The Effect of a Hypoglycemia Treatment Protocol on Glycemic Variability in Critically Ill Patients

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Abstract
Introduction: Hypoglycemia and glucose variability are independently associated with increased mortality in septic, surgical, and mixed intensive care unit (ICU) patients. Treatment of hypoglycemia with dextrose 50% can overcorrect blood glucose levels and increase glucose variability. The purpose of this study is to evaluate the effect of a hypoglycemia treatment protocol focused on minimizing glucose variability in critically ill patients. Methods: This retrospective analysis was conducted at a 772-bed community teaching hospital in Detroit, Michigan. A standardized nursing-driven hypoglycemia treatment protocol specific to critically ill patients was implemented. Glucose variability, amount of dextrose administered, subsequent glucose monitoring, hypoglycemia recurrence, and mortality were compared between pre- and postprotocol groups. Results: The coefficient of variability of blood glucose in the postprotocol group (n = 53) was decreased compared with the preprotocol group (n = 52), 40.9% versus 49.3%, respectively (P = .048). Dextrose usage was significantly reduced between groups (21.2 g preprotocol vs 11.5 g postprotocol; P < .001). The time to first blood glucose check was 36 minutes after protocol implementation compared to 61 minutes before the protocol (P = .003). Finally, the incidence of continued hypoglycemia following dextrose administration and ICU mortality was similar between groups. Conclusions: Implementation of the hypoglycemia treatment protocol described led to a reduction in glucose variability, while still providing a safe and effective way to manage hypoglycemia in critically ill patients.

Keywords
hypoglycemia, treatment, protocol, glucose variability, intensive care unit, dextrose

Introduction
Hypoglycemia is a frequent occurrence in critically ill patients and is associated with increased mortality.1-6 Many critically ill patients possess risk factors for becoming hypoglycemic such as liver dysfunction, renal dysfunction, nutrition status changes, and insulin use. Detecting hypoglycemia is difficult because these patients often have varying degrees of consciousness; therefore, recognition of hypoglycemia is accomplished by laboratory monitoring rather than physical signs or symptoms. The treatment of choice in the intensive care unit (ICU) is intravenous dextrose 50%, which provides rapid resolution of hypoglycemia in a dose-dependent manner. Unfortunately, treatment with dextrose 50% can often lead to overcorrection of blood glucose levels and potentiate glucose variability.

Glucose variability has been associated with increased mortality in studies involving septic, surgical, and mixed ICU patients.7-14 Glucose variability is defined as the extent of blood glucose fluctuations, in both magnitude and frequency. Multiple ways of measurement have been utilized, including the standard deviation and the coefficient of variability (standard deviation/mean blood glucose).15 Potential mechanisms by which glucose variability may cause adverse outcomes include activation of oxidative stress, neuronal damage, and mitochondrial damage.16,17 Given this information, it is prudent to explore opportunities to minimize glucose variability in patients who are critically ill.

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We have developed a novel hypoglycemia treatment protocol focused on minimizing glucose variability in critically ill patients through optimization of intravenous dextrose therapy. The purpose of this study is to evaluate the resolution of hypoglycemia and determine glucose variability prior to and following implementation of this protocol.

**Materials and Methods**

This study was conducted at St John Hospital and Medical Center, a 772-bed community teaching hospital, located in Detroit, Michigan. The study was approved by the St John Hospital and Medical Center institutional review board. Typical glycemic control practices at our institution target blood glucose values 80 to 110 mg/dL for our cardiac surgery and 120 to 150 mg/dL for all other critically ill patients. Insulin infusions are initiated in noncardiac surgery patients after 2 consecutive blood glucose values ≥180 mg/dL. Patients with suspected sepsis are initiated on an insulin infusion protocol after 2 consecutive blood glucose values ≥150 mg/dL.

Prior to development of the hypoglycemia protocol, the current practice of prescriber discretion was evaluated through review of the electronic medical records from April 1, 2011, to June 30, 2011. Adult patients admitted to an ICU with a documented hypoglycemic blood glucose value (<70 mg/dL as measured by either venipuncture or LifeScan SureStep Flexx point-of-care device) and subsequent treatment with intravenous dextrose 50% were included. Of note, point-of-care devices used met the International Organization for Standardization’s requirement of having readings accurate ±20% (ISO 15197). Patients were excluded if admitted for diabetic ketoacidosis, were pregnant, or intentionally overdosed on β-blockers, insulin, or insulin secretagogues.

Our initial approach to protocol development was modeled after a previously published equation developed to treat hypoglycemia, while avoiding overcorrection. After assessing the response to dextrose treatment in the preprotocol evaluation, a standardized, nurse-driven hypoglycemia treatment protocol was developed through multidisciplinary consensus (Figure 1). The protocol was implemented February 1, 2012, following a period of nursing and provider education. Postprotocol implementation data were collected via electronic chart review from February 1, 2012, to March 31, 2012. Adult patients admitted to an ICU who experienced at least 1 episode of hypoglycemia and subsequent treatment with intravenous dextrose 50% per the protocol were included. Exclusion criteria were identical to the preprotocol evaluation.

The primary outcome was glucose variability, defined as the coefficient of variability (standard division divided by mean blood glucose) of all blood glucose values ranging from initial hypoglycemic value through 4 hours after dextrose 50% administration. Mean coefficient of variability as well as patient subgroups describing the degree of variability (<15%, 15%-30%, 31%-50%, and >50%) were compared between the groups. Secondary outcomes included amount of dextrose administered, time between dextrose administration and the next consecutive blood glucose value, the total number of blood glucose measurements following the hypoglycemic value (through 4 hours), relative degree of blood glucose overcorrection (defined as the [first blood glucose value after dextrose treatment – 70 mg/dL]/70), and ICU mortality. The number of patients failing to reach a blood glucose value ≥70 mg/dL after initial treatment was collected to ensure protocol safety.

Descriptive statistics were generated to characterize the population with respect to demographic and clinical factors.

### Table 1. Baseline Characteristics. a,b

<table>
<thead>
<tr>
<th></th>
<th>Preprotocol (n = 52)</th>
<th>Postprotocol (n = 53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.3 ± 14</td>
<td>65.7 ± 17</td>
<td>.61</td>
</tr>
<tr>
<td>Male</td>
<td>24 (46.2)</td>
<td>26 (49.1)</td>
<td>.77</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.2 ± 31</td>
<td>74.2 ± 21</td>
<td>.02</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>7.1 ± 4</td>
<td>7.0 ± 9</td>
<td>.97</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.4 ± 21</td>
<td>21.5 ± 22</td>
<td>.96</td>
</tr>
<tr>
<td>Diabetic</td>
<td>26 (50)</td>
<td>22 (41.5)</td>
<td>.38</td>
</tr>
<tr>
<td>Renal failure c</td>
<td>22 (42.3)</td>
<td>29 (54.7)</td>
<td>.20</td>
</tr>
<tr>
<td>Liver failure d</td>
<td>14 (26.9)</td>
<td>11 (20.8)</td>
<td>.46</td>
</tr>
<tr>
<td>ICU location</td>
<td></td>
<td></td>
<td>.015</td>
</tr>
<tr>
<td>Medical</td>
<td>22 (42.3)</td>
<td>37 (69.8)</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>16 (30.8)</td>
<td>10 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>14 (26.9)</td>
<td>6 (11.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APACHE, acute physiology and chronic health evaluation score; ICU, intensive care unit.

a Continuous data are expressed as the mean ± standard deviation.

b Categorical data are expressed as n (%).

c Data only from patient’s initial hypoglycemic episode.

d Coefficient of variability = standard deviation/mean blood glucose.

e Preprotocol group, n = 48.

### Table 2. Endpoint Comparison. a,b,c

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Preprotocol (n = 52)</th>
<th>Postprotocol (n = 53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient of variability (CV), %</td>
<td>49.3 ± 0.2</td>
<td>40.9 ± 0.2</td>
<td>.048</td>
</tr>
<tr>
<td>CV groups</td>
<td></td>
<td></td>
<td>.013</td>
</tr>
<tr>
<td>CV &lt; 15%</td>
<td>2 (4.2)</td>
<td>1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>CV 15%-30%</td>
<td>4 (8.3)</td>
<td>18 (34)</td>
<td></td>
</tr>
<tr>
<td>CV 31%-50%</td>
<td>20 (41.7)</td>
<td>20 (37.7)</td>
<td></td>
</tr>
<tr>
<td>CV &gt; 50%</td>
<td>22 (45.8)</td>
<td>14 (26.4)</td>
<td></td>
</tr>
<tr>
<td>Dextrose, g</td>
<td>21.2 ± 10.4</td>
<td>11.5 ± 5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Degree of overcorrection, %</td>
<td>86.3 ± 0.7</td>
<td>54.5 ± 0.4</td>
<td>.009</td>
</tr>
<tr>
<td>Time to recheck, minutes</td>
<td>61 ± 47</td>
<td>36 ± 25</td>
<td>.003</td>
</tr>
<tr>
<td>Number of glucose measurements</td>
<td>1.6 ± 0.5</td>
<td>1.57 ± 0.5</td>
<td>.76</td>
</tr>
<tr>
<td>Mortality</td>
<td>13 (25)</td>
<td>12 (22.6)</td>
<td>.78</td>
</tr>
<tr>
<td>Treatment failure e</td>
<td>5 (9.6)</td>
<td>4 (7.5)</td>
<td>.71</td>
</tr>
</tbody>
</table>

a Continuous data are expressed as the mean ± standard deviation.

b Categorical data are expressed as n (%).

c Data only from patient’s initial hypoglycemic episode.

d Coefficient of variability = standard deviation/mean blood glucose.

e Preprotocol group, n = 48.

f Degree of overcorrection: (first blood glucose value after treatment – 70 mg/dL)/70; excluded patients who had a hypoglycemic value at first blood glucose measurement posttreatment.

g Patients failing to reach a blood glucose value ≥70 mg/dL after initial dextrose treatment.
For continuous variables, the mean and standard deviations were computed, and the frequency distributions were used for categorical values. All comparisons were computed using Pearson chi-square tests for categorical variables and Student *t* test for continuous variables. Confounding variables were controlled with via stepwise multivariate logistic regression. Statistical analysis was performed using SPSS Windows version 21.0 (SPSS Inc, Somers, New York).

**Results**

Of the 247 patients screened, 52 were included in the preprotocol group and 53 in the postprotocol group. Baseline characteristics such as age, acute physiology and chronic health evaluation (APACHE) II score, diabetes, renal failure, and liver failure were similar between the groups. Weight was significantly lower in the postprotocol group (*P* = .02; Table 1). The majority of patients in both the pre- and the postprotocol groups were located in the medical ICU; however, there was a significantly larger proportion of patients in the medical ICU postprotocol (42.3% preprotocol vs 69.8% postprotocol).

The primary outcome, coefficient of variability, was significantly decreased in the postprotocol group as compared with the preprotocol group (40.9% vs 49.3%, *P* = .048; Table 2). In addition to comparing mean coefficient of variability, coefficient of variability subgroups were compared (<15%, 15%-30%, 31%-50%, and >50%). Figure 2 demonstrates an overall shift in patient distribution toward lower coefficient of variability subgroups after protocol implementation. There were less patients in the

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**Table 3. Dextrose 50% Treatment.**

<table>
<thead>
<tr>
<th>Blood glucose, mg/dL</th>
<th>&lt;15</th>
<th>15-25</th>
<th>26-35</th>
<th>36-45</th>
<th>46-60</th>
<th>61-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grams of dextrose 50%</td>
<td>25</td>
<td>20</td>
<td>17.5</td>
<td>12.5</td>
<td>10</td>
<td>7.5</td>
</tr>
</tbody>
</table>

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**Figure 1.** Nonpregnant adult intensive care unit (ICU) hypoglycemia treatment.

*Discuss precipitating factors for hypoglycemia; ensure appropriate insulin/nutrition management; and consider initiating dextrose infusion (dextrose 5% or 10%).*
who remained hypoglycemic in the postprotocol group at first which was used as a marker of protocol safety. Of the 4 patients immediately following treatment was similar between the groups, dextrose 50 hypoglycemic despite receiving multiple administrations of the groups (25 vs 61 minutes; P = .009). Time to repeat glucose after treatment was reduced in the postprotocol group (36 vs 61 minutes; P = .003), while the total number of glucose measurements remained similar between groups. Intensive care unit mortality was not significantly different between the groups (25% preprotocol vs 22.6% postprotocol).

The number of patients who remained hypoglycemic immediately following treatment was similar between the groups, which was used as a marker of protocol safety. Of the 4 patients who remained hypoglycemic in the postprotocol group at first blood glucose check, 3 of them were first assessed >100 minutes after dextrose 50% administration. One patient remained hypoglycemic despite receiving multiple administrations of dextrose 50% in conjunction with a dextrose 10% infusion.

**Discussion**

Currently, there is no accepted standard measurement of glucose variability. A recent meta-analysis concluded that glucose variability was associated with increased mortality. Interestingly, the meta-analysis noted that 13 different measures of glucose variability were reported in 12 trials, most commonly standard deviation and the presence of hypo- or hyperglycemia.15

Krinsley et al have conducted 2 of the largest glucose variability studies in mixed ICU patients, which have demonstrated that an elevated coefficient of variability was associated with increased mortality in nondiabetic patients despite an overall acceptable mean blood glucose.9,10 Similar to the Krinsley studies, we calculated the coefficient of variability and divided patients into groups based on the degree of glucose variability. It is important to note that the coefficients of variability in our study are not directly comparable to the mortality outcomes found in the Krinsley study because of differences in timing of data collection. Our study included blood glucose measurements surrounding hypoglycemic episodes, while their study evaluated all levels during ICU stay. Although we demonstrated that optimizing the amount of dextrose required to treat hypoglycemia decreases glucose variability, there was no associated difference in mortality seen between the groups.

Unlike previous studies, we were specifically attempting to minimize glucose variability through optimization of dextrose 50% treatment. The relative degree of overcorrection ([first blood glucose value after dextrose treatment − 70 mg/dL]/70) was utilized as an indicator of excess blood glucose elevation independent of initial hypoglycemic value. The degree of overcorrection was found to be substantially reduced in the postprotocol group, signifying that patients using the hypoglycemia treatment protocol demonstrated more controlled blood glucose correction.

The American Diabetes Association (ADA) recommends a standardized approach to hypoglycemia management; however, many institutions do not have a standardized hypoglycemia treatment protocol in place specific to critically ill patients. Prior to protocol implementation, the majority of hypoglycemia episodes in our ICUs were treated with either 12.5 g or 25 g of dextrose 50% at the provider’s discretion, which is consistent with the current ADA recommendations.19 Following evaluation of previously published literature and institutional data related to hypoglycemia, we developed a protocol that provided dextrose treatment recommendations dependent on blood glucose value. Richardson et al evaluated an equation designed to treat hypoglycemia without overcorrection: 0.3 × (100 − blood glucose) = milliliters of dextrose 50%. This equation was used in patients with hypoglycemic values ranging from 27 to 69 mg/dL, resulting in 4.5 to 12.5 g of dextrose 50% administered.18 Our dextrose treatment table was developed using elements of this equation; however, the correction factor was increased from 0.3 to 0.4 to ensure hypoglycemic episodes were not undertreated (Table 3). Titrating dextrose administration based on the initial hypoglycemia value, as our protocol recommends, was recently endorsed by a Society of Critical Care Medicine guideline regarding the use of insulin infusions in critically ill patients.20
A study measuring the effect of 25 g/50 mL (1 ampule) of dextrose in healthy volunteers (baseline 82 mg/dL) demonstrated that blood glucose rises rapidly, with the peak effect around 5 minutes (244 mg/dL) following administration and normalizing after 30 minutes.\textsuperscript{21} Unfortunately, monitoring this frequently after dextrose administration is uncommon in clinical practice. Our protocol-specified blood glucose monitoring is to be done 15 minutes after dextrose administration, which is consistent with current recommendations from the ADA.\textsuperscript{19} Failing to monitor blood glucose levels in a timely manner likely explains the instances in our study where treatment failed to achieve a blood glucose of 70 mg/dL or higher. In 3 (75\%) of these instances, blood glucose was checked greater than 100 minutes following dextrose administration, making the observed blood glucose level unlikely to have been affected by the treatment administered and more likely related to other patient factors.

Our study has noted limitations. Inconsistent timing of blood glucose monitoring exceeding ADA and protocol recommendations may have contributed to an underestimation of true glucose variability. The quasi-experimental design of our study may have introduced selection bias by only including postprotocol patients who received dextrose treatment per the protocol. This study design, however, was necessary to accurately assess the true impact of the protocol. Patient factors such as diabetes status, disease severity, ICU location, renal and hepatic failure, gender, and patient weight were assessed as confounding variables and found to have minimal impact on our results.

In conclusion, this study demonstrated that implementation of a standardized hypoglycemia treatment protocol reduced the degree of glucose variability in critically ill patients at our institution. Although less dextrose 50\% was administered following protocol implementation, no difference was seen in the number of hypoglycemic events which persisted after initial treatment.

**Declaration of Conflicting Interests**

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