9% saline (1 mL of solution = 0.5 units of Insulin).		
5. Target BG Range on Insulin Drip: ___ mg/dL to ___ mg/dL (Suggested target 80-100 for ICU patients)* For each BG value, recalculate drip rate and disregard previous rate of infusion. Calculate Insulin Drip rate: $(BG - 60) \times \text{multiplier} = \text{units of Insulin per hour}$ ( × 2 to determine cc/hour) (Typical starting multiplier 0.02 but varies by insulin sensitivity) Adjusting Multiplier: BG > Target Range: Increase multiplier by 0.01 BG within Target Range: No change in multiplier BG < Target Range: Decrease multiplier by 0.01		
6. Treating Hypoglycemia: 6a. BG 60-80: Give D50W using formula: $(100 - BG) \times 0.3 = \text{mL D50W IV Push}$ . Adjust multiplier per protocol above 6b. BG <60: Give D50W using formula: $(100 - BG) \times 0.3 = \text{mL D50W IV Push}$ Decrease insulin drip to 50% of current infusion rate Recheck BG in 30 minutes BG >80: Decrease multiplier by 0.01 and then return to Step 5 formula BG 60-80: Repeat step 6a BG <60: Notify MD and repeat Step 6b		
7. Continuous IV fluids _____ at _____ mL/hour. (Consider changing to dextrose-based fluids when BG <250)		
8. Additional Orders:		

**Abbreviations:** BG, blood glucose; CII, continuous insulin infusion; IV, intravenous; q1h, every hour; q2h, every 2 hours.

## Research Design and Methods

This retrospective chart analysis was conducted in adult patients >18 years of age who were consecutively admitted to the general medical and surgical wards between July 1, 2004 and June 30, 2005 at Emory University Hospital, a 579-bed tertiary care facility staffed exclusively by Emory University School of Medicine faculty members and residents. The CII protocol, employing regular insulin (Novolin-R Novo Nordisk Pharmaceuticals, Princeton, NJ) with a very short half-life, in this study is a dynamic protocol<sup>14</sup> that has been available at all nursing stations at Emory Hospital for the past decade (Table 1). The insulin rate is calculated using the formula  $(BG - 60) \times (\text{multiplier}) = \text{units of insulin per hour}$ . The multiplier is a value used to denote the degree of insulin sensitivity based on glucose pattern and response to insulin. The multiplier typically starts at a value of 0.02 and is adjusted by the nurse as needed to achieve target BG levels based on bedside capillary glucose measurements. Blood glucose levels were checked every 1 to 2 hours by the nursing staff (nurse:patient ratio = 1:5) according to the protocol.

Of 1404 patients treated with CII during the hospital stay, 1191 patients received CII in the ICU and 213 patients received CII in non-ICU areas. The final analysis included a total of 200 non-ICU patient records after excluding 13 patients with diabetic ketoacidosis, incomplete documentation of glycemic records, or with duration of CII for less than 3 hours. Data collected included demographics, medical history, admission diagnoses, inpatient medications, inpatient laboratory values, bedside BG measurements, insulin doses

used, nutrition status during CII, length of stay, disposition at discharge, and mortality rate. Nutrition status was defined in 3 ways: (1) nil per os or nothing by mouth (NPO); (2) oral nutrition (PO-regular or PO-liquid); and (3) tube feeds or total parenteral nutrition (TF/TPN). Data collection was limited to the first 10 days of CII use. This study was approved by the Institutional Review Board at Emory University.

The primary aim of the study was to determine the efficacy (mean daily BG levels) and safety (number of hyperglycemic [ $\geq 200$  mg/dL] and hypoglycemic [ $\leq 60$  mg/dL] events) during CII. We also determined the presence of potential risk factors associated with hypoglycemic and hyperglycemic events (age, body mass index [BMI], nutrition status, renal function, corticosteroid therapy, and use of enteral and parenteral nutrition) during CII.

## Statistical Analysis

Two-sample Wilcoxon tests and analysis of variance (ANOVA) were used to compare continuous variables. Levine's test for homogeneity of variances and log transformations were used when necessary. For categorical variables, chi square ( $\chi^2$ ) analysis was used. Multivariate regression analyses controlling for age, gender, race, history of diabetes mellitus (DM), BMI, Cockcroft-Gault estimated glomerular filtration rate (GFR), steroid use, nutrition status (via oral route vs. NPO), and number of BG tests were performed based on repeated measures linear models or linear models and were used to determine the influence of demographic and clinical characteristics on the risk of hypoglycemia, hyperglycemia, mortality, and length of stay. Model building

followed the backward selection procedure. All data are expressed as mean  $\pm$  standard deviation. Statistical significance was defined as  $P < 0.05$ .

Statistical Analysis Software (SAS), version 9.1 (SAS Institute, Inc., Cary, NC), was used to perform the statistical analysis.

## Results

The cohort of 200 patients consisted of 54% males and 46% females, 53% Caucasian, 37% Black, with a mean age of  $52 \pm 16$  years (Table 2). Forty-five percent of patients were admitted to the general medicine service and the remaining 55% were admitted to the surgical service for admission diagnoses that included cardiovascular disorders, trauma/surgery gastrointestinal disorders, renal disorders, and infection.

The primary indication for CII was poor glycemic control in 93.4% of patients. Forty-one percent of subjects were receiving corticosteroids and 16% were continued on the insulin drip after transferring from an ICU. Nearly 90% of subjects had a history of diabetes and 11% were diagnosed with new-onset diabetes. The mean admission BG concentration was  $325 \pm 235$  mg/dL (mean  $\pm$  SD) and the mean A1c in 121 subjects in whom it was measured was  $9.1 \pm 3\%$ . The mean BG prior to the initiation of CII ( $323 \pm 184$ ) was similar to the admission BG.

Of the 173 subjects that had well-documented glycemic goals, the BG targeted during CII was  $\leq 150$  mg/dL in 85% of patients while the remaining subjects had a target BG goal that ranged from 70 to 250 mg/dL. The most commonly prescribed BG target goals were 80 to 110 mg/dL (41.6%), 80 to 120 mg/dL (13.9%), and 100 to 150 mg/dL (5.8%).

BG improved rapidly after the initiation of CII. BG on the first day of CII was  $182 \pm 71$  mg/dL; day 2:  $142 \pm 42$  mg/dL; day 3:  $131 \pm 38$  mg/dL; and day 4:  $132 \pm 43$  in response to receiving an average of  $84 \pm 66$  units/day,  $71 \pm 61$  units/day,  $70 \pm 61$  units/day, and  $64 \pm 29$  units/day, respectively (Table 3). Irrespective of the target BG goal, 67% of patients reached BG levels of  $\leq 150$  mg/dL by 48 hours of CII initiation. The duration of CII ranged between 4 and 240 hours, with an average of 41.6 hours and a median of 28 hours. The average insulin infusion rate during CII was  $4.29 \pm 2.99$  units/hour and the mean amount of insulin required to attain glycemic goals was  $1.96 \pm 1.88$  units/kg/day.

During CII, 48% and 35% of patients had at least 1 episode of hyperglycemia (BG  $>200$  mg/dL) on the second and third day of CII, respectively. Hypoglycemia (BG  $<60$  mg/dL) was noted at least once in 22% of the cohort (day 1: 11%; day 2: 16%; and day 3: 14%); however, severe hypoglycemia (BG  $<40$  mg/dL) only occurred in 5% of subjects. During the CII, 37% of patients experienced a BG  $<70$  mg/dL. When BG targets were stratified ( $<120$  mg/dL vs. 120–180 mg/dL vs.  $>180$  mg/dL), we found no significant association between the target BG goal and the frequency of hypoglycemic or hyperglycemic events during CII. None of the episodes of hypoglycemia were associated with significant or permanent complications.

The analysis of collected variables for influence on glycemic control (ie, BMI, age, corticosteroid use, renal function, and nutrition status) revealed that subjects with a creatinine level  $>1.5$  mg/dL may have an increased risk of hyperglycemia (BG  $>200$  mg/dL) ( $P = 0.047$ ) but not hypoglycemia. The analysis also found that younger patients ( $51 \pm 16$  years) were more likely to have episodes of hyperglycemia than older patients ( $57 \pm 13$  years) ( $P = 0.027$ ). Hospital length of stay and mortality rate (3%) were not associated with the rate of hyperglycemic or hypoglycemic events.

**TABLE 2. Patient Characteristics**

Age (years)	$52 \pm 16$
Gender (M/F)	108/92
Race (W/B/H/O)	106/74/13/17
Admitting service, Medical/Surgical (%/%)	45/55
BMI ( $\text{kg}/\text{m}^2$ )	$28.4 \pm 7.1$
Known diabetes/new onset (%/%)	90/11
Admission blood glucose (mg/dL)	$325 \pm 235$
A1c (%)	$9.1 \pm 3$
CrCl (mL/minute)	$59.5 \pm 44$
On steroids (%)	82 (41%)
Insulin drip duration (hours)	$41.6 \pm 37$
LOS (days)	$10 \pm 9$

NOTE: Data are means  $\pm$  SD.

Abbreviations: A1c, hemoglobin A1c; B, Black; BMI, body mass index; F, female; H, Hispanic; LOS, length of stay; M, male; O, other; SD, standard deviation; W, White.

**TABLE 3. Mean Blood Glucose Concentration and Daily IV Insulin Doses During the Continuous Insulin Infusion**

	Mean Daily Blood Glucose (mg/dL*)	Mean Daily IV Insulin Dose (units/day)
Preinfusion	$323 \pm 184$	N/A
Day 1	$182 \pm 71$	$84 \pm 66$
Day 2	$142 \pm 42$	$71 \pm 61$
Day 3	$131 \pm 38$	$70 \pm 61$
Day 4	$132 \pm 43$	$64 \pm 29$

NOTE: Data are means  $\pm$  SD.

Abbreviations: IV, intravenous; N/A, not applicable; SD, standard deviation.

\*To convert the values for glucose from mg/dL to mmol/L, multiply by 0.05551.

Eighty-two percent of patients received nutrition support at some point while on the CII: 48% PO-regular diet; 14% PO-liquid diet; and 20% TF/TPN. Due to the titration of nutrition from NPO at CII initiation to PO, NPO status was analyzed in a time-dependent fashion. Thus, among patients on CII on day 1, day 2, day 3, day 4, and days 5–10; 34.0%, 26.3%, 11.3%, 12.5%, and 10.5%, respectively, were NPO.

As compared to subjects maintained NPO, subjects that received oral nutrition while on CII had an increased rate of hyperglycemic events (BG >200 mg/dL: 86% vs. 76%,  $P = 0.19$ ; >300 mg/dL: 57% vs. 53%,  $P = 0.69$ ; >400 mg/dL: 32% vs. 21%,  $P = 0.22$ ) and a decreased rate of hypoglycemic events (BG <70 mg/dL: 33% vs. 41%,  $P = 0.39$ ; BG <60 mg/dL: 20% vs. 26%,  $P = 0.49$ ; and BG <40 mg/dL: 4% vs. 6%,  $P = 0.65$ ). The multivariate regression analyses, however, which considered age, gender, race, BMI, renal function, steroid use, history of diabetes, and number of BG tests, showed that nutrition status during CII was associated with increased frequency of hyperglycemic ( $P = 0.042$ ) and hypoglycemic events ( $P = 0.086$ ). As compared to NPO, oral intake (PO-regular or PO-liquid) was associated with a significantly increased frequency of hyperglycemic ( $P = 0.012$ ) and hypoglycemic events ( $P = 0.035$ ). Patients treated with TPN had lower BG values than those not on TPN. Although we observed no increased number of hypoglycemic events, TPN-treated subjects had higher mortality than non-TPN treated subjects ( $P < 0.001$ ).

## Discussion

Our study aimed to determine the safety and efficacy of CII in non-critically-ill patients with persistent hyperglycemia in general medicine and surgical services. We observed that the use of CII was effective in controlling hyperglycemia, with two-thirds of patients achieving their target BG  $\leq 150$  mg/dL by 48 hours of insulin infusion. The rate of hypoglycemic events with the use of CII in non-ICU patients was similar to that reported in recent ICU trials with intensive glycemic control<sup>7,8,15,16</sup> and is comparable to that reported in studies using SC insulin therapy in non-ICU settings.<sup>17,18</sup> The number of hypoglycemic and hyperglycemic events was significantly higher in patients allowed to eat compared to those patients kept NPO during CII. There is substantial observational evidence linking hyperglycemia in hospitalized patients (with and without diabetes) to poor outcomes. There is ongoing debate, however, about the optimal level of BG in hospitalized patients. Early cohort studies as well as randomized controlled trials (RCTs) suggest that intensive treatment of hyperglycemia reduces length of hospital and ICU stay, multiorgan failure and systemic infections, and mortality.<sup>7,9</sup> These positive reports led the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) to recommend tight glycemic control (target of 80–110 mg/dL) in critical care units. Recent multicenter controlled trials, however, have not been able to

reproduce these results and in fact, have reported an increased risk of severe hypoglycemia and mortality in ICU patients in association with tight glycemic control.<sup>15,16,19</sup> New glycemic targets call for more reasonable, achievable, and safer glycemic targets<sup>20,21</sup> in patients receiving CII in the ICU setting. The recent ADA/AACE Inpatient Task Force now recommends against aggressive BG targets of <110 mg/dL for patients in the ICU, and suggests maintaining glucose levels between 140 and 180 mg/dL during insulin therapy. However, lower targets between 110 and 140 mg/dL, while not evidence-based, may be acceptable in a subset of patients as long as these levels can be achieved safely by a well-trained staff.

There are no RCTs examining the effect of intensive glycemic control on outcomes or the optimal glycemic target in hospitalized patients outside the ICU setting. However, several observational studies point to a strong association between hyperglycemia and poor clinical outcomes, including prolonged hospital stay, infection, disability after hospital discharge, and death.<sup>1,3,5</sup> Despite the paucity of randomized controlled trials on general medical-surgical floors, a premeal BG target of <140 mg/dL with random BG <180 mg/dL are recommended as long as this target can be safely achieved.<sup>21</sup>

Our study indicates that the use of CII in the non-ICU setting is effective in improving glycemic control. After the first day of CII, the mean glucose level was within the recommended BG target of <180 mg/dL for patients treated with CII in the ICU. Moreover, the mean daily BG level during CII was lower than those recently reported with the use of SC basal-bolus and insulin neutral protamine hagedorn (NPH) and regular insulin combinations in non-ICU settings.<sup>17,18</sup> In the Randomized Study of Basal Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes (RABBIT 2) trial, a study that compared the efficacy and safety of an SC basal-bolus to a sliding scale insulin regimen, showed that 66% and 38% of patients, respectively, reached a target BG of <140 mg/dL.<sup>17</sup> The Comparison of Inpatient Insulin Regimens: DEtemir plus Aspart vs. NPH plus regular in Medical Patients with Type 2 Diabetes (DEAN Trial) trial reported daily mean BG levels after the first day of  $160 \pm 38$  mg/dL and  $158 \pm 51$  mg/dL in the detemir/aspart and NPH/regular group, respectively with an achieved BG target of <140 mg/dL in 45% of patients in the detemir/aspart and in 48% in the NPH/regular<sup>18</sup>; whereas in this study we observed that most patients reached the target BG goal by 48 hours of the CII regimen.

Increasing evidence indicates that inpatient hypoglycemia is associated with short-term and long-term adverse outcomes.<sup>22,23</sup> The incidence of severe hypoglycemia (<40 mg/dL) with intensified glycemic control has ranged between 9.8% and 19%<sup>7,15</sup> vs. <5% in conventional treatment. In the present study, 35% of patients experienced a BG <70 mg/dL, 22% had a BG <60 mg/dL, and 5% of patients had a BG <40 mg/dL. The lower rate of hypoglycemic events with the use of CII in the non-ICU setting

observed in this study is likely the result of a more relaxed glycemic target of 80 to 150 mg/dL for the majority of subjects, as well as fewer severe comorbidities compared to patients in the ICU, where the presence of sepsis or hepatic, adrenal, or renal failure increase the risk of hypoglycemia.<sup>22–24</sup>

Multivariate analyses adjusted for age, gender, race, BMI, renal function, steroid use, history of diabetes, and number of BG tests showed that nutrition status during CII was an important factor associated with increased frequency of hyperglycemic and hypoglycemic events. Compared to subjects maintained NPO, subjects who received oral intake while on CII had a significantly increased rate of hyperglycemic and hypoglycemic events. The increased risk of hypoglycemia for those allowed to eat is expected as the protocol would mandate an increase in the CII rate in response to the prandial BG increase but does not make provisions for BG assessments or CII adjustments in relationship to the meal. These results indicate that in stable patients who are ready to start eating, CII should be stopped and transitioned to SC insulin regimen. In patients who may benefit from the continued use of CII (eg, patients requiring multistep procedures/surgeries), treatment with CII could be continued with supplemental mealtime insulin (intravenous [IV] or SC).

CII may be useful in cases of patients with persistent hyperglycemia despite scheduled SC insulin regimen; in patients where rapid glycemic control may be warranted in order to decrease the risk of increased inflammation and vascular dysfunction in acute coronary syndromes; and to enhance wound healing status post surgical procedures. Other clinical scenarios in which CII may be preferred and no ICU bed is required include cases of new-onset diabetes with significant hyperglycemia (BG >300 mg/dL), type 1 diabetes poorly controlled with SC insulin, uncontrolled gestational diabetes, parenteral nutrition use, perioperative states, or the use of high-dose steroids or chemotherapy.

Our findings are limited by the retrospective nature of our study and the evaluation of patients in a single university medical center. Selection bias should be considered in the interpretation of the results since each index case was selected by the attending physician to be treated with CII as opposed to another regimen for inpatient glycemic control. The selection bias, however, may be limited by the fact that the subjects in this study placed on CII seemed to be similar to those in the general hospital population. A previous pilot study from a different academic institution, however, reported that implementing CII protocols in non-ICU patients is safe and improved glycemic control without increasing hypoglycemia.<sup>25</sup> In addition, because most subjects in this study had a history of diabetes prior to admission, these results may not be generalizable to populations with stress-induced hyperglycemia.

In summary, our study indicates that a CII regimen is an effective option for the management of patients with persistent hyperglycemia in the non-critical care setting. Most patients achieved and remained within targeted BG levels

during CII. The overall rate of hypoglycemic events was similar to that reported in recent randomized clinical trials in the ICU and with SC insulin therapy. The frequency of hypoglycemic and hyperglycemic events was significantly increased in patients allowed to eat during CII suggesting that CII should be stopped and patients should be transitioned to an SC insulin regimen once oral intake is initiated. Future prospective, randomized studies are needed to compare the efficacy and safety of CII protocols to SC insulin protocols in the management of patients with persistent hyperglycemia in the non-ICU setting.

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