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Predisposing Factors for Hypoglycemia and Its Relation With Mortality in Critically Ill Patients Undergoing Insulin Therapy in an Intensive Care Unit

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Abstract

Background: Hypoglycemia is a common and the most important complication of intensive insulin therapy in critically ill patients. Because of hypoglycemia's impact on the cardinal organs as a fuel, if untreated it could results in permanent brain damage and increased mortality.

Objectives: In this study, we aim to evaluate the incidence of hypoglycemia, its risk factors, and its relationship with mortality in critically ill patients.

Patients and Methods: Five hundred adult patients who admitted to an intensive care unit (ICU) were enrolled in this study. A program of glycemic control with a target of 100 - 140 mg/dL was instituted. We used the threshold of 150 mg/dL for septic patients, which were monitored by point of care devices for capillary blood measurement. We detected hypoglycemia with a blood sugar of less than 50 mg/dL and with the detection of each episode of hypoglycemia, blood glucose measurement was performed every 30 minutes.

Results: Five hundred patients experienced at least one episode of hypoglycemia, almost always on the third day. Of 15 expired patients who had one hypoglycemia episode, the most common causes were multiple trauma and sepsis. Increases in the sequential organ failure assessment (SOFA) number augmented the hypoglycemia risk to 52% ($P < 0.001$). Moreover, in patients with acute kidney injury (AKI), the risk of hypoglycemia is 10 times greater than in those without AKI (RR: 10.3, CI: 3.16 - 33.6, $P < 0.001$). ICU admission blood sugar has a significant relationship with mortality (RR: 1.01, CI: 1.004 - 1.02, $P < 0.006$). Hypoglycemia increased the mortality rate twofold, but it was not significant (RR: 1.2, CI: 0.927 - 1.58, $P = 0.221$).

Conclusions: Our results showed that the SOFA score, AKI, and hemoglobin A1c are the independent risk factors for the development of hypoglycemia and demonstrated that ICU admission blood glucose, Hba1c, and hypoglycemia increased the risk of death, but only ICU admission blood glucose is significantly related to increased mortality.

Keywords: Hypoglycemia, Risk Factors, Mortality, Intensive Care Unit

1. Background

Dysglycemia is common in critically ill patients. Hyperglycemia is associated with adverse outcomes, including increased mortality, so insulin therapy and glucose control had been recommended to improve patient outcomes (1-9). However, intensive insulin therapy is associated with an increased risk of hypoglycemia, which is a possible predictor of morbidity and mortality in critical ill patients (10, 11) and a limiting factor for intensive insulin therapy. Over the past two decades, many studies have been conducted on intensive insulin therapy in critically ill patients, demonstrating controversial results. Spontaneous episodes of severe hypoglycemia are rare during the management of critical ill patients, and many factors contribute to its occurrence, such as underlying disease, malnutrition, infection, different glucose measurement methods, and chronic liver or kidney diseases (12). Since the introduction of intensive insulin therapy strategies in intensive care units (ICUs), hypoglycemia has become a daily concern during the management of critically ill patients (13).

An absolute or relative insulin excess with inadequate energy intake together with limited exogenous glucose production and increased glucose utilization are the fundamental causes of hypoglycemia in ICUs. Several studies

have shown that the number of hypoglycemic episodes may not be increased by intensive insulin therapy (14, 15). There is some evidence that hypoglycemic episodes are directly responsible for an increased mortality rate in critical ill patients (10, 16). However, another case control study in critically ill patients receiving insulin therapy showed that the occurrence of hypoglycemia was not associated with an increased risk of mortality (17, 18). As a result of several interventional clinical trials performed in critically ill patients, intensive monitoring and treatment of glucose levels in critically ill patients is emerging as a standard of care for these patients. So there are some concerns about which patients should be treated, the target level of hyperglycemia, and the incidence and risk factors for hypoglycemia, as hypoglycemia is a major limiting factor for the implementation of intensive insulin therapy and related mortality and was a reason for the early termination of the multicenter Glucontrol and VISEP trials (14). The typical manifestations of hypoglycemia is not routinely seen in critical ill patients, mostly because of the masking of their clinical pictures and physiologically blunted response. Little is known about the pathophysiology and consequences of hypoglycemia in ICUs, in contrast with an extensive body of literature on the pathophysiology and consequences of hypoglycemia in diabetes mellitus. Therefore, recognizing the risk factors for hypoglycemia would help to identify patients who are at increased risk for hypoglycemia.

2. Objectives

In this study, we aim to evaluate the incidence of hypoglycemia, its risk factors, and its relationship with mortality in critically ill patients.

3. Patients and Methods

3.1. ICU Setting

Five hundred critically ill patients from Feb 2011 to Sept 2013 were enrolled in this study. Two ICUs of Tabriz University of Medical Sciences (Shohada hospital and the ICU general of Imam Reza hospital) with mixed surgical and medical patients were included in this study. Cardiac surgeries were not performed at these two hospitals. All routine managements guided by protocols and a team of intensivists as directors of a multidisciplinary approach. The nurse patient ratio was 1:2 and full-time respiratory therapists accompanied the team. Inclusion criteria were all patients who admitted to theses ICUs. The study was approved by the ethics committee of Tabriz University of Medical Sciences.

3.2. Glucose Control Protocol

A program of glycemic control with a target of 100 - 140 mg/dL was instituted. We used the threshold of 150 mg/dL for septic patients. This protocol was monitored by point of care devices for capillary blood measurement, and central laboratory values of venous blood were gathered to detect blood glucose at the specific time schedules and the accuracy of glucometers. Insulin therapy was performed by the frequent use of subcutaneous regular insulin as well as continuous intravenous regular insulin. We did not use any other type of insulin in our protocol. Blood glucose measurements were performed every hour, and if 4 consecutive measure were in the target range, the intervals were increased to 2 hours. If 3 consecutive measurements were in the target range, we performed measurements every 4 hours. If glucose was not in the target range, the measurement intervals were reduced to every hour. We detected hypoglycemia with blood sugar of less than 50 mg/dL, and with the detection of each hypoglycemia episode, blood glucose was measured every 30 minutes. All patients received energy from the enteral rout, except when they had contraindications, in which case we started parenteral nutrition. We calculated patients' daily caloric needs based on 25 kcal/kg.

3.3. Data Collection

Patients' demographic characteristic were noted. Data collection consisted of acute physiologic and chronic health evaluation (APACHE) scores, previous history of diabetes, HbA1c, hypoglycemia episodes, diagnostic category (medical, surgical) sepsis, shock, liver or renal failure, previous history of renal replacement therapy, and drug history (beta blocker, pentamidine, aspirine, disopiramid, cotrimoxazol, coticsteroid, metfomin, glibenclamid).

3.4. Statistical Analysis

We used SPSS version 16 for statistical analysis. Data were presented as mean ± standard deviation. We used Student's t-test to compare two quantitative parameters. The chi-square test was used for the analysis of qualitative variables. To identify the predictors of hypoglycemia, we performed a stepwise logistic regression model for the mentioned variables. A p-value of less than 0.05 was considered significant. To assess the association between hypoglycemia and ICU mortality, we carried out a multivariate stepwise Cox proportional hazard regression model, adjusting for the abovementioned variables.

Because the occurrence of hypoglycemia is also time-dependent, the time until the first occurrence of hypoglycemia was included. The results were expressed as adjusted hazard ratios (AHRs) and 95% CIs. Additionally, we carried out the same analyses stratified by selected variables. Continuous variables were categorized into two groups based on the median values.

4. Results

A total of 500 critically ill patients who admitted to the ICUs of Shohada and Imam Reza hospitals (Tabriz Uni-

versity of Medical Sciences) from Feb 2011 to Sept 2013 were enrolled in this study. Patients' demographic characteristic are shown in Table 1. As shown in Table 1, their most common diagnoses were multiple traumas, brain tumors, and lower limb fractures. Almost half the patients received one of the following drugs: aspirin, corticosteroid, or beta blocker. All patients except 10 received enteral nutrition. Forty-six patients died during the study, of which 26 were men and 20 were female. Fifty patients experienced at least one episode of hypoglycemia, which was almost always on the third day. Of 15 expired patients who experienced one episode of hypoglycemia, the most common causes were multiple trauma and sepsis. The effects of age, sex, APACHE, sequential organ failure assessment (SOFA), admission blood sugar, blood urea nitrogen, acute kidney injury (AKI), and HbA1C on hypoglycemia occurrence were analyzed using the logistic regression method and after 8 times modeling SOFA, AKI, and hemoglobin A1c were recognized as effective (independent) variables on hypoglycemia. The analysis showed that increases in the SOFA number augmented the risk of hypoglycemia to 52% ($P < 0.001$) (Table 2).

Table 1. Characteristics of Patients With and Without Hypoglycemia[a]

Characteristic	Hypoglycemia	No Hypoglycemia	P Value
No of patients	50 (10)	450 (90)	
Age	72.14 ± 19.6	54.56 ± 17.8	< 0.001
APACHE	28.50 ± 8.8	19.84 ± 6.9	< 0.001
SOFA	13.72 ± 4.1	9.26 ± 3.5	< 0.001
Blood Sugar	167.74 ± 38.5	131.27 ± 25,9	< 0.001
BUN	30.94 ± 18.5	24.32 ± 15.2	< 0.001
Creatinine	1.74 ± 0.8	1.91 ± 1.1	< 0.001
Hemoglobin	10.9 ± 2.1	12.3 ± 3	< 0.001
Bilirubin	0.69 ± 0.5	0.55 ± 0.3	0.110
Diabetes Mellitus	39 (78)	55 (12)	< 0.001
Renal Failure	2 (4)	2 (0.4)	0.007
Liver Failure	6 (12)	0	0.001
HbA1C	8.9 ± 4.5	5.8 ± 2.9	< 0.001
Acute Kidney Injury	33 (66)	27 (6)	< 0.001
Corticosteroid/Aspirin/Beta Blocker	43 (86)	199 (44)	< 0.001
Metformin/Glibenclamid	40 (80)	52 (11)	< 0.001
Mortality	15 (30)	31 (7)	< 0.001
Gender			0.06
Male	24	276	
Female	2	174	
Nutrition			< 0.001
E	42	428	
E+P	8	2	

[a]Values are expressed as No. (%) or mean ± SD.

Table 2. Risk Factors Associated With Hypoglycemia Modeled Using Logistic Regression Analysis[a]

	B	S.E.	Wald	df	P Value	Exp (B)	95.0% C.I. for EXP(B)	
							Lower	Upper
SOFA	2.20	0.06	12.497	1	0.000	1.52	0.988	1.053
AKI	2.9	0.05	10.887	1	0.000	10.3	3.162	33.63
HbA1C	1.21	0.019	8.70	1	0.031	3.2	1.93	5.88
Constant	3.264	0.746	12.866	1	0.00	0.002	NA	NA

Abbreviations: AKI, acute kidney injury; lower, lower bound for 95% C.I. for the OR; NA, not available; OR, odds ratio; upper, upper bound for 95% C.I. for the OR.
[a]The Hosmer and Lemeshow test showed an acceptable model fit (chi-square (4) = 6.52; P = 0.12).

Table 3. The Effect Size of Hypoglycemia and Other Factors on Mortality Using Logistic Regression Analysis[a]

	B	S.E.	Wald	df	P Value	Exp (B)	95.0% C.I. for EXP (B)	
							Lower	Upper
Age	0.20	0.16	1.497	1	0.12	1.020	0.988	1.053
Hypoglycemia	1.9	0.45	1.887	1	0.22	1.2	0.927	1.58
ICUad BS	1.607	0.684	5.514	1	0.006	1.01	1.004	1.02
HbA1C	0.21	0.119	1.70	1	0.161	1.2	0.93	1.58
APACHE	0.129	0.080	2.553	1	0.11	1.137	0.971	1.332
SOFA	0.227	0.209	1.190	1	0.27	1.255	0.834	1.889
Constant	-6.264	1.746	12.866	1	0.00	0.002	NA	NA

Abbreviations: ICUad BS, ICU admission blood sugar; lower, Lower bound for 95% C.I. for the OR; NA, not available; OR, odds ratio; upper, upper bound for 95% C.I. for the OR.
[a]The Hosmer and Lemeshow test showed an acceptable model fit (chi-square (7) = 5.22, P = 0.52).

In addition, in patients with AKI, the risk of hypoglycemia is 10 times greater than in patients without AKI (RR: 10.3, CI: 3.16 - 33.6, P < 0.001). HbA1c has a direct correlation with the occurrence of hypoglycemia, as with increasing HbA1c the risk of hypoglycemia is increased threefold (Table 2).

ICU admission blood sugar has a significant relationship with mortality (RR: 1.01, CI: 1.004 - 1.02, P = 0.006). Hypoglycemia increased the mortality rate 20%, but it was not significant (RR: 1.2, CI: 0.927 - 1.58, P = 0.221). HbA1c increased the mortality rate 20%, but it was not statistically significant (RR: 1.2, CI: 0.93 - 1.58, P = 0.161) (Table 3).

5. Discussion

Since the first leuven study intensive insulin therapy has led to improved inflammation and infection (19) which is associated with improved patient survival (20-24). Although numerous studies have concluded that tight glycemic control can positively impact the clinical outcomes in ICU patients (25), the apparent benefit of narrowly regulated tight glycemic control may come at the expense of an increased rate of hypoglycemia (26, 27). We determined that hypoglycemia is common in critically ill patients, and in this study hypoglycemic patients were significantly older and had higher HbA1c and APACHE scores, which was similar to the results of previous (28, 29) studies. Patients with type 1 diabetes and patients with longstanding type 2 diabetes may have an impaired counter-regulatory response. This may help to explain why patients who used insulin before ICU admittance were at a higher risk of developing hypoglycemia (30). But in our study, logistic regression modeling after matching patients based on age, sex, and APACHE showed that only SOFA, AKI, and HbA1c are independent variables related to hypoglycemia. In Van den Bergh's study (19), the most important risk factor for developing hypoglycemia was a discontinuation of nutrition or a reduction in glucose intake. ICU admission blood glucose, HbA1c, and hypoglycemia in our study increased the risk of death, but only ICU admission blood glucose is significantly related to increased mortality. As the lowering or discontinuation of nutrition without adjusting insulin therapy was associated with hypoglycemia, after any changes in the nutrition protocol, we decreased the blood sampling to 30 minutes to detect hypoglycemia more rapidly, which did not lead to higher mortality. The incidence of hypoglycemia was almost 10%, which differs from other studies (10, 15, 19). The difference in hypoglycemia incidence might be related to the type of patients, the intensity of protocols, the sampling methods (arterial vs venous), and the measurement frequency. Our study results showed that there is no association between the first episode of hypoglycemia and mortality, but Egi et al. (31) showed that an early onset of hypoglycemia following ICU admission is related to higher mortality levels. There are three explanations for the association between hypoglycemia and outcomes: first, the severity of hypoglycemia may be associated with the severity of the illness. Second, hypoglycemia may be a biomarker of imminent death. Third, hypoglycemia might have a deleterious biological effect on critically ill patients. This study showed that hypoglycemia did not have a significant effect on mortality, which was similar to the results of NICE SUGAR (32) and Arabi (28), but inconsistent with the results of Egi et al.'s study, which showed that the severity of hypoglycemia was significantly related to mortality (31). Our study showed that there were no gender differences for hypoglycemia, which contradicts Merimee et al.'s finding of a lower counter-regulatory threshold in women compared to men (33).

Several studies have shown that severe hypoglycemia is independently associated with a higher risk of death with a greater duration of hospital stay (14, 34, 35). These researchers have suggested that every hypoglycemic event may increase the mortality rate, which is in contrast with our results, possibly due to the delayed recognition and impaired counter-regulatory responses in critically ill patients, which leads to poor clinical outcomes. Our results suggest that the duration of hypoglycemia episodes may be short, largely due to intensive monitoring.

A limitation of this study was that we did not examine the permanent neurologic dysfunction after hypoglycemia, secondary outcomes (i.e., renal replacement therapy, critical illness neuromuscular complications, nosocomial infections), or data on the blood glucose variability on outcomes. Moreover, we did not mention mechanical ventilation as a predisposing risk factor for hypoglycemia via a direct or indirect effect by sedation.

Our results showed that the SOFA score, AKI, and HbA1c are the independent risk factors for the development of hypoglycemia and demonstrated that ICU admission blood glucose, HbA1c, and hypoglycemia increased the risk of death, but only ICU admission blood glucose is significantly related to increased mortality.

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Footnote

Authors' Contribution: All authors have read and approved the manuscript. Ata Mahmoodpoor, Hadi Hamishehkar, Hassan Soleimanpour, Mohammadtagi Beigmohammadi, and Sarvin Sanaie performed the data collection, literature review, and drafting of the manuscript. Saeed Safari and Ahsan Rahimi undertook the major parts of the study design and performed the statistical analysis.

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