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Hyperglycemia in Critically Ill Patients: Management and Prognosis

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ABSTRACT

Introduction: Hyperglycemia is a common complication of critical illness. Patients in intensive care unit with stress hyperglycemia have significantly higher mortality (31%) compared to patients with previously confirmed diabetes (10%) or normoglycemia (11.3%). Stress hyperglycemia is associated with increased risk of critical illness polyneuropathy (CIP) and prolonged mechanical ventilation. Intensive monitoring and insulin therapy according to the protocol are an important part of the treatment of critically ill patients. **Objective**: To evaluate the incidence of stress hyperglycemia, complications and outcome in critically ill patients in our Medical intensive care unit. **Materials and methods**: This study included 100 patients hospitalized in Medical intensive care unit during the period January 2014–March 2015 which were divided into three groups: Diabetes mellitus, stress-hyperglycemia and normoglycemia. During the retrospective-prospective observational clinical investigation the following data was obtained: age, gender, SAPS, admission diagnosis, average daily blood glucose, highest blood glucose level, glycemic variability, vasopressor and corticosteroid therapy, days on mechanical ventilation, total days of hospitalization in Medical intensive care unit, and outcome. **Results**: Patients with DM treated with a continuous insulin infusion did not have significantly more complications than patients with normoglycemia, unlike patients with stress hyperglycemia, which had more severe prognosis. There was a significant difference between the maximum level of blood glucose in recovered and patients with adverse outcome ($p = 0.0277$). Glycemic variability (difference between max. and min. blood glucose) was the strongest predictor of adverse outcome. The difference in glycemic variability between the stress-hyperglycemia and normoglycemic group was statistically significant ($p = 0.0066$). There was no statistically significant difference in duration of mechanical ventilation and total days of hospitalization in the intensive care unit between the groups. **Conclusion**: Understanding of the objectives of glucose regulation and effective glycemic control is essential for the proper optimization of patient outcomes.

Keywords: hyperglycemia, critical illness.

1. INTRODUCTION

Hyperglycemia is a common complication of critical illness. It was originally considered to be part of the adaptive stress-response which is beneficial for survival. However, over the past two decades, there is growing evidence that hyperglycemia is associated with increased mortality and morbidity. It is important to emphasize that hyperglycemia itself does not cause poor clinical outcome, but that is only a marker of severity of disease. Insulin resistance is an important additional factor, and it has been observed in more than 80% of critically ill patients (1). Stress hyperglycemia is defined as an increase in blood glucose above 11,1 mmol/l in the presence of acute illness, without previously diagnosed diabetes. Stress-hyperglycemia is caused by endogenous and exogenous factors. Critical illness leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis, which results in the release of cortisol. Cortisol stimulates gluconeogenesis and decreases glucose utilization. Other counter-regulatory hormones (glucagon, catecholamines and growth hormone) are also released. These hormones stimulate insulin resistance through lipolysis of adipose tissue, skeletal muscle proteolysis, and hepatic gluconeogenesis. All these processes lead to impaired glucose utilization in peripheral tissues, increased circulating free fatty acids, and stimulation of gluconeogenesis and glycogenolysis. Exogenous factors (parenteral and enteral nutrition, vasopressors, glucose infusions and corticosteroids) further exacerbate hyperglycemia. If not treated, osmotic diuresis leads to dehydration, which impairs renal function and worsens hyperglycemia. It further causes

mitochondrial damage, endothelial dysfunction, immune suppression, which leads to an increased risk for infection (2).

Stress hyperglycemia is associated with increased risk for critical illness polyneuropathy (CIP). The pathogenesis of CIP is not fully explored, but the release of cytokines is a presumed cause. Patients with CIP have longer mechanical ventilation and longer hospitalization in intensive care unit. In a study by Falciglia et al., 30% of critically ill patients with hyperglycemia had clinical manifestations of CIP. All of these complications may increase mortality, regardless of the severity of underlying disease (3).

Guidelines for hyperglycemia control in critically ill patients

Various associations and organizations have published different guidelines for control of hyperglycemia in critically ill patients, reflecting the discrepancy in literature. American College of Physicians guidelines in 2011 do not recommend intensive glycemic control (4.4 to 6.1 mmol/l), but rather liberal range of 7.7 to 11.1 mmol/l. The American Diabetes Association (ADA) in 2012 recommended similar glycemic goal of 7.7 to 9.9 mmol/l (4). Society of Critical Care Medicine (SCCM) has released slightly different recommendations (target blood glucose 5.5 to 8.3 mmol/l) with maximum blood glucose of 9.9 mmol/l. In a randomized study of septic patients treated with hydrocortisone, there was no significant difference in mortality in patients with target blood glucose 4.4 to 6.1 mmol/l and those with target blood glucose of 8.3 mmol/l and less (5). Similarly, in patients with severe sepsis, glycemic target of 4.4 to 6.1 mmol/l was not associated with reduced mortality, but was associated with more side effects, such as hypoglycemia (6). Current guidelines recommend target blood glucose levels from 7.7 to 10.0 mmol/l and not more strict target (4.4 to 6.1 mmol/l) or liberal range (10.0 to 11.1 mmol/l). This way, severe hyperglycemia is avoided and the risk of iatrogenic hypoglycemia and its consequences is minimized.

Management of stress hyperglycemia

Stress hyperglycemia in critically ill patients is a common therapeutic challenge. There is no universally accepted insulin regimen for glycemic control in critically ill patients. Limiting fluctuations in blood glucose is essential for success and minimizing negative outcomes. In a large retrospective cohort study of patients in sepsis and septic shock, glucose variability was independently associated with increased mortality (7). Similar studies have shown that higher blood glucose fluctuations are associated with negative outcomes, indicating that the reduction of glycemic variability is an important therapeutic goal (8). Insulin can be administered subcutaneously or by continuous intravenous infusion. Patient-specific factors should be taken into account when selecting administration route. Ideal candidates for insulin infusion are patients who are hemodynamically unstable, in therapeutic hypothermia, edematous, on vasopressor therapy or high-dose corticosteroids, or have diabetes type 1 or unpredictable nutrition. Insulin infusion should be administered by the protocol. The ideal protocol should quickly achieve and maintain target blood glucose levels, taking into account rate of change in glycemia and blood glucose levels, establish balance and stability, and lead to a minimal incidence of hypoglycemia. Also, the protocol should clearly communicate instructions for titration and frequency of glucose monitoring to the nurses, as shown in Table 1 (9).

Glucose level (mmol/l)	
7.8–10.0	Start IV insulin infusion with 1 IU/h
10.1-11.1	Start IV insulin with 2 IU/h
11.2-13.8	Bolus 2 IU insulin IV and start IV insulin infusion with 2 IU/h
13.9-16.6	Bolus 4 IU insulin IV and start IV insulin infusion with 2 IU/h
>16.6	Bolus 4 IU insulin and start IV insulin infusion with 4 IU/h

Table 1. Protocol for intravenous insulin infusion

SAPS

Simplified Acute Physiology Score (SAPS) is calculated 24 hours after admission of the patient and correlates with mortality rate, as shown in Table 2 (10).

SAPS score	Mortality
29 points	10 %
40 points	25 %
52 points	50 %
64 points	75 %
77 points	90 %

Table 2. Correlation between SAPS and mortality rates

2. AIMS

Aims of the research are: a) to evaluate the incidence of stress hyperglycemia in critically ill patients b) to correlate the presence of hyperglycemia and glycemic variability with complications and outcome in critically ill patients.

3. MATERIALS AND METHODS

The study included 100 patients hospitalized in Medical intensive care unit in the period January 2014–March 2015 which are divided into three groups: DM, stress-hyperglycemia and normoglycemia. In retrospective-prospective observational clinical study the following data was obtained: age, gender, SAPS, reason for admission, average daily blood glucose, highest blood glucose, glycemic variability, vasopressor and corticosteroid therapy, days on mechanical ventilation, total days of hospitalization in the intensive care unit, and outcome.

4. RESULTS

Out of 100 patients, 55% were male and 45% female. The mean age of patients was 61.54 ± 16.9 years. The youngest patient was 21 and the oldest 88 years old. The reasons for admission were grouped in five categories: sepsis / septic

Reason for admission	Patients (%)
Respiratory	43 %
Cardiovascular	17 %
Sepsis / septic shock	15 %
Neurologic	15 %
Other	10 %

Table 3. Reasons for admission in intensive care unit

Characteristics	Diabetes mellitus	Stress- hyperglycemia	Normoglycemia
Age **± SD**	69.0 ± 12.9	61.5 ± 14.9	56.1 ± 11.1
Gender, n (%)			
Male	19 (54.3 %)	12 (61.3 %)	24 (52.2 %)
Female	16 (45.7 %)	9 (47.3%)	22 (47.8 %)
Reason for admission			
Sepsis / septic shock	5 (14.3 %)	4 (21.1 %)	6 (13.0 %)
Respiratory	18 (51.4 %)	6 (31.6 %)	19 (41.3 %)
Cardiovascular	5 (14.3 %)	7 (36.8 %)	5 (10.9 %)
Neurologic	5 (14.3 %)	2 (10.5 %)	8 (17.4 %)
Other	2 (5.7 %)	0 (0%)	8 (17.4 %)
SAPS	50 ± 21	59 ± 16	46 ± 13
Blood glucose			
Min glucose (mmol/l)	6.9	7.2	5.1
Max glucose (mmol/l)	14.2	16.5	7.6
Mean glucose (mmol/l)	10.6	11.9	6.3
Glycemic variability (mmol/l)	7.5	9.3	2.5
Therapy			
Vasopressors i.v.	11 (31.4 %)	13 (68.4 %)	10 (21.2%)
Corticosteroids i.v.	12 (34.3%)	9 (47.4 %)	12 (26.1 %)
Insulin i.v.	26 (74.3 %)	16 (84.2%)	2 (4.3 %)
Type of nutrition, n (%)			
Oral	9 (22.3 %)	5 (26.3 %)	13 (28.2 %)
Enteral	27 (77.7%)	14 (73.7 %)	33 (71.8 %)
Outcome			
Exitus letalis, n (%)	17 (48.6%)	10 (52.6 %)	17 (36.9 %)
Recovery, n (%)	18 (51.4%)	9 (47.4%)	29 (63.1 %)
Days on mechanical ventilation	6.5 ± 1.8	6.7 ± 2.3	6.0 ± 1.7
Total days in intensive care	8.1 ± 1.6	9.4 ± 2.7	8.1 ± 1.2

Table 4. Characteristics of patients divided into three categories.

shock, respiratory, cardiovascular, neurologic and other causes (Table 3).

SAPS was calculated in all patients 24 hours after admission. The mean SAPS was 49.9 points, indicating the expected mortality rate of nearly 50%.

Out of all patients, 35% had already diagnosed diabetes mellitus, 19% had stress-hyperglycemia (glucose> 11.1 mmol / l), and 46% of patients were normoglycemic. The characteristics of the patients divided into these three categories are shown in Table 4.

The maximum value of blood glucose was 17.4 ± 9.6 mmol/l in patients with adverse outcome, while the maximum value of the blood glucose level was 12.7 ± 4.8 mmol/l in patients who have recovered. There was a significant difference between the maximum level of blood glucose in recovered and patients with adverse outcome ($p = 0.0277$). Glycemic variability (difference between max. and min. blood glucose) was the strongest predictor of adverse outcome. Glycemic variability in patients with stress hyperglycemia was 9.1 ± 2.2 mmol/l, and 3.1 ± 0.8 mmol/l in the normoglycemic group. The difference between the two groups was statistically significant ($p = 0.0066$).

There was no statistically significant difference in duration of mechanical ventilation and total days of hospitalization in the intensive care unit between the three groups.

5. DISCUSSION

In this study, the overall prevalence of patients with hyperglycemia was 54% (35% with diabetes mellitus and 19% with a stress hyperglycemia). This percentage is higher than in earlier studies where the prevalence of hyperglycemia was estimated at about 40% (11).

Patients with stress-hyperglycemia had higher mortality (52.6%) compared to patients with previously diagnosed diabetes (48.6%) or normoglycemia (36.9%), which correlates with the results of earlier studies (3, 12).

Our study demonstrated a statistically significant difference between the maximum level of blood glucose in recovered and patients with poor outcome, which is consistent with earlier studies (13, 14).

Glycemic variability was the most significant predictor of mortality which is consistent with the MacKenzie et al. study (15). Our study has not confirmed the correlation between hyperglycemia and CIP, as was demonstrated in the study of Nanas et al. which showed an independent association between CIP and elevated glucose levels (16).

6. CONCLUSION

Based on our research, we reached the following conclusions:

* Out of the 100 critically ill patients, 35% had already diagnosed diabetes mellitus, 19% had stress- hyperglycemia, and 46% of patients were normoglycemic.

* Glycemic variability was the strongest predictor of adverse outcome. There was a statistically significant difference in glycemic variability in patients with stress hyperglycemia and normoglycemia.

* There was no statistically significant difference in length of mechanical ventilation and total days of hospitalization in intensive care unit between the three groups.

* Patients with stress-hyperglycemia had a higher rate of mortality than patients with previously diagnosed diabetes and nondiabetic patients.

* Conscientious understanding of target glycemia and effective glycemic control is essential for optimization of the patient outcome.

CONFLICTS OF INTEREST: NONE DECLARED.

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