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Original Investigation

Stress Hyperglycemia Incidence in Critically Ill Patients: Cross-Sectional Observational Study

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Abstract

Objective: Stress hyperglycemia is a common condition in intensive care units. It is associated with poor prognosis and mortality. We aimed to determine the frequency of stress hyperglycemia and its relation to morbidity and mortality in intensive care units.

Material and Methods: This study was prospectively conducted at the medical and anesthesiology intensive care unit. Patients ≥18 years of age who stayed in this intensive care unit for 48 hours or more were included in this study.

Results: In total, 50 patients were included in the study. The mean age of the patients was 42.8±18.8 years. The most common cause of admission to the intensive care unit was trauma (56%). Laboratory blood glucose level of the patients on the first day of study was 129.9±51.0 mg/dL. The HbA1c value was 4.98±0.46 on the day of admission to the intensive care unit. On the first day of the study, laboratory blood sugar was found to be ≥140 mg/dL in 14 patients (28%). The number of patients with stress hyperglycemia during a one-week period was 32 (64%). During the time patients were in the intensive care unit, the development of new infection occurred in 19 patients (38%). The median duration of stay in the intensive care unit was 7.5 (range, 3-78) days, and the median duration of stay in the hospital was 13 (range, 3-101) days. The rate of new infection development was higher in patients with stress hyperglycemia (50%) than in those without (26.0%) (p=0.02). The duration of stay in the intensive care unit was found to be higher in patients with stress hyperglycemia (median, 9.5 days; range, 3-78 days) than in those without (median, 5 days; range, 3–31 days) (p=0.012). The duration of stay in hospital was found to be higher in patients with stress hyperglycemia (median, 14 days; range, 3-101 days) than in those without (median, 11 days; range, 3-50 days) (p=0.07). The total rate of mortality in the intensive care unit was 20%. Intensive care mortality was 20% in all patients. The rate of mortality in the intensive care unit was higher in patients with stress hyperglycemia (28.1%) than in those without (5.6%) (p=0.05).

Conclusion: Stress hyperglycemia was found to be high in critically ill patients. Mortality and new infection rates were higher in patients with stress hyperglycemia.

Keywords: Critical illness, hyperglycemia, mortality, morbidity

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Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erciyes University Clinical Research (Decision No: 2017/340).

Informed Consent: Written informed consent was obtained from patients or patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

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Introduction

Hyperglycemia, a result of endocrine and metabolic responses to stress, occurs in 20.33% of critically ill patients admitted to the intensive care unit (1, 2). According to the American Diabetes Society, patients are classified as normoglycemia (fasting blood glucose level <100 mg/dL or random blood glucose below 140 mg/dL), mild hyperglycemia (those whose fasting blood glucose level is 100 to 125 mg/dL or

random or postprandial 2nd hour blood glucose levels are 140 to 199 mg/dL) and severe hyperglycemia (those whose fasting blood glucose level is 126 mg/dL or more, or random blood glucose level without diabetes or 2-hour postprandial blood glucose level is 200 mg/dL or more) (3). There is no clear blood glucose value for stress hyperglycemia, and it differs in studies. The physiopathologic mechanisms in the development of stress hyperglycemia are different from type 1 and type 2 diabetes. An increase occurs in glucagon, epinephrine, cortisol, growth hormone and norepinephrine (4). This increase in counter-regulatory hormones causes an increase in endogenous glucose production by gluconeogenesis (predominantly hepatic) and glycogenolysis. Under normal physiological conditions, glucose homeostasis is strictly regulated by the uptake of insulin-mediated glucose in peripheral tissues (skeletal, cardiac muscle, adipose (GLUT 4) and liver (GLUT2)) and in inhibition of hepatic glucose production (5). Tumor necrosis factor-alpha can contribute to it by increasing glyconeogenesis and plasma glucagon. Insulin production also increases, but sepsis and critical disease affect the signaling pathway of insulin. Therefore, GLUT-4 mediated glucose uptake is therefore reduced and leads to insulin resistance. Stress hyperglycemia is also aggravated by hyperglycemic agents such as vasopressors, parenteral nutrition, and corticosteroids (6). Stress hyperglycemia is a common problem in critical patients and has been associated with poor outcome (7, 8).

Stress hyperglycemia usually means transient hyperglycemia during the disease and is limited to patients who have not had diabetes symptoms before (9, 10). In a study, in-hospital mortality was significantly higher in hyperglycemic patients with no previous diagnosis of diabetes compared to patients with a previous history of diabetes and to normoglycemic patients (11). The importance of strict glycemic control was demonstrated after the randomized controlled study which was carried out by Van der Berge et al. by involving 1548 patients in mechanical ventilation in 12 months, because the study showed that when normoglycemia (80-110 mg / dL) was ensured, a 42% reduction in mortality in the surgical intensive care unit patients was achieved. In both groups, the APACHE II scores in the first 24 hours were median 9 (range: 7-13). In this study, it was shown that intensive insulin therapy decreased the attacks of septicemia by 46% and the number of ventilator days was fewer (12).

Although there are studies evaluating the frequency of stress hyperglycemia and its relation with morbidity and mortality in critical patients in the literature, these studies are not sufficient in our country. The primary aim of this study is to determine the frequency of stress hyperglycemia in intensive care units. Our secondary aim is to determine the relationship between stress hyperglycemia and morbidity and mortality.

Material and Methods

This is a prospective cross-sectional observational study. The patients, who were monitored in the Medical and Anesthesia Intensive Care Unit between 1 April 2017 and 1 August 2017, who were 18 years of age and older, and who were hospitalized for 48 hours and more, were included in the study. The study was approved by the Erciyes University Clinical Research Ethics Committee (Ethics Committee Approval No: 2017/340). Written consent was obtained from the patients or from the first degree relatives of the patients who were unable to give consent.

Patients with diabetes mellitus (Type 1, 2), chronic renal failure, chronic liver disease, pregnancy, chronic steroid use, solid organ tumor, and hemoglobin level below 7 g/dL were not involved in the study.

Demographic data, APACHE-II (Acute Physiology and Chronic Health Evaluation) score, height, weight, hospitalization reason, laboratory blood glucose on admission and HbA1c value were recorded for each patient.

Patients included in the study were followed for a maximum of 7 days in terms of blood glucose. Daily measured laboratory blood glucose, and venous capillary and arterial blood glucose values measured from the fingertip during intraday follow-ups were recorded. In order to evaluate organ failure on a daily basis, the SOFA (Sequential Organ Failure Score) score, the patients' daily calorie intake and the amount of insulin administered, vasopressor requirement, mechanical ventilation (invasive and/or non-invasive) requirement were recorded daily for seven days.

Furthermore, during the follow-up period of the patient in the intensive care unit, new infection development was recorded by using the Centers for Disease Control and Prevention (CDC) criteria by the Departments of Infectious Diseases and clinicians performing the follow-ups (13, 14). The number of days of hospitalization of patients in intensive care units, the number of days of hospital stay and ICU mortalities were recorded.

Definition of Stress Hyperglycemia

According to the American Diabetes Society, patients are classified as normoglycemia (fasting blood glucose level <100 mg/dL or random blood glucose below 140 mg/dL), mild hyperglycemia (those whose fasting blood glucose level is 100 to 125 mg/dL or random or postprandial 2nd hour blood glucose levels are 140 to 199 mg/dL) and severe hyperglycemia (those whose fasting blood glucose level is 126 mg/dL or more, or random without diabetes or 2-hour postprandial blood glucose level is 200 mg/dL or more) (3). Since the blood glucose was measured randomly in the intensive care unit, values of 140 mg/dl and more were accepted as hyperglycemia. In the study, it was accepted that there was stress hyperglycemia if the blood glucose measured (laboratory and/or fingertip) at any time during the follow-up (maximum seven days) was 140 mg/dL and above.

Measurement

The fingertip blood glucose of the patients was measured by a FreeStyle Optimum Neo® (Abbott) device. The laboratory blood glucose of the patients was measured by the hexokinase method using a Cobas 6000® (Roche) or Cobas 8000® (Roche) device. The HbA1c measurement was performed by using a Cobas 6000® (Roche) device by the immunoturbidimetric method.

Statistical Analysis

Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. The chi-square test was used to determine significant differences in the ratios between categorical variables. Student's t-test and the Mann-Whitney U test were used to compare the differences of continuous variables. The p-value <0.05 was considered statistically significant. All data were checked for normal distribution. Those with normal distribution were presented as mean, and those without normal distribution were presented as the median. Different statistical methods were used according to their distributions.

Results

Only patients included in the study were recorded. Fifty patients were included in the study. Sixty six percentof the patients were male, and

the mean age of the patients was 42.8±18.8 years. The most common reasons for hospitalization in the intensive care unit were trauma (56%) and sepsis/septic shock (14%). The mean APACHE II score was 11.7±6.5. The median SOFA score on the first day was 4 (range: 0-14). The patient's HbA1c value on the day of admission to the intensive care unit was 5±0.46%. The mean laboratory blood glucose value of the patients on the day of inclusion in the study was 129.9±51.0 mg/dL. The patients' mean blood glucose values measured on a daily basis in the laboratory and from fingertips are presented in Figure 1. Furthermore, stress hyperglycemia rates are given in Figure 2.

During the one week period when the patients were monitored in the intensive care unit, the patients' blood glucose levels were measured in the laboratory and from the fingertip, and the number of patients, whose blood glucose level was measured as 140 and above once and more times was 32 (64%) (Table 1). The rate of development of a new infection in patients during their stay in the intensive care unit was 38%. The median number of days of stay in the intensive care unit was 7.5 (range: 3-78), and the median number of days of hospitalization was 13 (range: 3-101). The rate of development of a new infection was higher in patients with stress hyperglycemia (50%) compared to those without stress hyperglycemia (16%) (p=0.02). The number of days of stay in the ICU was higher in patients with stress hyperglycemia (median: 9.5, range: 3-78) compared to patients without stress hyperglycemia (median: 5, range: 3-31) (p=0.12). The number of days of hospitalization was higher in patients with stress hyperglycemia (median: 14, range: 3-101) compared to patients without stress hyperglycemia (median: 11, range: 3-50) (p=0.07). Vasopressors were needed for 18% of the patients and mechanical ventilation for 50% of the patients. All nine patients who needed vasopressors had stress hyperglycemia. Mechanical ventilation need was higher in patients with stress hyperglycemia (65.6%) compared to those without stress hyperglycemia (22.2%) (p=0.003).

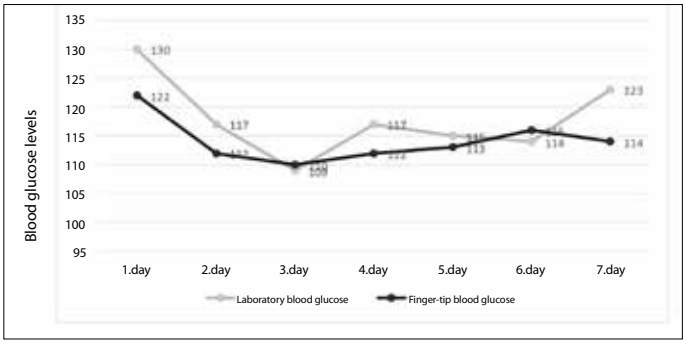

Figure 1. Mean blood glucose levels for the period of seven days

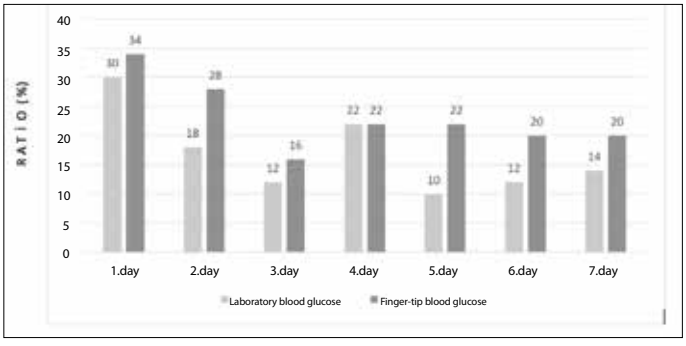

Figure 2. Stress hyperglycemia frequency within seven days

The ICU mortality rate of the patients was determined as 20%. Mortality in the patient group with stress hyperglycemia (28.1%) was determined to be higher compared to those without stress hyperglycemia (5.6%) (p=0.05) (Table 2).

Discussion

Stress hyperglycemia is a common problem in critically ill patients, irrespective of the acute condition they are exposed to, and is associated with poor outcome in the intensive care unit (10). Since the definition of stress hyperglycemia in critically ill patients varies according to the studies, the incidence varies accordingly (15-17). As a result of this study, the incidence of stress hyperglycemia was 64% in critically ill patients monitored in the ICU. The mortality rate was determined to be higher in the stress hyperglycemia group (28.1%).

The incidence of stress hyperglycemia differs according to the study methods and definitions.

Cely et al. (18) determined the incidence of hyperglycemia in ICUs in the prospective cohort study they carried out in the medical ICU with the involvement of 100 patients as 23%. Blood glucose levels of the patients were followed up for 120 hours (5 days) starting from the admission both from fingertips and in the laboratory. In the follow-ups, 23 patients

Table 1. Demographic and clinical characteristics of the patients

Variables	
Age ± SD (years)	42±18
Gender, n (%)	
Male	33 (66)
Female	17 (34)
BMI ± SD	25.19±4.23
APACHE-II score ± SD	11.7±6.5
SOFA score, (range)	4 (0-14)
The reason for admission to the intensive care unit n (%)	
Trauma	28 (56)
Sepsis/septic shock	7 (14)
Gastrointestinal hemorrhage	5 (10)
Neurological	4 (8)
Acute respiratory failure	3 (6)
Other	3 (6)
Laboratory blood glucose on admission, (range) mg/dl,	129 (74-358)
HbA1c ± SD	4.9±0.5
First day laboratory. blood glucose ≥140mg/dL, n (%)	14 (28)
Blood glucose for seven days ≥140mg/dL, n (%)	32 (64)
Mechanical ventilation requirement, n (%)	25 (%50)
Vasopressor requirement, n (%)	9 (%18)
Number of days of hospital stay, (range)	13 (3-101)
Number of days of stay in the intensive care unit, (range)	7.5 (3-78)
Intensive care mortality, n (%)	10 (20)

BMI: body mass index; APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment

received hydrocortisone, and four patients needed norepinephrine. The mean blood glucose levels of the patients were determined as 154±51 mg/dL. The blood glucose level of 200mg/dL and above was accepted as stress hyperglycemia.

In the prospective observational study carried out by Llompart-Pou et al. (19) with the involvement of 60 patients in medical and surgical intesive care units the incidence of stress hyperglycemia was determined as 75%. In this study, the value of 115mg/dL and above was taken for stress hyperglycemia. Ten patients needed vasopressors, and 8 of them had stress hyperglycemia.

In the multicenter prospective observational study carried out by Sharma et al. (2) with the involvement of 536 patients in medical ICUs, the incidence of stress hyperglycemia was determined as 20.33%. The values of 200 mg/dL and above were accepted for stress hyperglycemia. The reason for the incidence of stress hyperglycemia to be high in our study may be the stress hyperglycemia diagnosis of patients who had a blood glucose threshold value of 140 mg/dL and above, which is a lower level compared to other studies (18).

The ICU mortality was found to be 20% for all patients included in the study. The mortality rate was found to be higher (28.1%) in the patient group with stress hyperglycemia compared to the patient group (5.6%) without stress hyperglycemia (p=0.05). Similarly, Llompart-Pou et al. (19) found out that the mortality rate was higher in patients with stress hyperglycemia (13.3%) compared to those without stress hyperglycemia (6.7%) (p=0.67).

Table 2. Comparison of the demographic and clinical parameters of the patients with and without stress hyperglycemia

Variables	Hyperglycemia (+) (n=32)	Hyperglycemia (-) (n=18)	p
Age ± SD (years)	46±17	35±19	0.04
Gender, n (%)			
Male	21 (63.6)	12 (36.4)	0.941
Female	11 (64.7)	6 (35.3)	
BMI ± SD (kg/m2)	26.04±4.42	23.66±3.50	0.05
APACHE-II score ± SD	13.8±6.2	7.9±5.3	0.01
SOFA score, (range)	5 (0-14)	2.5 (0-8)	0.01
New infection development in the ICU, n (%)	16 (50)	3 (16)	0.02
Mechanical ventilation requirement n (%)	21 (%65.6)	4 (%22.2)	0.003
Vasopressor requirement, n (%)	9 (%28.1)	0 (%0)	0.013
Number of days of stay in the intensive care unit, (range)	9.5 (3-78)	5 (3-31)	0.012
Number of days of hospital stay, (range)	14 (3-101)	11 (3-50)	0.07
Intensive care mortality, n (%)	9 (28.1)	1 (5.6)	0.05

BMI: body mass index; APACHE II: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment

In the retrospective study carried out by Rau et al. (8) with the involvement of 1798 patients with isolated head trauma in the Brain Surgery ICU in 2017, mortality was higher in patients with stress hyperglycemia (41.4%) compared to those without stress hyperglycemia (7.2%). In this study, patients with blood glucose levels of 200 mg/dL and above were diagnosed with stress hyperglycemia. The mean age of the patients was 52.4±18.7, and the Glasgow Coma Scale in 63.6% of the patients was 8 and below. Subarachnoid hemorrhage was detected in 53.4% of the patients. Similarly to our study, mortality was found to be high in hyperglycemic patients.

In 2015, Moradi et al. investigated the relationship between the development of stress hyperglycemia and diabetes mellitus. In this analytical cross-sectional study, all patients who applied to the emergency service due to trauma, myocardial infarction, subarachnoid hemorrhage, head trauma, sepsis, cerebrovascular accident, and abdominal surgery were evaluated. Stress hyperglycemia was defined as the blood glucose level higher than 180 mg/dL without the previously known history of diabetes. The patients were referred to the endocrinology clinic three months after the first evaluation and re-evaluated in terms of diabetes mellitus. In the prospective analytical study of 98 patients with stress hyperglycemia, diabetes mellitus was developed in 28% of the patients with stress hyperglycemia, and a prediabetic condition developed in 25.8% of the patients (24).

A high rate of hyperglycemia was also detected in the present study. Great attention should be paid to the development of diabetes in the subsequent follow-up of these patients.

While on the first day of the study, the rate of patients with laboratory blood glucose levels above 140 mg/dL was 28%, on any day during seven days the rate of patients with laboratory blood glucose levels above 140 mg/dL was 64%. This increase may be related to oral, enteral or parenteral nutrition initiated during the follow-ups.

Study Limitations

There are several limitations in this study. The first and most important limitation is the small number of patients. The second one is that the study was not multi-centered. Therefore, the results cannot be generalized. The third one is that the APACHE-II and SOFA scores were not similar between the two groups. They were higher in the group with stress hyperglycemia. The fourth limitation is that the relation between the patients' oral, enteral, parenteral nutrition and the incidence of stress hyperglycemia was not examined. The fifth one is that the results cannot be generalized to the patient group with pregnancy, malignancy, chronic renal failure, chronic liver failure and hemoglobin level below 7g/dL since they were not included in the study.

The strong aspect of this study was the exclusion of patients with diabetes mellitus, chronic liver disease, chronic kidney disease, and chronic steroids. HbA1C was examined in all patients included in the study.

Conclusion

The rate of stress hyperglycemia was found to be high in critically ill patients. Mortality was higher in patients with stress hyperglycemia. These patients should be followed up in terms of the development of permanent diabetes mellitus. For this purpose, multicentered studies are needed.

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