



# HYPOLYCEMIC EVENTS IN INTENSIVE CARE PATIENTS: ANALYSIS BY INSULIN ADMINISTRATION METHOD AND SAMPLE TYPE

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**Background** Intensive insulin treatment is associated with an increased risk of hypoglycemia, so strict glycemic monitoring is essential. The best type of sample for identifying hypoglycemia remains under debate.

**Objectives** To establish the number of hypoglycemic events in intensive care patients relative to insulin administration method and the method used to collect the blood sample.

**Methods** Retrospective descriptive study lasting 6 months. Hypoglycemia was defined as a blood glucose level less than 80 mg/dL (mild: 50-79 mg/dL, severe: <50 mg/dL), measured with a bedside glucometer and blood from the arterial catheter or fingerstick, in critically ill patients who require insulin administered subcutaneously (with sliding scales) or via continuous intravenous perfusion (intense infusion protocol with a nurse-managed insulin therapy algorithm).

**Results** Analysis of the 6636 samples from 144 critically ill patients revealed 188 mildly hypoglycemic samples (2.8%) and 3 severely hypoglycemic samples (0.04%). The prevalence of mild hypoglycemia was greater when insulin was administered intravenously (3.2%) rather than subcutaneously (2.3%;  $P = .04$ ). Among patients receiving insulin intravenously, hypoglycemia was found more often in arterial (4.5%) than in capillary (2.8%) blood ( $P = .01$ ). The prevalence of hypoglycemia in capillary blood samples did not differ significantly between subcutaneous (2.3%) and intravenous (2.8%) insulin therapies ( $P = .21$ ).

**Conclusions** With a target blood glucose level of 110 to 140 mg/dL, few hypoglycemic events are detected in critically ill patients, regardless of whether insulin is administered intravenously or subcutaneously. Analysis of solely arterial samples may yield a higher prevalence of hypoglycemia than otherwise. (*American Journal of Critical Care*. 2011;20:e115-e121)

Scientific societies<sup>1,2</sup> recommend strict control of glycemia in critically ill patients because of the clear association of such control with reduced morbidity and mortality in these patients.<sup>3-8</sup> Nonetheless, various studies<sup>9-15</sup> have shown a greater incidence of hypoglycemia when patients receive intensive insulin therapy via a continuous insulin infusion protocol (IIP).

In a meta-analysis of 29 studies (8432 patients), Wiener et al<sup>16</sup> assessed the risk/benefit factor of tight glucose control in critically ill patients and was able to draw a clear conclusion: the incidence of hypoglycemia was higher among patients receiving intensive insulin therapy, and the increase in incidence was in proportion to the tightness of the glucose control. In 2 later studies,<sup>7,13</sup> hypoglycemia was associated with mortality as an independent factor. In addition, in an international clinical trial, Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR),<sup>17</sup> investigators found more deaths from cardiovascular causes and more episodes of hypoglycemia (<40 mg/dL; to convert to millimoles per liter, multiply by 0.055) in the IIP group and concluded that hypoglycemia might simply be a strong marker of illness severity.

In a subsequent consensus statement on inpatient glycemic control, the American Association of Clinical Endocrinologists and the American Diabetes Association<sup>18</sup> recommended use of an IIP to control hyperglycemia in intensive care unit (ICU) patients, with the protocol to begin being used when glucose values are close to 180 mg/dL, maintaining an optimum range between 140 and 180 mg/dL.

Published analyses to date do not differentiate by the type of blood sample used for analysis of glucose level. The objective of the present study was

to assess the number of hypoglycemic events found in ICU patients according to the type of sample analyzed (fingerstick or arterial blood), as well as the type of rapid insulin administration used (subcutaneous or intravenous).

## Materials and Methods

The retrospective study included glycemia tests of ICU patients hospitalized between April 1 and September 30, 2008. Patients studied were in a multipurpose 10-bed ICU that serves all medical and surgical specialties except cardiac, thoracic, and neurological cases.

Our IIP was based on the Yale insulin infusion protocol.<sup>19</sup> Therefore, hypoglycemia was considered as a blood glucose level less than 80 mg/dL, with a value of 50 to 80 mg/dL categorized as mild hypoglycemia and less than 50 mg/dL as severe hypoglycemia<sup>20,21</sup> because our IIP requires intravenous insulin at this value to prevent the neurological complications associated with hypoglycemia, even if the patient is asymptomatic.

In our standard protocol, used in this study, an Optium Xceed glucometer (Abbott Diabetes Care, MediSense Products, Doncaster, Australia) calibrated per manufacturer instructions is assigned to each patient, and strips appropriate to that calibration are documented and kept in that patient's box of supplies in the ICU. Our unit requires 3 point-of-care measurements to confirm hypoglycemia. When the glycemia measurement is less than 80 mg/dL, the measurement is repeated twice with the same glucometer but with 2 different samples, to ensure against any error in the fingerstick technique or in reading the glucometer.

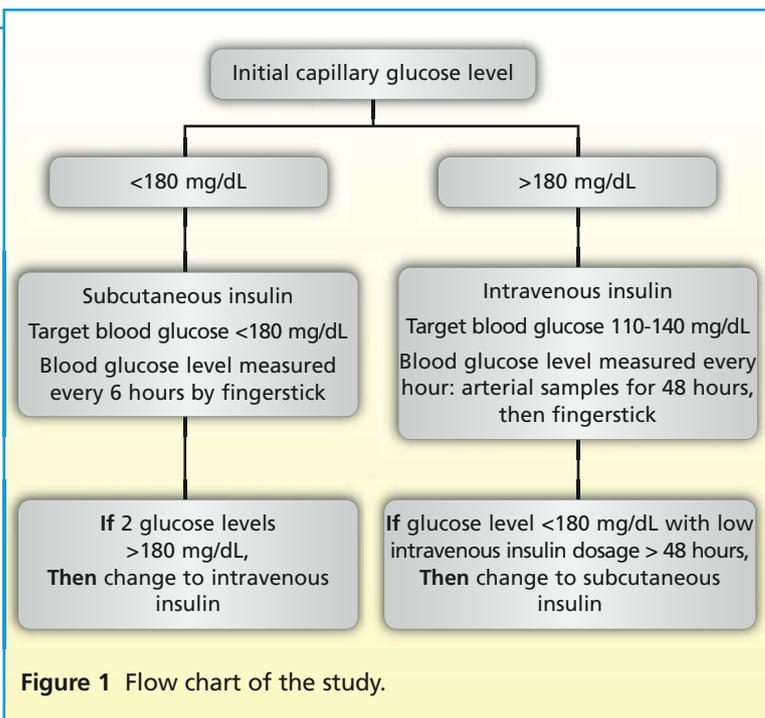
Two insulin therapy protocols were used: (1) the unit's normal standard, under which patients with a blood glucose level less than 180 mg/dL receive subcutaneous rapid insulin, with blood glucose level checked every 6 hours and insulin administered according to a predefined sliding scale of blood glucose levels) and (2) intravenous insulin therapy following a new IIP in the unit that uses

The incidence of hypoglycemia is higher in patients receiving intensive insulin therapy.

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dynamic scales (perfusion velocity adjusted as the blood glucose level changes), administered for patients with blood glucose levels greater than 180 mg/dL or patients with a blood glucose level greater than 150 mg/dL who meet at least 1 of the following clinical criteria: sepsis with failure of 2 or more organs, invasive mechanical ventilation for more than 5 days and insulin-dependent diabetes.<sup>2,22</sup> Briefly, those protocols are defined as follows:

*Sliding-scale protocol: blood collection at 6-hour intervals.* With subcutaneous administration of insulin, blood samples for glucose testing are collected via fingerstick because these patients do not have an arterial catheter. The guideline for subcutaneous administration of insulin is every 6 hours, and therefore our protocol requires testing of blood glucose level at 6-hour intervals; more frequent sampling (as in IIP patients, next) would reflect the therapeutic effect of the previously administered dose of insulin.

*IIP with dynamic scales: hourly blood collection.* Whether the sample is obtained from the arterial catheter (first 48 hours) or fingerstick (thereafter), more frequent

monitoring is required to determine the speed with which intravenously administered insulin is infused, depending on the blood glucose level measured. Before the arterial sample is collected for analysis, 2 mL of diluted blood is discharged from the dead space of the arterial catheter.

About 62% of hypoglycemia occurred with insulin infusion; 38%, with subcutaneous insulin therapy.

The therapeutic protocols were interchangeable throughout the study period: if a patient receiving 1 treatment met the criteria for the other, the treatment was changed (see Figure 1). The therapeutic objective for subcutaneous insulin therapy was to maintain a blood glucose level of 180 mg/dL or less; the IIP objective was to achieve a blood glucose level within a range of 110 to 140 mg/dL. The same type of insulin (Aspart, Novo Nordisk A/S, Copenhagen, Denmark) was administered, whether subcutaneously or intravenously.

Clinical histories were included for patients with at least 4 blood glucose measurements recorded per day, whether from capillary or arterial blood. Patients were excluded if they had sustained hypoglycemia for 4 hours or longer despite discontinuation of the intravenous insulin therapy.

The variables analyzed were blood glucose values (in milligrams per deciliter) measured in arterial or capillary blood samples from patients treated with intensive IIP and capillary samples of patients treated with subcutaneous insulin.

All patients included in the study, or their guardians, provided informed consent, and the protocol was approved by the hospital's Committee on Ethics and Clinical Research.

### Statistical Analysis

SPSS version 16.0 (SPSS, Inc, Chicago, Illinois) was used for statistical analysis. A  $\chi^2$  test was used to compare differences in the incidence of hypoglycemia between different groups. A *P* value less than .05 is considered statistically significant. Data are presented either as a mean (SD) or as a percentage.

### Results

Of 144 patients admitted to the ICU during the study period who required insulin therapy, 44 patients were excluded (42 had an insufficient number of recorded blood glucose levels [ $<4$  per day] and 2 had sustained hypoglycemia for more than 4 consecutive hours despite suspension of the IIP perfusion). For the 100 patients included, 6636 glycemia tests were available for analysis.

Most of the included patients (74%) had a blood glucose level less than 180 mg/dL with subcutaneous insulin and did not meet the criteria for inclusion in the IIP group (see Figure 1). However, under the dynamic therapeutic protocol, 21% received both subcutaneous and intravenous insulin at different points in their ICU stay, in general requiring intravenous insulin therapy during the most serious period of the problem for which they were hospitalized. Only 5% received intravenous insulin exclusively.

The mean (SD) age of the study participants was 66.4 (17.5) years, 67% were male, and the mean (SD) score on the Acute Physiology and Chronic Health Evaluation (APACHE) II at admission was 16.3 (7.4). Diagnoses on admission to the ICU included sepsis (30.9%), heart disease (24.7%), acute respiratory failure (15.9%), postoperative monitoring referred by surgical specialties (10.6%), hepatopancreatic abnormalities (7.1%), and medication imbalance (4.4%). Diabetes was diagnosed in 22% of study participants.

Of the hypoglycemia detected, 62.1% were from patients being treated with intravenous insulin therapy when the sample was collected and 37.9% were from patients receiving subcutaneous insulin therapy when the sample was collected. Patients treated with intravenous insulin therapy showed a mean (SD) blood glucose level of 150.6 (54.5) mg/dL, and patients receiving subcutaneous insulin therapy had a mean (SD) blood glucose level of 153.3 (50.2) mg/dL (Figure 2).

Categorical analysis of the blood glucose measurements by insulin administration protocol is detailed in Figure 3. In the case of intravenous insulin therapy, we observed a trend toward lower values (<110 mg/dL) at the expense of high values (>140 mg/dL), although this difference was not statistically significant.

We detected 188 (2.8%) mild hypoglycemic events (130 in the intravenous group and 58 in the subcutaneous group; 3.2% vs 2.3%;  $P = .04$ ). The 58 mild hypoglycemic events in the subcutaneous group were spread across the 74 patients treated with subcutaneous insulin only (APACHE score: mean, 14.4; SD, 7.03). The 130 hypoglycemic events in the intravenous group were split between 109 events (83.8%) in 21 patients who alternated between both protocols (APACHE score: mean, 15.6; SD, 7.01) and only 21 events (16.2%) in 5 patients treated exclusively with intravenous insulin (APACHE score: mean, 28; SD, 3.03), of which 18 hypoglycemic events were detected in capillary samples and 3 hypoglycemic events were detected in arterial samples.

Of the 130 hypoglycemic events in patients receiving insulin intravenously, 35 hypoglycemic events were detected in 771 arterial blood samples and only 95 events were detected in the 3353 capillary blood samples, resulting in a significant difference (4.5% vs 2.8%,  $P = .01$ ). In capillary samples, obtained by fingerstick, the numbers of hypoglycemic events detected did not differ between patients receiving subcutaneous insulin therapy (2.3%) and patients receiving intravenous insulin therapy (2.8%;  $P = .21$ , see Table). Severe hypoglycemic events were detected in just 3 samples (0.04%), 2 of these in

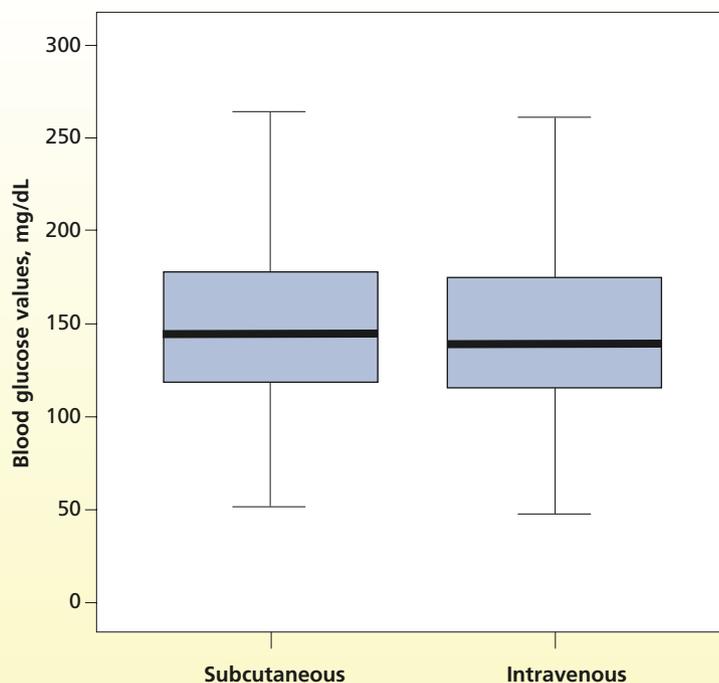


Figure 2 Blood glucose values and type of insulin administration.

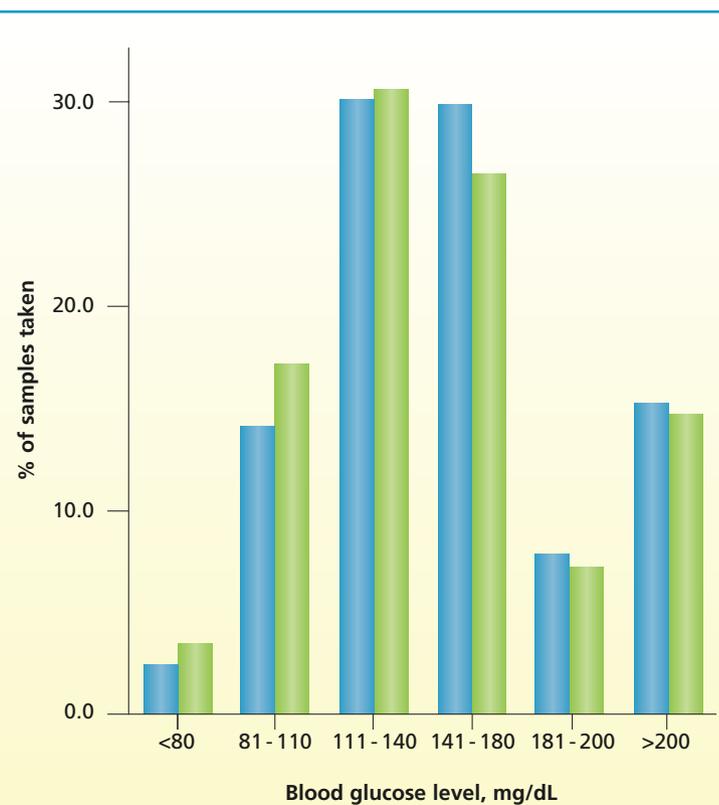


Figure 3 Distribution of blood glucose values by range and type of insulin therapy: subcutaneous (with sliding scales; blue bars) and continuous intravenous (intensive infusion protocol with nurse-managed algorithm; green bars).

**Table**  
**Number of hypoglycemic events less than 80 mg/dL categorized by insulin administration protocol and type of sample analyzed**

Type of sample <sup>a</sup>	Type of insulin administration <sup>b</sup>		P
	Subcutaneous	Intravenous	
Total	58 (2512)	130 (4124)	.04
Capillary	58 (2512)	95 (3353)	.21
Arterial	0 (0)	35 (771)	

<sup>a</sup> Difference in number of hypoglycemic events between capillary and arterial samples was significant ( $P = .01$ ).

<sup>b</sup> Values in table are number of hypoglycemic events less than 80 mg/dL (total samples).

capillary samples from patients receiving intravenous insulin therapy and the third in a capillary sample from a patient receiving subcutaneous insulin therapy.

## Discussion

The number of mild hypoglycemias was slightly higher in patients receiving intravenous insulin therapy than in patients receiving subcutaneous insulin, which makes sense if one considers the stricter therapeutic objective in patients treated intravenously. However, the use of infusion protocols with demonstrated safety and efficacy results in the detection of low levels of hypoglycemia.<sup>18</sup> In our ICU, the objective is to achieve blood glucose levels of 110 to 140 mg/dL, a bit higher than the target values initially recommended, because the literature suggests that intensive insulin therapy with lower target levels for blood glucose is associated with a

higher incidence of hypoglycemic events and only scant improvement in morbidity and mortality.<sup>7,23</sup> Our unit has chosen a target blood glucose level for patients receiving intravenous insulin therapy that is within the recommended guidelines of the American Association of Clinical

Endocrinologists and the American Diabetes Association in their consensus statement on inpatient glycemic control.<sup>18</sup>

Our findings concur with results of other studies in which different blood glucose ranges were compared, whether in a comparison of subcutaneous insulin therapy and IIP<sup>24,25</sup> or between 2 IIPs with different ranges.<sup>6,7,12,13,15,17</sup>

Other than our study, we found only 6 studies<sup>14,19,22,24,26,27</sup> in which mild hypoglycemic events were analyzed. In most clinical trials,<sup>6,7,10,12,13,17</sup> only severe hypoglycemia is considered. The defining value of hypoglycemia varies in these studies, which makes comparisons difficult. Braithwaite et al<sup>26</sup> reported a

2.4% incidence of hypoglycemias less than 70 mg/dL and did not find any hypoglycemic events less than 50 mg/dL. Bland et al<sup>22</sup> reported a 2.1% incidence of moderate hypoglycemia (40-60 mg/dL) in the group treated with intensive insulin therapy, and a 0.1% incidence of severe hypoglycemias, very similar to our results in both cases. Goldberg et al<sup>19</sup> also obtained similar results (0.2% hypoglycemia <70 mg/dL), whereas Osburne et al<sup>27</sup> reported a 6.9% incidence of hypoglycemia in the 60 to 80 mg/dL range and only a 0.9% incidence for hypoglycemia less than 60 mg/dL. In all of these studies, and in our study, percentages were calculated against the total number of samples taken. In other studies<sup>14,17</sup> in which slight hypoglycemia was assessed, researchers calculated the incidence on the basis of the number of patients who had at least 1 hypoglycemic episode. With respect to severe hypoglycemia, published clinical trials have reported frequencies of 5% to 18%, much higher than our findings, as reflected in a meta-analysis done after NICE-SUGAR was completed.<sup>28</sup>

The differences in results may be attributable to differences in methods.<sup>20,29</sup> In addition, despite having a similar study protocol, different centers in other clinical trials had different routines for sampling and analysis of blood glucose levels<sup>10,17,30,31</sup> or considered capillary and arterial blood samples to be interchangeable for purposes of analysis.<sup>12,13,20,21,31,32</sup> Our study addresses this gap in the literature by comparing blood glucose determinations on the basis of the type of sample analyzed. Differences between the 2 groups were found only when we included arterial samples in the analysis (as in the previous studies). This finding could have important implications in treating critically ill patients because it supports studies such as those by Scott et al,<sup>32</sup> Lacara et al,<sup>33</sup> and Slater-MacLean et al,<sup>34</sup> who found that capillary blood glucose values were higher than the corresponding arterial blood glucose values, and NICE-SUGAR,<sup>17</sup> which recommended against use of fingerstick samples for analysis of blood glucose levels.

With respect to sampling procedures, the literature establishes that blood glucose values obtained from fingerstick samples result in overestimates of blood glucose level in comparison with "reference standard" laboratory techniques.<sup>33,35-38</sup> Bedside glucometer readings in critically ill patients result in overestimates of blood glucose level<sup>39-42</sup> and lack precision<sup>2,18,32,34,43</sup> for a variety of reasons: fluid accumulation in the fingertips, poor peripheral perfusion due to shock or administration of vasopressors, anemia, sample volume insufficient for analysis, or sampling method used.<sup>20</sup> In addition, glucometers must be calibrated frequently, but such calibration

Capillary blood glucose values are higher than the corresponding arterial blood values.

may be neglected in clinical practice. In our study, each patient was provided with a box of supplies that included the patient's assigned Optium-Xceed glucometer, calibrated per the manufacturer's instructions,<sup>44</sup> and strips appropriate to that calibration; if additional strips were needed and came from a different lot, the glucometer was recalibrated.

Limitations of this study include its retrospective, observational design and the fact that the samples are not simultaneous in these critically ill patients. Case-control studies are needed to verify that the results obtained are not the result of any clinical and/or metabolic instability in the included patients. In addition, under our standard clinical protocol, the hypoglycemia readings were confirmed by repeated measurements with point-of-care devices rather than by control laboratory measurements.

Even though blood samples were collected from arterial catheters hourly, discarding 2 mL of diluted blood each time (which was returned to the patient's circulatory flow to avoid iatrogenic anemia), little has been published about arterial catheter sampling techniques that do not increase collateral effects such as anemia, infection, and ischemia/pseudoaneurysm of the radial artery. The complications of hypoglycemia move researchers to search for systems with higher sensitivity and specificity to detect hypoglycemia. In this sense, our group is conducting a clinical trial to determine whether the use of an arterial catheter permits more precise monitoring of glycemia, as this system offers the important advantage of avoiding the hourly fingersticks that produce discomfort for both patients and nurses.<sup>19,22,45</sup>

## Conclusions

With a target for blood glucose level of 110 to 140 mm Hg, the number of hypoglycemic events detected in critically ill patients is low, regardless of the type of administration of insulin therapy (intravenous IIP with a nurse-managed insulin therapy algorithm or subcutaneous with sliding scales). Nonetheless, a higher incidence of hypoglycemia less than 80 mg/dL was detected in arterial than capillary blood samples with a bedside glucometer. Therefore, if only arterial samples are analyzed in critically ill patients, the incidence of hypoglycemia could be higher than if capillary and arterial samples are used.

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