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Evidence for strict inpatient blood glucose control: time to revise glycemic goals in hospitalized patients

Abbas E. Kitabchi[a,*], Amado X. Freire[a], Guillermo E. Umpierrez[b]

[a]University of Tennessee Health Science Center, Memphis, TN 38163, USA
[b]Emory University School of Medicine, Atlanta, GA 38163, USA

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Abstract

Inpatient hyperglycemia in patients with and without a history of diabetes is common and is associated with increased hospital morbidity and mortality. The objectives of this communication are to examine results of randomized clinical trials of strict inpatient glucose control in medical and surgical intensive care units and to provide guidelines for achieving and maintaining glycemic control in patients admitted to critical and noncritical settings. We propose a more conservative approach of glycemic control than current American Association of Clinical Endocrinology recommendations until results of prospective, multicenter, randomized studies become available.

Inpatient hyperglycemia is a frequently observed phenomenon, particularly in patients with trauma, burns, cardiac surgery, stroke as well as unrecognized diabetes [1-3]. In a previous study, we reported that hyperglycemia was present in 38% of patients admitted to the hospital; and about one third of these patients had no history of diabetes before the admission [2]. Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiologic or benign condition, but is a marker of poor clinical outcome and mortality [2,4-8]. Most observational and retrospective studies have reported that hyperglycemia in critical illness, in patients with and without diabetes, is associated with an increased risk of complications, a longer hospital and intensive care unit (ICU) stay, and a higher mortality rate [2,4,9-11].

During the past decade, several prospective randomized trials reported that intensified glycemic control reduces short- and long-term mortality, multiorgan failure and systemic infections, length of hospital and ICU stay, and total hospitalization cost. The randomized multicenter Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study demonstrated that aggressive intervention to control glucose levels significantly reduced morbidity and mortality, regardless of a patient's prior diabetes status [12-14]. In this study, a total of 620 patients with admission glucose values greater than 198 mg/dL were randomized to receive either conventional diabetes care or intravenous (IV) glucose-insulin-potassium (GIK) acutely after acute myocardial infarction (AMI) to maintain levels of blood glucose (BG) to less than 210 mg/dL (11.7 mmol/L) followed by intensive subcutaneous insulin therapy for 3 or more months. In this study, mean BG at 24-hour admission to the hospital was 173 mg/dL in the experimental group vs 211 mg/dL in the control group. At discharge, the glucose values were 173 vs 148 mg/dL, respectively. Although the mortality rate in the hospital (control 11% vs insulin glucose infusion 9%) or in 3 months (1% vs 12%) were not significantly different, the values at 1 year were reduced from 26% (control) to 19% (insulin glucose infusion), with a 28% reduction in mortality ($P = .01$).

In a prospective study of 2467 consecutive diabetic patients who underwent an open heart surgery procedure, Furnary et al [15] compared the effect of continuous IV infusion of insulin (CII) to monitor BG of between 150 and 200 mg/dL vs sliding scale subcutaneous insulin injection. The incidence of deep sternal wound infection was 0.8% (12/1499) in the CII group vs 2.0% (19/968) ($P = .01$) in the subcutaneous insulin injection group. In addition, CII used for the first 3 postoperative days demonstrated

* Corresponding author. Division of Endocrinology, Department of Medicine, University of Tennessee, Health Science Center, Memphis, TN 38163, USA. Tel.: +1 901 448 2610.
E-mail address: akitabchi@utmem.edu (A.E. Kitabchi).

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reduction in absolute and risk-adjusted mortality of 57% and 50%, respectively.

In another prospective study of 3554 consecutive diabetic patients who underwent coronary artery bypass graft, Furnary et al [16] reported that aggressive insulin therapy with IV insulin with BG range of 177 ± 30 mg/dL compared with subcutaneous insulin with BG levels of 213 ± 4 mg/dL ($P < .001$) resulted in significantly lower mortality rate (2.5% [65 out of 2612] vs 5.3% [59 out of 942]) [12,13]. The higher the BG concentration, the greater was the level of mortality rate (ie, BG >250 mg/dL resulted in 14.5% mortality compared with BG <150 mg/dL, which reduced mortality to 0.9%) [15]. These reports were followed by a study of Krinsley [17] in a single medical/surgical ICU in which the institution of a glycemic control protocol resulted in a marked reduction of ICU mortality. This controlled prospective study analyzed the outcomes of 800 consecutive critically ill subjects immediately after a protocol for intensive glucose control was instituted, and compared them with those of 800 consecutive patients admitted before the protocol was instituted. The protocol was designed to keep the BG level lower than 140 mg/dL with subcutaneous insulin injections and, if the BG level exceeded 200 mg/dL on 2 consecutive readings, insulin infusions. The mean BG levels decreased from 152 mg/dL before the protocol to 131 mg/dL with the protocol. In-hospital mortality was 20.9% before the protocol vs 14.8% with the protocol, a 29.3% reduction.

In a landmark study, Van den Berghe et al [18,19] investigated the effect of intensive insulin therapy in 1548 critically ill patients in a surgical ICU setting. They reported that near normalization of BG levels, using an intensive insulin protocol to maintain BG levels between 80 and 110 mg/dL, reduced ICU mortality from 8% to 4.6% (42%) and reduced the risk of multiorgan failure by 34%, systemic infection and sepsis by 40%, incidence of acute renal failure by 41%, need for blood transfusions by 50%, and need for prolonged mechanical ventilatory support by half. The beneficial effect was attributed to its effects on mortality among patients who remained in the ICU for more than 5 days (ie, 20.2% vs 10.6%, respectively) but not for shorter duration of stay. These investigators also showed that for each 20 mg/dL (1.1 mmol/L) of glucose level greater than 100 mg/dL (5.5 mmol/L), the risk of ICU death was increased by 30%. The rate of severe hypoglycemia (glucose <40 mg/dL) was 0.78% in the control and 5% in the intensive therapy groups.

Based on these studies and other less well-controlled studies (see Inzucchi [3], Capes et al [5], and Umpierrez and Kitabchi [20] for review), the American Association of Clinical Endocrinologists (AACE) developed a consensus report recommending a target BG level of 110 mg/dL (6.1 mmol/L) in ICU patients regardless of presence or absence of prior diagnosis of diabetes and a premeal target of 110 mg/dL and maximal BG target of <180 mg/dL (10 mmol/L) in non-ICU patients [21]. In-depth examination of the data on which the AACE report was generated does not appear to justify such a sweeping statement with the implication that "one protocol would fit all." This controversial report has generated passionate arguments, with 2 recent opposing views [22,23]. The main criticisms to the AACE consensus on inpatient hyperglycemia are as follows: (*a*) The studies on which the recommendations were based were obtained in surgical ICU patients and not in medical ICU or in regular wards. (*b*) With the exception of a few studies [12,16,18], most studies were not randomized or controlled, the criterion standard in clinical research. (c) These studies did not demonstrate differences in mortality between the intensive vs control group during the first 3 to 5 days of ICU care; and more importantly, an increasing number of recent prospective randomized clinical trials have failed to show beneficial effects of intensified glycemic control in the critically ill patients.

Three recent studies in patients with AMI reported no improvement in mortality with intensified insulin treatment vs conventional management. The DIGAMI 2 trial [24] included 1253 patients with a history of diabetes mellitus or admission BG >198 mg/dL admitted with AMI. Subjects were randomized to (1) a 24-hour insulin-glucose infusion followed by an intensified outpatient insulin regimen, (2) a 24-hour insulin-glucose infusion followed by standard glucose control, and (3) routine metabolic management according to local practice. The median study duration was 2.1 years. The overall mortality in all patients was 18.4%. Mortality among groups did not differ significantly (group 1, 23.4%; group 2, 22.6%; and group 3, 19.3%). There were no significant differences in morbidity expressed as cases with nonfatal reinfarction, congestive heart failure, and strokes among the 3 treatment groups. Among other things, the DIGAMI 2 failed to recruit an adequate number of patients and could not replicate the results of the original DIGAMI study [12] that reported significant difference in mortality after 1 year in the intensive insulin group (l9%) and the standard of care group (control, 26%). The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE-ECLA) trial [25] was a randomized controlled trial conducted in 470 centers worldwide among 20 201 patients with ST elevation myocardial infarction. Patients were randomized to receive GIK by IV infusion for 24 hours plus usual care or to receive usual care alone. This large study showed no differences at 7- and 30-day mortality or in the rate of heart failure, cardiac arrest, or reinfarction between treatment groups. Symptomatic hypoglycemia was more frequent in the GIK infusion group (0.4%) than in the control group (0.1%).

More recently, the Hyperglycemia: Intensive Insulin Infusion In Infarction study [26] recruited 240 patients with known history of diabetes or with admission BG >140 mg/dL admitted with ST-segment elevation MI. Subjects were randomized to receive insulin/dextrose infusion therapy for at least 24 hours to maintain a glucose

level <180 mg/dL or conventional therapy. Despite significant differences in glucose levels, insulin/dextrose infusion did not reduce mortality at the inpatient stage (4.8% vs conventional 3.5%), 3 months (7.1% vs 4.4%), or 6 months (7.9% vs 6.1%). There was, however, a significantly lower incidence of cardiac failure (12.7% vs 22.8%) and reinfarction within 3 months (2.4% vs 6.1%). When analyzed by mean BG achieved during the first 24 hours, mortality was lower among subjects with a mean BG >140 mg/dL (2% vs 11% at 6 months).

Several recent randomized controlled studies in medical and surgical ICUs have failed to show benefits or have raised serious safety concerns with the use of intensive insulin therapy vs less stringent glucose target levels. In 2006, Van den Berghe et al [27] reported a study of 1200 adult patients in medical ICU who were randomly assigned to receive intensified treatment to achieve a target BG of 80 to 110 mg/dL or to conventional insulin therapy started when the BG level exceeded 215 mg/dL to achieve a target BG <180 mg/dL. In the intention-to-treat analysis, despite reduction in BG levels (153 vs 111 mg/dL), there were no differences in in-hospital mortality (40% in the conventional-treatment group vs 37.3% in the intensive-treatment group, $P = .33$). The rate of hospital complications, however, was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. Among patients who stayed in the ICU for less than 3 days, mortality was greater among those patients receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for 3 or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5% to 43.0% ($P = .009$) and morbidity was also reduced. This medical ICU study failed to replicate the results of the previous study in the surgical ICU [18]. Furthermore, it showed that hypoglycemia was an independent risk factor for mortality [27].

A study was conducted on 523 patients in a combined medical-surgical ICU in Saudi Arabia randomized to receive intensive insulin therapy (BG target, 80-110 mg/dL) vs standard therapy (BG target, 180-200 mg/dL) [28]. The average BG was 117 vs 171 mg/dL ($P < .0001$). There was no significant difference in ICU mortality between the intensive insulin therapy and standard therapy groups (13.5% vs 17.1%, $P = .3$). Hypoglycemia occurred more frequently with intensive insulin therapy (9.1/100 treatment days vs 0.9/100 treatment days, $P < .0001$), but it was not independently associated with increased mortality. There was no difference between treatment groups in the ICU or hospital length of stay, mechanical ventilation duration, need for renal replacement therapy, or blood transfusion.

Two recent completed European studies also failed to show benefits of intensified insulin therapy, and both trials were stopped prematurely because of serious "safety concerns." The VISEP Trial (NCT00135473) [29], a multicenter study by the German Competence Network Sepsis, evaluated the efficacy of volume substitution and insulin therapy in sepsis. A total of 488 patients with sepsis were randomized to intensive insulin therapy (target BG, 80-110 mg/dL) or conventional therapy (target BG, 180-200 mg/dL). Intensified insulin therapy was associated with increased rate of hypoglycemia (BG <40 mg/dL; 12.1% vs 2.1%, respectively; $P < .001$). There were no differences in 28-day (21.9% vs 21.6%, $P = 1.0$) and 90-day (32.8% vs 29.5%, $P = .43$) mortality rates between treatment groups. The Glucontrol Trial (NCT00107601) was a randomized multicentric study recently presented at the 36th Critical Care Congress of the Society of Critical Care Medicine, Orlando, FL, 2007 [30]. This project aimed to determine the effects of 2 regimens of insulin therapy (80-110 mg/dL in group A vs 140-180 mg/dL in group B) on clinical outcome. The study anticipated recruiting 3500 patients; however, it was stopped prematurely because of safety concerns and the high rate of unintended protocol violations. A total of 1082 patients were recruited, 536 patients in group A and 546 patients in group B. During treatment, the mean BG was 118 mg/dL (104-131 mg/dL) vs 144 mg/dL (127-163 mg/dL). There were no differences in ICU mortality (16.97% vs 15.20%), hospital mortality (24.6% vs 20.7%), 28-day mortality (19.8% vs 16.1%), or ICU length of stay (6 days [3-13 days] vs 6 days [3-13 days]). The rate of hypoglycemia was greater in the more intensified treatment regimen (8.6% vs 2.4%). Of interest, mortality among people with a BG <40 mg/dL during treatment was increased (32.6% vs 53.8%).

Guidelines for effectiveness of intervention in clinical trials have been established based on assignment of grading system for evidence-based studies as A, B, or C, as follows [31,32]: grade A would consist of results from at least 2 or more multicenter, prospective, randomized, controlled trials; grade B would consist of results from one multicenter trial with the same high-quality criteria; and grade C would consist of results from a 1-center study with prospective, randomized, controlled protocol. By these definitions, most of these studies may not qualify for global recommendation of strict BG control until such time that other multicenter trials verify these findings, both in surgical and medical ICUs. The latter statement, however, does not contradict the acceptance of the well-established beneficial effects of standardized BG control in diabetic patients with severe hyperglycemia and acute metabolic decomposition of diabetic ketoacidosis or hyperglycemic hyperosmolar state [33], as well as diabetic patients undergoing various surgical procedures [9,34].

The flurry of enthusiasm on the use of IV insulin therapy for strict BG control in ICU under any circumstances, as proposed by AACE, prompted us to evaluate the status of 1185 of our patients admitted to our inner-city medical ICU from July 1999 to December 2002, excluding those with diabetic ketoacidosis, those with hyperglycemic hyperosmolar state, or patients with BG >280 mg/dL and <80 mg/dL [35]. The objective of this study was to determine if the highest serum glucose within 24 hours after ICU admission

was associated with increased hospital mortality after adjustment for confounders. Our patients were predominantly African American (79%), with a mean age of 49.2 years. On univariate analysis, survivors (n = 945) and nonsurvivors (n = 240) showed the Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation, hypoalbuminemia, lactic acidosis, and logistic organ dysfunction to be hospital mortality predictors, but not ICU admission hyperglycemia. The most important risk factors for mortality on logistic regression analysis (odds ratio [OR]) were the Acute Physiology and Chronic Health Evaluation II score (OR, 1.06; 95% confidence interval [CI], 1.02-1.11), the need for mechanical ventilation (OR, 3.06; 95% CI, 1.34-6.96), severe albuminemia (2.98 g/dL; 95% CI, 1.3-7.02), and severe lactic acidosis (>8 mmol/L; OR, 7.3; 95% CI, 2.14-24.9), but not the glucose level during the first hospitalization day. Therefore, conventional risk factors of disease severity predict hospital mortality in an inner-city medical ICU, but not BG values during the first 24 hours after ICU admission [35].

Furthermore, in medical and surgical ICUs, it is important to remember that maintenance of BG between 80 and 110 mg/dL is fraught with difficulties of high rate of hypoglycemia [27-30,36,37]. As many patients are critically ill, detection of hypoglycemia in noncommunicating, sedated patients with mechanical ventilation requires frequent monitoring of accurate BG. This may not be possible with ordinary glucometers in severely ill patients with low hematocrit, hypoxia, and the use of interfering drugs such as dopamine [38,39], as well as other confounding variables discussed in a recent review [40]. Hence, frequent use of glucose monitoring by glucose analyzer (as was done by the Van den Berghe group) or continuous glucose monitoring system may be necessary. The development of hypoglycemia (BG <40 mg/dL) in insulin-treated patients has been associated with near doubling of the mortality rate compared with those without hypoglycemia.

Several large multicenter clinical trials on strict glucose control in hospitalized patients are currently under way [41], with results expected to be available in the near future. Until clinical recommendations supported by prospective randomized trials become available, it is prudent to approach management of hospitalized patients with caution [42-44], but with the understanding that any BG threshold greater than 180 mg/dL must be avoided. We believe that in the absence of specific data, an advisable in-hospital target, including ICUs, is to maintain fasting and preprandial glucose levels between 100 and 130 mg/dL, respectively, and a random glucose level less than 180 mg/dL.

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