Journal of Critical Care 36 (2016) 13–17

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Medication-induced and spontaneous hypoglycemia carry the same risk for hospital mortality in critically ill patients☆

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ARTICLE INFO

Available online xxxx
Keywords:
Hypoglycemia
Iatrogenic disease
Insulin
Blood glucose
Intensive care
Mortality

ABSTRACT

Purpose: Hypoglycemia is associated with increased mortality, but the role of its etiology is unclear. This study aimed to examine the impact of hypoglycemia etiology on mortality risk among critically ill patients.
Methods: This single-center, retrospective, cohort study evaluated adult patients admitted to the medical or surgical intensive care unit, who experienced medication-induced or spontaneous hypoglycemia (blood glucose <70 mg/dL) during intensive care unit admission. Patients who became hypoglycemic following receipt of glucose-lowering therapy within a predefined time period were categorized in the medication-induced group. Periods were determined for each agent based on expected pharmacokinetics in critically ill patients. Patients who became hypoglycemic with no identifiable cause were categorized in the spontaneous group. Primary analysis compared medication-induced and spontaneous hypoglycemia with a primary endpoint of all-cause hospital mortality. Secondary analyses stratified patients by diabetes, severity of hypoglycemia, and glycemic variability.
Results: A total of 642 patients were eligible for inclusion (305 medication-induced and 337 spontaneous). When adjusted for covariates, no difference in hospital mortality was observed based on hypoglycemia etiology (odds ratio, 1.22 [0.77-1.93]; $P = .39$). Regardless of etiology, hypoglycemic severity, frequency, and glycemic variability were significantly associated with higher odds of hospital mortality. Hypoglycemic etiology did not impact hospital mortality when patients were stratified by presence or absence of diabetes.
Conclusions: Medication-induced hypoglycemia appears to be equally harmful as spontaneous hypoglycemia during critical illness. Future studies should aim to identify strategies to minimize hypoglycemia regardless of etiology, while also minimizing glycemic variability associated with hypoglycemia treatment.

1. Introduction

Although early studies suggested significant survival benefits from intensive insulin therapy (goal blood glucose [BG] 80-110 mg/dL) among critically ill patients, increased hypoglycemia and mortality rates have raised concerns about this approach [1-4]. More recent studies have identified severe hypoglycemia (BG <40 mg/dL), as well as mild and moderate hypoglycemia, as independent predictors of mortality [5-9]. Other related factors including glycemic variability have been demonstrated to contribute to negative sequelae in the presence of hypoglycemia [9].

Despite increasing evidence supporting an association between hypoglycemic severity and increased risk of mortality, it remains unclear whether the cause of hypoglycemia in hospitalized patients impacts clinical outcomes [8,10]. It is generally accepted that spontaneous hypoglycemia is harmful, although it may be a marker of illness severity rather than a cause of mortality as it may be precipitated by factors such as hepatic impairment or adrenal insufficiency. In patients with acute myocardial infarction, Kosiborod and colleagues [10] demonstrated that only spontaneous hypoglycemia was associated with increased mortality. The few data published regarding the impact of medication-induced hypoglycemia are less clear. In secondary analysis in a general critical care population, Egi and colleagues [8] found no difference in the association between mortality and medication-induced vs spontaneous hypoglycemia. Therefore, there is a need to further explore hypoglycemic etiology as primary analysis. Differentiating the impact of medication-induced and spontaneous hypoglycemic etiology on mortality may provide insight into optimal glycemic management. Therefore, we aimed to clarify the impact of hypoglycemic etiology on

☆ Conflicts of interest: none.

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http://dx.doi.org/10.1016/j.jcrc.2016.06.010
0883-9441/

clinical outcomes in the general critical care population to identify whether medication-induced and spontaneous hypoglycemia has equal consequence. We hypothesized that critically ill patients with spontaneous hypoglycemia have a higher risk for hospital mortality than those with medication-induced hypoglycemia.

2. Materials and methods

This single-center, retrospective, cohort study at an academic tertiary care medical center compared medication-induced hypoglycemia and spontaneous hypoglycemia with a primary endpoint of all-cause hospital mortality. Adult patients, 18 to 89 years of age, with hypoglycemia (defined as BG <70 mg/dL) while admitted to the medical or surgical intensive care unit (ICU) between April 24, 2010, and August 31, 2011, were eligible for evaluation. This study was approved by the Ohio State University Institutional Review Board.

Patients who experienced at least 1 BG <70 mg/dL during ICU admission were evaluated for etiology and classified as either medication-induced or spontaneous. If capillary and plasma measurements fell within different ranges within 1 hour of being drawn, the plasma value superseded the capillary value for determining hypoglycemia occurrence. Medication-induced hypoglycemia was defined by receipt of glucose-lowering therapy including sulfonylureas, meglitinides, and subcutaneous or intravenous insulin before the hypoglycemic event. A temporal relationship for hypoglycemia was determined by reviewing the medication administration record within a defined time period preceding hypoglycemia. We considered hypoglycemic events to be medication-induced if they occurred within 6, 12, 24, and 48 hours, respectively, for insulin lispro or aspart; insulin regular; insulin NPH or 70/30; insulin detemir, glargine, sulfonylureas or meglitinides. These time intervals were chosen based on published durations of action and potential for delayed absorption, and/or prolonged effect in the critically ill population due to obesity, edema, hypoperfusion, and the prevalence of renal failure. Home medications taken before admission and medications administered in the emergency department were not available for evaluation. Spontaneous hypoglycemia was defined as hypoglycemic episodes with no identifiable preceding insulin or glucose-lowering therapy.

Patients were excluded from the study if they were pregnant, incarcerated, admitted for diabetic ketoacidosis or hyperosmolar nonketotic state, or if they received peritoneal dialysis. Patients with more than 1 occurrence of contradictory plasma and capillary measurements within 1 hour of being drawn (eg, plasma BG <70 mg/dL vs capillary BG ≥70 mg/dL) and patients who met criteria for both medication-induced and spontaneous hypoglycemic events at different times throughout their ICU admission were excluded.

Estimates from previous literature were used to estimate probabilities and odds ratios (ORs) for the calculation of the sample size. With a sample size of 558 (223 insulin-induced and 335 spontaneous), this study would have at least 80% power to detect a hospital mortality OR of 1.75 for the primary analysis comparing insulin-induced vs spontaneous hypoglycemia, given a 0.2 probability of hospital mortality for the insulin-induced group.

Demographic characteristics and medical histories were collected from medical records. Patients with hepatic insufficiency, chronic pancreatitis, and diabetes were identified by medical history documented in history and physical notes. Diabetes was not differentiated by type (ie, 1 or 2). Admission data including location (ie, medical or surgical ICU), reason for ICU admission (ie, respiratory, trauma/burn, abdominal, neurologic, cardiovascular, other), liver function tests, and Acute Physiology and Chronic Health Evaluation (APACHE) II score at the time of ICU admission were also recorded. The Cockcroft-Gault formula was used to estimate creatinine clearance.

Glycemic variables collected included total number of BG measurements and number of hypoglycemic events. Duration of hypoglycemia was determined as the time of the hypoglycemic BG value to the time of the first subsequent BG measurement of at least 70 mg/dL. Severity of hypoglycemia was determined by categorizing minimum BG measurements in the following ranges corresponding with severe, moderate, and mild hypoglycemia: <40, 40 to 54, and 55 to 69 mg/dL, respectively. All glucose values measured in the ICU were evaluated for mean, minimum, and maximum, time-weighted mean glucose (TWMG), and glycemic variability as indicated by the glycemic lability index (GLI) [11,12]. Time-weighting of mean glucoses was used to avoid bias of varying frequency of BG measurements. The TWMG is a measure of total glucose exposure, which is calculated using the trapezoidal rule divided by the total time in hours [3]. In the time-weighted assessment, glucose measures that are obtained close together carry less overall influence on the mean than similar values that are farther apart in time. The TWMG is significantly lower than unadjusted mean glucose, but higher than mean morning glucose due to the varying sampling interval produced by capillary glucose monitoring that is concentrated during daytime hours [11]. The GLI is a measure of glucose variability, determined by the sum of the square of the difference between successive glucose measurements, divided by the difference in time between measurements [12]. Importantly, the calculation of GLI takes into account the rate of change in glucose, whereas other commonly used measures of variability, the standard deviation and coefficient of variation, do not.

Glucose management during the study period was initially via subcutaneous sliding scale with insulin administration indicated for BG 120 mg/dL or greater. Glucose monitoring occurred every 6 hours following admission BG measurement, and 2 consecutive BG values 200 mg/dL or greater despite sliding scale therapy warranted escalation to a continuous insulin infusion. Continuous therapy could also be initiated at the discretion of the provider. Continuous insulin infusions were titrated hourly based on point-of-care BG values using a standardized nursing protocol with a target BG of 110 to 150 mg/dL. This range was chosen to minimize risks of hypoglycemia that have been associated with intensive insulin therapy.

2.1. Statistical design and analysis

Summary statistics are reported separately for medication-induced and spontaneous hypoglycemia patients as mean (SD) or median (interquartile range [IQR]) for continuous variables and frequency (%) for categorical variables. Demographic and clinical variables were compared between hypoglycemic groups using Wilcoxon rank sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables, as appropriate.

The primary outcome, all-cause hospital mortality, was analyzed as the dependent variable using logistic regression. The independent variable of interest was hypoglycemic status: medication-induced or spontaneous. The model also contained covariates to adjust for severity and frequency of hypoglycemia, age, sex, APACHE II score (without age component), admission location (ie, medical or surgical ICU), diabetes, and chronic pancreatitis. Age was removed from the APACHE II score because age was included in the model as a covariate. Subgroup analyses of patients with and without diabetes were also performed.

In secondary analyses glycemic variability and severity, duration, and frequency of hypoglycemia were evaluated as predictors of hospital mortality. The models assessing these variables contained the same core covariates as the model for our primary outcome (all those above except severity and frequency of hypoglycemia).

Glycemic variability was evaluated using the GLI of all ICU blood glucose measures for each patient. The GLI was calculated daily for each patient as the sum of the time-weighted variability measures: the squared differences in successive blood glucose measures divided by the time between measures (in hours). The median of daily GLI measures was calculated for each patient to obtain 1 GLI per patient. The GLI was calculated daily to prevent instances of large intervals between measures (eg, several days) from being overly influential. The GLI were included