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Higher insulin infusion rate but not 24-h insulin consumption is associated with hypoglycemia in critically ill patients☆

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ABSTRACT

Aims: To assess the association between insulin infusion rates, and 24-h insulin consumption on hypoglycemia in the intensive care unit (ICU).

Methods: This was a retrospective case–control study, conducted at an academic institution in the United States. Adult patients admitted to the ICU receiving intravenous insulin infusions for blood glucose control were included. Hypoglycemic (blood glucose <70 mg/dL) patients were matched 1:1 with non-hypoglycemic controls based on age, gender, and body mass index. Multivariable conditional logistic regression analyses were conducted to determine the effect of: (1) weight-adjusted insulin infusion rate (units/kg/h), (2) non-weight-adjusted insulin infusion rate (units/h), or (3) 24-h insulin consumption (units/day) on hypoglycemia.

Results: A total of 122 patients were included in the study (61 cases, 61 controls). Compared to those patients who received <0.05 units/kg/h, the odds of hypoglycemia was higher in those who received was ≥0.1 units/kg/h (OR 4.57, 95% CI 1.45–14.41, $p = 0.010$). Compared to those patients who received <4 units/h, the odds of hypoglycemia was higher in those who received was ≥8 units/h (4.17, 95% CI 1.18–14.75, $p = 0.027$). The risk of hypoglycemia did not increase with higher 24-h insulin consumption.

Conclusions: Higher insulin infusion rates rather than 24-h insulin consumption may be associated with hypoglycemia in critically ill patients in the ICU.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; NPH, neutral protamine hagedorn; SOFA, sequential organ failure assessment; WBC, white blood cell.

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1. Introduction

Hyperglycemia in the intensive care unit (ICU) has been associated with increased morbidity and mortality [1–3]. Thus correction of elevated blood glucose is considered to be the standard of care in the critically ill [4]. In the past, tight glucose control entailed maintaining serum concentrations between 80 and 110 mg/dL [1,3]. However, this has been shown to be associated with greater hypoglycemia and mortality compared to less stricter limits such as less than 180 mg/dL [5,6]. Thus the occurrence of hypoglycemia, defined as a blood glucose level of less than 70 mg/dL, continues to be a concern in the ICU [4]. Currently, most institutions balance the benefits of glucose control with the risk of hypoglycemia by treating patients in the ICU with a continuous intravenous (IV) infusion of insulin to maintain blood glucose concentrations of less than 150–180 mg/dL [4,5]. This is done in conjunction with hourly blood glucose measurements and infusion titration. These definitions, goals, and practice are consistent with consensus guidelines from the American Association of Clinical Endocrinologists and the American Diabetes Association [7]. Unfortunately, hypoglycemia continues to occur in some patients and there is a gap in the literature with regard to insulin dosing thresholds that increase risk of occurrence.

In the non-ICU setting, 24-h insulin consumption was associated with hypoglycemia [8]. In a case–control study by Rubin et al., a 24-h insulin consumption of greater than 0.6 units/kg was associated with a 2- to 3-fold increased risk of hypoglycemia compared to patients who received less than 0.2 units/kg [8]. This study provides a valuable threshold of 0.6 units/kg, below which the risk of hypoglycemia is low. It guides clinicians with regard to the safe use of insulin in hospitalized non-ICU patients. However, patients in this study were treated with subcutaneous insulin regimens from varying sources, limiting extrapolation to the critically ill who receive continuous IV infusions of insulin. Also, 24-h insulin consumption is not an intuitive measure in the ICU where dosing is based on infusion rates rather than daily values. Due to this strategy of dosing in the ICU and the dynamic nature of insulin titration that can occur on an hourly basis, it is possible that maximum insulin infusion rates rather than 24-h insulin consumption would be associated with hypoglycemia in this setting.

We hypothesized that in patients in the ICU, maximum insulin infusion rates would predict hypoglycemia rather than 24-h insulin consumption. The purpose of this study was to determine the association between insulin infusion rates and 24-h insulin consumption on the occurrence of hypoglycemia in critically ill patients receiving continuous IV insulin infusions.

2. Subjects, materials and methods

2.1. Study design and setting

This was a retrospective, case–control study conducted at a tertiary care, academic medical center in the United States. Blood glucose goals in the ICU were 110–170 mg/dL. Blood glucose control was managed via an insulin infusion of 100 units insulin regular mixed in 100 ml of normal saline. Point of care finger stick blood glucose was measured every hour while on the insulin infusion. Insulin dosing and titration did not incorporate patient weight. Instead insulin was initiated between 1 and 4 units/h based on blood glucose value. Nurses used a matrix that incorporates last insulin infusion rate, last blood glucose value and current blood glucose value to determine insulin dose change. This protocol has been implemented in multiple institutions and described in detail by Balkin et al. [9]. However, our protocol does not utilize simultaneous dextrose 10% infusions along with insulin. The hospital site review authority and the University's institutional review board approved the study.

2.2. Selection of participants

Consecutive adult (≥18 years) patients admitted to the ICU receiving IV regular insulin infusions for the management of hyperglycemia between January 1st 2008 and March 30th 2013 were included in the study. Patients experiencing a hypoglycemic event while on a continuous IV insulin infusion were matched 1:1 with non-hypoglycemic controls based on age, gender, body mass index, and hospital day of hypoglycemia similar to a previous study [8]. Hypoglycemia was defined as a blood glucose reading of <70 mg/dL (point-of-care values), consistent with current guidelines [4]. Patients were excluded if they had a primary diagnosis of hypoglycemia on admission, experienced hypoglycemia within 24 h of admission, or if they had a primary diagnosis of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome.

2.3. Data collection and variables

Data were collected on standardized data collection instruments. Data were first collected on the cases in a consecutive manner to minimize selection bias. All data pertained to the first episode of hypoglycemia for each case. After all cases of hypoglycemia were identified, each case was matched to a control using the variables previously described. Variables collected included patient demographics, primary service (medical or surgical); laboratory parameters such as blood glucose, serum creatinine, aspartate aminotransferase, alanine aminotransferase, white blood cell count, albumin, hematocrit; comorbidities such as history of diabetes and history of liver disease; Charlson Comorbidity Index. Lab values were obtained from the day of the hypoglycemic event or matched control day. Severity of illness was measured by calculating the Sequential Organ Failure Assessment (SOFA) score. Outcome data collected included hospital length of stay, ICU length of stay and 28-day mortality.

Detailed information was collected regarding insulin use during the period prior to the hypoglycemic event or matched control day. This included insulin infusion rates and 24-h insulin consumption prior to the event. Concurrent or previous hypoglycemic agent use was also recorded. Similar to the study by Rubin et al. [8], a 24-h insulin consumption was categorized using the following intervals: <0.2, 0.2 to <0.4, 0.4 to <0.6, 0.6 to <0.8, and ≥0.8 units/kg/day. The highest insulin infusion rate was categorized as <0.05, 0.05 to <0.1, and ≥0.1