Relationship between hypoglycemia and mortality in critically ill children*

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**Objectives:** To determine the prevalence of hypoglycemia in critically ill nondiabetic children and the association of hypoglycemia with mortality and worsening organ function in critically ill children.

**Design:** Retrospective cohort study with matched-cohort analysis.

**Setting:** Academic pediatric intensive care unit.

**Patients:** A total of 899 nondiabetic patients <18 yrs old admitted to the pediatric intensive care unit for >1 day with at least one blood glucose measurement. Forty-two patients with a blood glucose level of <50 mg/dL (<2.8 mmol/L) were matched with 126 nonhypoglycemic patients.

**Interventions:** None.

**Measurements and Main Results:** Hypoglycemia, based on point-of-care blood glucose measurements, occurred in 2.2% (<40 mg/dL [<2.2 mmol/L]) to 7.5% (<60 mg/dL [<3.3 mmol/L]) of the patients. Hypoglycemia was more common in patients on mechanical ventilation and/or vasopressor support. Severity of hypoglycemia correlated with an increased mortality rate. The highest odds ratio of mortality was 4.49 (95% confidence interval [CI], 1.69–11.96; p < .01) at a blood glucose level of <40 mg/dL (<2.2 mmol/L). In the matched analysis, hypoglycemia was an independent risk factor for mortality. The unadjusted, covariate-adjusted, and propensity score-adjusted odds ratios of mortality were 3.69 (95% CI, 1.78–7.68; p < .01), 4.16 (95% CI, 1.53–11.32; p < .01), and 8.45 (95% CI, 1.75–40.86; p < .01), respectively. Hypoglycemia was associated with worsening organ function in the covariate-adjusted model (odds ratio, 2.37; 95% CI, 1.12–5.01; p = .02) but not in the unadjusted and propensity-score adjusted models.

**Conclusions:** Hypoglycemia is common in critically ill children. It is associated with increased mortality rates in critically ill nondiabetic children. Our data suggest that hypoglycemia is also associated with worsening organ function. Hypoglycemia may merely be a marker of severity of illness. Further investigations are needed to establish the mortality risk with hypoglycemia due to insulin compared to spontaneous hypoglycemia. (Pediatr Crit Care Med 2010; 11:690–698)

**Key Words:** intensive care; insulin; severity of illness; glucose; outcome measure

Results of recent studies examining glycemic control in critically ill patients have highlighted the significance of hypoglycemia. In a landmark study by Van den Bergh et al (1), tightly controlling blood glucose (BG) levels at 80–110 mg/dL (4.4–6.1 mmol/L) with intravenous insulin achieved an absolute reduction of 3.4% in mortality rate in mechanically ventilated adult surgical patients.

The rate of severe hypoglycemia, which is the most important adverse outcome with insulin use, with BG at <40 mg/dL (<2.2 mmol/L), was six-fold higher in the intervention group compared to the control group in which BG was maintained at 180–200 mg/dL (10.0–11.1 mmol/L). Subsequent trials (2–4) designed to confirm the validity of the Van den Bergh et al study results failed to demonstrate any improvement in mortality rate. Higher hypoglycemia rates in the insulin-treated intervention groups have been postulated to negate the survival benefit of glycemic control (4, 5). Despite these findings, professional organizations (6–8) continue to recommend glycemic control in critically ill adults. In children, on the basis of the adult experience and in conjunction with nominal pediatric data, intravenous insulin is commonly used to achieve glycemic control in select subsets of critically ill children (9–12). Although hypoglycemia is a significant concern among pediatric intensivists (9, 13), the risks and outcomes of hypoglycemia in critically ill children are uncertain.

The prevalence of hypoglycemia in critically ill children has been previously reported (14, 15). However, the published rates were derived from all patients admitted to the pediatric intensive care unit (ICU). Hypoglycemia rates in critically ill children receiving vasopressor support and/or on mechanical ventilation, which are the target populations for glycemic control in children (11, 12, 16, 17), are unknown. Vasopressor support and mechanical ventilation are significant risk factors for hypoglycemia in critically ill adults (18, 19) and are also expected to affect the rates of hypoglycemia in children.

The relationship between hypoglycemia and mortality in children is unclear. Although implicated as a cause of "death-in-bed" syndrome in diabetic children, the risk of mortality has not been adequately quantified (20, 21). Wintergerst et al (14) reported an increased risk of mortality in critically ill nondiabetic children with hypoglycemia. However, the risk of mortality was only adjusted for hyperglycemia and glucose variability. Other factors, particularly severity of ill-

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*See also p. 752.

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ness and organ dysfunction, significantly affect outcomes in critically ill patients. Therefore, adjustments should be made for these factors to determine accurately the association between hypoglycemia and mortality. Hirshberg et al (15) and Kyle et al (22) did not detect increased mortality rates with spontaneous hypoglycemia and low BG due to insulin, respectively, in children because of insufficient sample size. The association between hypoglycemia due to insulin vs. spontaneous hypoglycemia on mortality is also important to determine. Increased rates of hypoglycemia in prematurely terminated trials on glycemic control (2, 4, 23) may not necessarily result in increased mortality in insulin-treated patients compared to patients with spontaneous hypoglycemia. From the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study (3), which is the largest trial to date on glycemic control in critically ill adults, significantly higher hypoglycemia and mortality rates in the insulin-treated group have been reported, but the effect of hypoglycemia on mortality is unknown. Results of the study by Egi et al (24) and the secondary analysis of the studies by Van den Bergh et al (25) and Arabi et al (26) for critically ill adults and Vlasselaers et al (27) for children indicated that hypoglycemia due to insulin does not increase mortality rates.

Routine glycemic control has not yet been adopted as standard practice by most pediatric ICUs. The fear of hypoglycemia is frequently cited as one of the primary concerns of this practice by pediatric intensivists (9, 13). The prevalence and outcomes of hypoglycemia should be more clearly defined. In this study, we aimed to determine the prevalence of hypoglycemia in non-diabetic critically ill children and the association of hypoglycemia with mortality and worsening organ function in children before the use of glycemic control in our ICU.

PATIENTS AND METHODS

We performed a retrospective cohort study with additional matched-cohort analysis. The setting was an 11-bed multidisciplinary pediatric ICU within a 944-bed not-for-profit private academic teaching hospital. The study included patients admitted to our ICU from January 1, 2000, to December 30, 2004. During this 5-yr period, the decision to control BG was left to the discretion of the attending physician. In all cases, insulin was used to treat hyperkalemia or glucosuria. During the study period, urine was examined for glucose spillage in patients with a BG level of >180 mg/dL (>10.0 mmol/L). The presence of more than trace amounts of glucose in the urine triggered treatment. There was no standard protocol for the treatment of glucosuria. BG was typically lowered below 180 and 200 mg/dL (10.0 and 11.1 mmol/L) by using a sliding scale of intravenous or subcutaneous insulin.

The study was approved by our institution’s Human Investigation Committee, which waived the need to obtain informed consent.

Subjects

All patients <18 yrs old admitted to the ICU during the study period were included if they had at least one point-of-care BG measurement and stayed in the ICU for >1 day (primary study group) (14, 15). The most recent admission was included for analysis to maximize the cases of mortality (14). Exclusion of readmissions and patients who stayed in the ICU for <1 day facilitated comparison with previous pediatric studies, which had similar exclusion criteria (14, 15). Prevalence and mortality analyses were performed on the primary study group. We also determined the prevalence of hypoglycemia among all patient admissions during the study period and in short-stay patients who were in the ICU for <1 day. Patients with diabetes mellitus and other disorders that can cause hypoglycemia, such as liver failure and inborn errors of metabolism (International Classification of Diseases, Ninth Revision codes 250.00, 250.01, 250.10, 250.11, 250.13, 251.1, 251.2, 271.0, 571.5, 571.6, 572.3, 775.6, and 751.62), were excluded (15).

In the matched analysis, patients with a BG level of <50 mg/dL (<2.8 mmol/L) from the primary study group were classified as case-patients (15, 28, 29). The hypoglycemic measurement was matched to a BG value from a patient chosen from the primary study group with a BG level between 80 and 110 mg/dL (4.4 and 6.1 mmol/L) but not having a BG measurement of <50 mg/dL (<2.8 mmol/L). Each case-patient was matched to controls with the same disease category (i.e., sepsis, respiratory syncytial virus, postoperative cardiovascular surgery, other medical conditions, and other surgical conditions). Disease category was used as a surrogate for severity of illness, because these data were not available in the databases. From among the control patients with the same disease category, secondary matching was performed on the basis of patient ages and number of days before the index event (i.e., hypoglycemic episode in cases or normoglycemic episode in controls), which minimizes the effect of ICU length of stay and its determinants that may affect the circumstances surrounding index events (19, 27). Control patients with ages and number of days before the index event closest to the case-patients were chosen for analysis. Each case-patient was matched with three controls to increase the statistical power of the analysis.

Data Source

Data were obtained from the hospital administrative cost-accounting database and medical records. BG measurements obtained with a SureStep Flexx Meter (LifeScan, Inc., Milpitas, CA) were recorded as part of the laboratory quality-assurance process for point-of-care testing in our Department of Laboratory Medicine. Data tables were exported from each of the data systems, imported into a relational database (Microsoft Access XP, Microsoft Corp, Redmond, WA), and linked by unique study numbers.

Measurements and Analysis

BG was obtained from arterial, venous, or capillary blood. It was common practice in our ICU to repeat the measurement with an arterial or venous blood if low BG was detected from capillary blood. BG values taken within 1 hr of a previous measurement were considered duplicates (19). The first BG value was used in the analysis unless the second value was >50 mg/dL (>2.8 mmol/L), which was the threshold in our ICU for treating hypoglycemia. In this case, the second value was used because it was assumed that the second value was used in making the clinical decision. The patient’s lowest BG level was used as an independent variable, and inhospital mortality was the primary outcome. Increasing Pediatric Logistic Organ Dysfunction (PELOD) score on the day of the index event, which is a composite measure of worsening organ function, was used as the secondary outcome in the nested study (27, 30, 31).

Hypoglycemia was defined on the basis of three cutoff values: <40 mg/dL (<2.2 mmol/L) (severe); <50 mg/dL (<2.8 mmol/L) (moderate); and <60 mg/dL (<3.3 mmol/L) (mild) (11, 15, 28). The prevalence of hypoglycemia among all patients and in patients receiving different organ support was computed as percentage of patients. The odds ratio (OR) of hypoglycemia in patients who received different organ support compared to patients without organ support were also estimated.

ORs were calculated to determine the association between mortality and hypoglycemia. Adjustments were made for age, disease category, vasopressor support, use of mechanical ventilation, hyperglycemia, and glucose variability. Because severity-of-illness score was not available for the primary study group, disease category, vasopressor support, and mechanical ventilation were used as surrogates because they are often used to define organ dysfunction (31, 32). Hyperglycemia (i.e., BG
>150 mg/dL [>8.3 mmol/L]) and glucose variability (i.e., glucose variability index ≥20 mg/dL/hr [≥1.1 mmol/L/hr]) were previously shown to be independently associated with mortality (14, 15, 28, 33). Except for age, all variables were coded dichotomously. Hypoglycemia was further characterized as isolated or recurrent. We also attempted to classify hypoglycemia in the primary study group as spontaneous or caused by insulin. However, our databases did not contain the time that insulin was given to the patients to allow us to correlate the hypoglycemia with insulin administration.

In the matched analysis, severity-of-illness (Pediatric Index of Mortality 2 [PIM2]) (34) and PELOD scores were collected on the day of admission. The following data were obtained on the day of the index event from the patients’ medical records: weight, presence of renal or liver dysfunction (31, 32), sepsis, and PELOD score. Within an hour of the index event, the following variables were collected: use of mechanical ventilation, vasopressor support, use of renal replacement therapy, insulin administration, presence of enteral feeds, and total calories from carbohydrates. Presence of hyperglycemia, glucose variability, and percentage of days that the patient was hyperglycemic were evaluated over the patient’s entire ICU stay (14, 28). Although hyperkalemia did not predispose to hypoglycemia, it was included because insulin was administered for hyperkalemia during the study period. Medications such as β blockers, steroids, oral hypoglycemic agents, and octreotide may affect the development of hypoglycemia (18, 19). However, even after a review of the patients’ medical records, we could not accurately determine the medications each patient received and the time the medications were administered. These medications were not included in the analysis. All factors were coded as dichotomous variables except for weight, PIM2 score, percentage of hyperglycemic days, and caloric intake.

The association between hypoglycemia and mortality in the matched-cohort analysis was assessed by using propensity score–adjusted and covariate-adjusted models (35, 36). Propensity scores are commonly used to minimize selection bias in quasi-randomized studies. Bivariate analysis, using conditional logistic regression, was performed to determine which patient factors were significantly different between the case-patients and controls at p < .25. With hypoglycemia as the dependent variable, multivariate logistic regression with backward variable selection was performed. Glucose variability, percentage of hyperglycemic days, PIM2 score, mechanical ventilation, and caloric intake were included in the final equation describing the propensity score for the development of hypoglycemia. The score and its interaction with hypoglycemia were incorporated as covariates in the final model with mortality as the dependent variable. This method theoretically normalizes the likelihood of development of hypoglycemia and may effectively adjust for unobserved confounding and selection bias, thereby refining the regression estimates (36).

Because insulin was used for life-threatening hyperkalemia during the study period, we developed an additional conditional logistic regression model with hypoglycemia, the propensity score for the development of hypoglycemia, the interaction between hypoglycemia and the propensity score, insulin use and hyperglycemia as covariates, and mortality as the dependent variable. This will determine whether any association between hypoglycemia and mortality was due to hyperkalemia and/or insulin.

In the covariate-adjusted model, the variables used in creating the propensity score were entered as covariates in a conditional logistic regression model with mortality as a dependent variable. The procedure was repeated with worsening organ function as a dependent variable.

Summary statistics are presented as mean ± SD or frequency (%). Student’s t test, Mann-Whitney U test, or Pearson chi-square test was used as appropriate. Outcome measures are expressed as ORs with 95% confidence intervals (CIs). A p value of <.05 was considered statistically significant. Pearson’s correlation was used to assess collinearity between variables in the different regression models. A P value of >.80 was considered significant for correlation. Statistical analyses were performed by using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Patient Population

During the study period, there were 3,557 admissions to the ICU with 1,312 different patients who stayed in the ICU for >1 day (Fig. 1). A total of 899 patients had at least one BG measurement and were included in the analysis as the primary study group. Patients with BG measurements were younger, had usually undergone cardiovascular surgery, were more likely to be treated with vasopressor support or mechanical ventilation, and had a higher mortality rate (Table 1). A total of 11,738 BG measurements were obtained from the patient cohort, with an average of 13.1 ± 3.0 BG measurements per patient.

There were 540 readmissions during the study period (Fig. 1). At least one BG measurement was obtained from 1,050 of the 3,348 patient admissions. The baseline characteristics in all patient admis-
Table 1. Characteristics and outcomes of nondiabetic patients admitted to the intensive care unit during the study period

<table>
<thead>
<tr>
<th>Patients With Length of Stay &gt;1 Day</th>
<th>All Patient Admissions: Patients With Glucose Measurements (n = 1050)</th>
<th>Patients With Length of Stay &lt;1 Day: Patients With Glucose Measurements (n = 425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With Glucose Measurements</td>
<td>Patients Without Glucose Measurements</td>
<td>Patients With Glucose Measurements</td>
</tr>
<tr>
<td>(n = 899)</td>
<td>(n = 413)</td>
<td>(n = 1050)</td>
</tr>
</tbody>
</table>

| Age, yrs                          | 4.9 ± 6.0                                      | 4.5 ± 5.5                                      | 6.3 ± 5.9                                      |
| Male gender                       | 490 (54.5)                                     | 591 (56.3)                                    | 224 (52.7)                                    |

| Disease category                  |                                                |                                                |                                                |
| Medical                            | 360 (40.0)                                     | 448 (42.7)                                    | 148 (34.8)                                    |
| Sepsis                             | 27 (3.0)                                       | 29 (2.8)                                      | 11 (2.6%)                                     |
| RSV                                | 44 (4.9)                                       | 54 (5.1)                                      | 7 (1.6%)                                      |
| Surgical                           | 249 (27.7)                                     | 259 (24.7)                                    | 160 (37.6%)                                   |
| CV surgery                         | 192 (21.4)                                     | 234 (22.2)                                    | 98 (23.1)                                     |
| TBI                                | 27 (3.0)                                       | 26 (2.5)                                      | 1 (0.2%)                                      |
| Mechanical ventilation             | 229 (24.5)                                     | 291 (27.7)                                    | 44 (10.4%)                                    |
| Vasopressor support                | 138 (15.4)                                     | 186 (17.7)                                    | 13 (3.1%)                                     |
| Mortality rate                     | 82 (9.1)                                       | 77 (7.3)                                      | 14 (3.3%)                                     |

| RSV, respiratory syncytial virus; CV, cardiovascular; TBI, traumatic brain injury. |                                                |                                                |                                                |

Patients with lengths of stay >1 day with blood glucose measurements were used as referents for the comparisons. Values expressed are mean ± sd or n (%). \( p < .05; \) \( p < .01. \)

Table 2. Characteristics of hypoglycemic case-patients and normoglycemic control patients

<table>
<thead>
<tr>
<th>Patients With BG &lt;50 mg/dL (≤2.8 mmol/L) (n = 42)</th>
<th>Patients With BG Between 80 and 110 mg/dL (4.4–6.1 mmol/L) (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>0.7 ± 1.9</td>
</tr>
<tr>
<td>Male gender</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>Disease category</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>RSV</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Surgical</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>CV surgery</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Number of days to index event</td>
<td>7.8 ± 12.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>5.8 ± 5.8</td>
</tr>
<tr>
<td>PIM2, %</td>
<td>15.3 ± 23.4</td>
</tr>
<tr>
<td>PELOD score on admission(^a)</td>
<td>14 ± 13</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>Glucose variability</td>
<td>7 (16.7)</td>
</tr>
<tr>
<td>Percentage of days hyperglycemic(^b)</td>
<td>3.1 ± 7.1</td>
</tr>
<tr>
<td>Mechanical ventilation(^c)</td>
<td>38 (90.5)</td>
</tr>
<tr>
<td>Vasopressor support(^d)</td>
<td>27 (63.4)</td>
</tr>
<tr>
<td>Renal replacement therapy(^e)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Insulin(^f)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Enteral feeds</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Total calories from carbohydrate source, kcal/kg/hr</td>
<td>1.0 ± 0.6</td>
</tr>
</tbody>
</table>

\( BG, \) blood glucose; \( RSV, \) respiratory syncytial virus; \( CV, \) cardiovascular; \( PIM2, \) Pediatric Index of Mortality 2; \( PELOD, \) Pediatric Logistic Organ Dysfunction.

\(^a\) Values expressed are mean ± sd median (1st quartile–3rd quartile), or \( n \) (%).
Increased blood glucose defined as blood glucose non-episodes had two- to six-fold increased odds of hypoglycemia. Patients receiving both interventions were between four- to four-fold increased odds of death compared with patients with BG levels above the corresponding threshold values. Because a BG level of 80 mg/dL (4.4 mmol/L) is often used as a lower limit for glycemic control (1, 2, 4, 11, 26, 37–39), we compared the mortality rates of patients with hypoglycemia with the mortality rates of patients with the lowest BG level of at least 80 mg/dL (4.4 mmol/L). The adjusted OR of mortality was significantly higher in hypoglycemic patients at all threshold values. The OR of mortality was 7.22 (95% CI, 2.17–24.04; p < .01) with severe hypoglycemia, 2.52 (95% CI, 1.53–8.10; p < .01) with moderate hypoglycemia, and 3.32 (95% CI, 1.57–7.06; p < .01) with mild hypoglycemia.

The presence of recurrent hypoglycemia at any threshold value was highly related with mortality (Table 4). Among patients with isolated episodes of hypoglycemia, only severe hypoglycemia increased the odds of death. The mean duration from the last episode of hypoglycemia to death was 12.5 days for severe hypoglycemia (range, 0–91 days), 14.3 days for moderate hypoglycemia (range, 0–91 days), and 24.9 days for mild hypoglycemia (range, 0–138 days).

In the matched analysis of patients with moderate hypoglycemia, hypoglycemia was associated with mortality inde-
dependent of age, disease category, length of stay in the ICU before the index event, glucose variability, percentage of hyperglycemic days, PIM2 score, use of mechanical ventilation, and caloric intake (Fig. 4A). Unadjusted, covariate-adjusted, and propensity score-adjusted ORs of mortality were 3.69 (95% CI, 1.78–7.68; \( p < .01 \)), 4.16 (95% CI, 1.53–11.32; \( p < .01 \)), and 8.45 (95% CI, 1.75–40.86; \( p < .01 \)), respectively. The association between hypoglycemia and mortality cannot be attributed to hyperkalemia or to insulin. In the propensity score–adjusted model, which incorporated hyperkalemia and insulin as covariates, the OR of mortality was 5.78 (95% CI, 1.10–30.26; \( p < .05 \)) for hypoglycemia and 2.52 (95% CI, 0.41–15.31; \( p = .32 \)) for hyperkalemia; we were unable to calculate the OR for insulin.

The association between hypoglycemia and worsening organ function was not consistent among the different statistical models used (Fig. 4B). Only the covariate-adjusted model reached statistical significance (OR, 2.37; 95% CI, 1.12–5.01; \( p = .02 \)). No significant correlation was detected between the variables included in the different logistic regression models.

**DISCUSSION**

We report that hypoglycemia is common in critically ill nondiabetic children, especially in patients who require vasopressor support or mechanical ventilation. Hypoglycemia is an independent risk factor for mortality with odds of death higher with increased severity of...
hypoglycemia, with recurrent hypoglycemia at all three threshold values evaluated, and with isolated episodes of severe hypoglycemia. Our data suggest that hypoglycemia is also associated with worsening organ function.

The hypoglycemia rates in our study were primarily based on nondiabetic critically ill children who stayed in the ICU for >1 day and had at least one BG measurement. The prevalence of hypoglycemia in our study is comparable to previously reported rates in critically ill children with the same patient characteristics and adults (1–4, 15, 27, 37). Inclusion of all nondiabetic patient admissions during the study period slightly increased the prevalence of mild hypoglycemia but not moderate and severe hypoglycemia.

It is important to determine the prevalence of hypoglycemia on the basis of BG level. However, it is also essential to determine the prevalence of hypoglycemia on the basis of severity of illness, including amount of organ support (12, 18, 19). Variations in reported hypoglycemia rates may partly be due to differences in severity of illness and organ support that the patients were receiving at the time of BG measurement (12, 40). Patients who stayed in the ICU for <1 day were, in general, less ill and had lower prevalence rates of hypoglycemia, although a small cohort of short-stay patients were much sicker and died within a day of admission. On the contrary, hyperglycemic patients who required organ support, who were the sickest patients in the ICU, had hypoglycemia rates at least four-fold higher than patients who were not on vasopressor or mechanical ventilation. These patients are thought to benefit the most from glycemic control (11, 12, 16, 17). Studies (11, 12, 22, 27, 41) on glycemic control protocols in children that target similar patient populations reveal hypoglycemia rates ranging from 0% to 25% of patients, depending on the targeted BG range.

Patients who received mechanical ventilation and/or vasopressor support had increased rates of hypoglycemia in our study population. It is interesting to note that mechanical ventilation and/or vasopressor support are also risk factors for hyperglycemia in critically ill children (28, 40). Multiple organ dysfunction has been implicated in glucose dysregulation in critically ill patients (22). Children with at least three organ dysfunctions have more prolonged hyperglycemia and higher incidence of hypoglycemia. BG levels in these patients are also more difficult to control. It is highly likely that the association between hypoglycemia and mechanical ventilation and/or vasopressor support is a reflection of the underlying association between low BG level and multiple organ dysfunction. Treatment with these interventions should alert the clinician to the possibility of abnormal glucose metabolism.

We found that hypoglycemia is associated with mortality independent of several factors that affect outcomes in critically ill children, including severity of illness. Wintemberger et al (14) reported the same association, although no adjustment for severity of illness was performed in their study. Similar to the study by Egí et al (24) of critically ill adults, we note that mortality increased with the severity of hypoglycemia. Even mild and moderate hypoglycemia was also associated with mortality. In the same study, recurrent and severe isolated hypoglycemic episodes were associated with increased odds of death similar to what we report. It is unlikely that the association between hypoglycemia and mortality in our study was due to hyperkalemia and use of insulin based on the lack of statistical significance on the analysis performed.

We attempted to determine the association between spontaneous or insulin-induced hypoglycemia with mortality. Our inability to confirm definitely the temporal relationship between hypoglycemia and insulin administration in the primary study group and the small sample size in the matched analysis prevented us from making any conclusions.

Hypoglycemia can be physiologically linked to increased mortality. Acutely, low BG levels can lead to lethal neurologic and cardiac effects (20, 21, 27, 42). In the ICU, critical illness and sedation may mask seizures and coma but not significant arrhythmias. None of the patients in this study had documented seizures, coma, or arrhythmias.

Hypoglycemia may be another marker of severity of illness. Several lines of evidence from our study support this argument. The prevalence of hypoglycemia is highest in severely ill patients and lower in less ill patients. Isolated episodes of low BG levels, unless severe, do not increase the risk of death, whereas recurrent hypoglycemia at all levels is associated with mortality. Deaths, if directly due to hypoglycemia in our study, would be expected to occur close to the hypoglycemic event. Patients, on average, died 2 to 3 weeks after the last episode of hypoglycemia.

Hypoglycemia in critically ill patients is thought to result from impairment of counterregulatory hormones, which leads to insulin resistance and impaired gluconeogenesis (42). It may be expected that, with greater severity of illness and higher risk of death, the patient's ability to regulate BG levels will be highly impaired, which leads to severe and recurrent hypoglycemia. The association of hypoglycemia and mortality in our study was independent of PIM2 score. The PIM2 does not incorporate BG levels in the scoring system.

The low mortality rate in children requires prohibitively large sample sizes for interventional trials. Alternative outcome measures, such as PELOD score, are being evaluated (30, 43). It is conceivable that an improvement in the PELOD score can be expected with glycemic control on the basis of the trial by Vlasselaers et al (27). Kyle et al (22) also noted a significant association between severe hypoglycemia and at least three organ dysfunctions. However, Yung et al (30) found that early hyperglycemia was associated with death but not with worsening PELOD score. Our data suggest that there is an association between hypoglycemia and worsening PELOD score. Hypoglycemia was found to be an independent risk factor for worsening organ function in the covariate-adjusted model but not in the other models. The PIM2 score, which is related to hypoglycemia and worsening organ function, produced a suppressive effect when the association was not adjusted for severity of illness. The patients in the study by Kyle et al (22) had higher initial PELOD scores. The authors also used a lower BG threshold in their study. The significantly increased unadjusted OR of hypoglycemia in patients receiving vasopressor support or mechanical ventilation in our study further supports the association between hypoglycemia and worsening organ function.

Our study has several strengths. The prevalence of hypoglycemia was calculated at different thresholds for patients receiving diverse interventions. Evaluation of hypoglycemia rates with other institutions and studies may be facilitated by comparing patients receiving similar treatments and severity of organ dysfunction (12, 40). The relationship between hypoglycemia and mortality was analyzed by using different study designs and statistical models. Consistency of the results
surements were used to diagnose hypoglycemia. In pediatric studies in which laboratory BG measurements in critically ill children are similar to other pediatric studies, our reported prevalence rates are likely to be less severe. Our study also has limitations that deserve consideration. Risks of mortality were based on a select subset of patients. We specifically obtained information on patients who stayed in the ICU for >1 day, with at least one BG measurement, and during the patient’s most recent admission to detect the highest mortality rate. The mortality rate of 9.1% in the patient cohort was higher than the average mortality rate reported in pediatric ICUs (22, 33, 44). This may, therefore, overestimate the reported OR of mortality. However, due to the low rate of mortality and hypoglycemia in children, significantly larger sample sizes will be needed to prove the association between mortality and hypoglycemia if less severely ill patients are chosen.

BG levels were measured by using a point-of-care device. We do not routinely send blood samples to the laboratory for confirmation of hypoglycemic values; thus, we do not have data to validate our measurements from the glucometer with laboratory data. Due to the rapidity of the results, clinical decisions are made on the basis of point-of-care measurements in our unit and other ICUs (22, 26, 45, 46). Inaccuracies with bedside glucometers, particularly due to patient factors such as anemia, poor perfusion, and use of vasopressor support, have been highlighted in previous publications (45–47). Direct comparisons between different glucometers and laboratory BG measurements in critically ill patients have indicated that glucometers frequently provide falsely elevated values, especially in the hypoglycemic range (48–51). The use of glucometers, therefore, poses a risk with glycem control, because patients may be provided insulin for a factitiously elevated BG. In our study, the falsely elevated BG values obtained from the glucometer may underestimate the prevalence of hypoglycemia in our primary study group. The potential error in our estimates does not seem to be significantly large, because our reported hypoglycemia rates are similar to other pediatric studies in which laboratory BG measurements were used to diagnose hypoglycemia. The use of different threshold values should minimize the diagnostic bias introduced in the prevalence estimates.

The absence of glucose measurements in one-third of the patients might have led to selection bias. It is highly likely that none of the excluded patients had hypoglycemia on the basis of age and severity of illness. In such a case, our reported prevalence rate would be an overestimation of the true rate. Calculating for the potential error, hypoglycemia might be as low as 1.5% to 5.1% depending on the severity of hypoglycemia, which is still consistent with reported rates. However, the crude OR of mortality would be as high as 17.4 at the lowest BG threshold. To reduce the unadjusted OR to nonsignificant levels, >20%, 35%, and 47% of the patients without BG measurements should have severe, moderate, and mild hypoglycemia, respectively, which are unlikely considering the patients’ presumed severity of illness and reported prevalence rates. The exclusion of seven patients with moderate hypoglycemia with missing charts from the matched analysis did not affect our conclusion. The OR of mortality in the matched analysis was similar to the odds calculated from the primary study group.

The increased prevalence of hypoglycemia in patients receiving mechanical ventilation or vasopressor support suggests that these patients should be closely monitored. Continuous glucose monitors may improve our ability to detect abnormal BG measurements in critically ill patients (52). Provision of adequate calories is also important for minimizing hypoglycemia in this patient population. Additional studies on hypoglycemia are needed. Large patient samples are required to determine the effects of hypoglycemia due to insulin on mortality compared to spontaneous hypoglycemia. The effect of hypoglycemia due to insulin may also vary at different ages and needs to be investigated (53). Although we focused primarily on the acute outcomes of hypoglycemia, specifically mortality and worsening organ function, long-term effects of low BG on nondiabetic children, including neurodevelopmental outcomes, are equally important. Risk factors for the development of hypoglycemia in children should also be studied to better identify ICU patients at risk for low BG. Finally, biological mechanisms that lead to hypoglycemia in critically ill children are also warranted.

CONCLUSION

In critically ill non-diabetic children who stayed in the ICU for >1 day with at least one BG measurement, we report that hypoglycemia was common, particularly in children who received mechanical ventilation or vasopressor support. Hypoglycemia is independently associated with mortality. However, hypoglycemia may merely be a marker of severity of illness. Low BG, especially when severe or recurrent, is associated with mortality. Our data suggest that hypoglycemia is also associated with worsening organ function. Further investigations are needed to establish the mortality risk with hypoglycemia due to insulin compared to spontaneous hypoglycemia.

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REFERENCES


