

Hyperglycemia: A Predictor of Death in Severe Head Injury Patients

Simin Babaie Kafaki¹, Kamaledin Alaedini¹, Ashkan Qorbani², Leila Asadian¹ and Kaveh Haddadi³

¹MD, Mazandaran University of Medical Science, ²MD, School of Medicine, Mazandaran University of Medical Science, Sari, Iran.

³Associated Professor, Department of Neurosurgery, Diabetes Research Center, Emam Hospital, Diabetes Research Center, Mazandaran University of Medical Science, Sari, Iran.

ABSTRACT

OBJECTIVES: Management of hyperglycemia during an acute sickness in adults is accompanied by improved outcomes. We have designed a prospective study with meticulous attention to exclude all diabetes patients by checking hemoglobin A1c (HbA1c or glycated hemoglobin) to avoid the ill-effects of hyperglycemia in patients with traumatic head injury admitted to the intensive care unit (ICU).

METHODS: This prospective study included adults with traumatic primary brain injury with a Glasgow coma score of ≤ 8 necessitating mechanical ventilation treated in the period 2012–2015. After screening 311 patients, 220 were included in the study. Both blood glucose and HbA1c levels of all the patients at admission, as well as blood glucose level after 72 hours, were obtained from the records. The patients were later grouped based on their admission blood glucose levels (< 200 mg/dL or ≥ 200 mg/dL). Injury severity score (ISS) was documented for every patient. As a final point, the outcomes were determined based on the hospital length of stay (HLS) and ICU length of stay (ILS), plus mortality rates.

RESULTS: About 39% ($n = 85$) of patients were admitted with hyperglycemia during the study period. The mortality rate in patients with glucose ≥ 200 mg/dL was 65.8% ($N = 56$), against 23.7% ($N = 32$) in the group with glucose < 200 mg/dL, with mortality rising as the blood glucose level increased ($P = 0.014$).

CONCLUSIONS: We conclude that admission hyperglycemia is related with increased mortality rate in head injury patients, and comprehensive treatment of hyperglycemia can improve the outcome of severe head injury patients.

KEYWORDS: hyperglycemia, injury severity score, mortality

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CORRESPONDENCE: Kaveh Haddadi, kh568hd@yahoo.com

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Introduction

Traumatic brain injury (TBI) promotes numerous fundamental and functional alterations that contribute to the worsening of the patient's condition, as observed under clinical and investigational situations. These events occur in parallel and serially.¹ Related injuries lead to unusually diverse results. Patients appear to respond to the strain of trauma diversely. Some are discharged after a comparatively ordinary hospital stay, whereas others progress through a relatively complicated sequence, with a few even expiring as a result of injuries. Because there is little that medics can do to improve the effects of primary brain injury, the goals of head injury treatment are directed towards preventing secondary insults.^{2,3} Clinically imperative hyperglycemia has conventionally been described as a blood glucose concentration > 200 mg/dL.^{4,5} But, some reports have confirmed a relationship between lower hyperglycemic levels (< 200 mg/dL) and divergent outcomes in hospitalized patients, spurring investigators to examine the lower "limits" for blood glucose ranges.^{5,6} Management of hyperglycemia during an acute

disorder in adults is linked to better outcomes.^{6,7} Surely, the active management of blood glucose is rarely stressed as a significant feature of the management of head injuries.^{8,9} Usually, the amount of the stress reaction is related to the extent of tissue disturbance. Similarly, stress hyperglycemia has been linked to amplified danger of death, congestive heart failure, and cardiogenic shock.¹⁰ A prospective randomized study showed that trauma patients with persistent hyperglycemia have significantly higher rates of morbidity and mortality.¹¹ In another study, patients with raised blood glucose levels experienced significantly higher occurrence of infection, intensive care unit (ICU) length of stay (ILS), hospital length of stay (HLS), hospitalization, and death.¹² Particularly, studies have established a connection between blood glucose concentrations and outcomes in patients hospitalized with head trauma, in addition to inpatients with nontraumatic damages.¹³ A few studies have investigated this relationship in trauma, not restricting the study to patients with traumatic head injuries,¹⁴ but the difference between absolute diabetes mellitus and stress-induced hyperglycemia



was not detected in previous studies. We design a prospective study with meticulous attention to exclude all diabetes patients by checking hemoglobin A1c (HbA1c or glycated hemoglobin) to study the effect of hyperglycemia in traumatic head injury patients admitted in ICU.

Materials and Methods

This is a prospective study to determine the effect of the hyperglycemic state on the prognosis of traumatic definitely nondiabetic patients admitted to the ICU. This study was approved by the Institutional Ethics Committee of the Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran (Code: IR. MAZUMS. REC.8/4/1393). Informed consent was obtained from each patient's relatives. The research was conducted in accordance with the principles of the Declaration of Helsinki.

This study included adults with traumatic primary brain injury with a Glasgow coma score (GCS) of ≤ 8 necessitating mechanical ventilation treated in the period 2012–2015. After initial screening, 220 of 311 patients were included in the study. Exclusion criteria were as follows: (1) history of diagnosed diabetes mellitus and treatment; (2) HbA1c $\leq 6.5\%$; (3) other variables influencing mortality (such as kidney or liver function), secondary infection, and chronic diseases (such as rheumatic disorders, atherosclerosis, arrhythmias, acute cardiac diseases, and cardiovascular complications; or even cancer). Demographic, diagnostic, and physiological documents for the first 24 hours in the ICU were compiled manually for every patient from the ICU charts and the patient's minutes. The data were later entered into a computerized file at regular intervals. We obtained the blood glucose level of each patient at admission and at 72 hours from the file. The patients were subsequently divided based on their admission blood glucose levels: <200 mg/dL or ≥ 200 mg/dL. Persistent hyperglycemia >200 mg/dL was treated with suitable insulin injections by an internist physician. In addition, we did not focus on the reasons for hyperglycemia (catecholamines, cortisol, and growth hormone levels or stress hyperglycemia, although these may strongly influence the evolution and final outcome of the disease), but we just analyzed the level of blood glucose. Age, gender, and injury severity score (ISS) were recorded for all patients. ISS was considered according to the Abbreviated Injury Scale (AIS 90). Because we measured HbA1c levels in our patients, it is not conceivable that we have unintentionally included a few patients previously diagnosed with diabetes and this is the strength of our study. Finally, the outcomes were determined according to the hospital length of stay (HLS) and ICU length of stay (ILS), plus mortality rates.

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences (SPSS). Analytical paired *t*-test was used for quantitative variables, and chi-square test was used for qualitative variables. The level of significance was taken as $P < 0.05$.

Table 1. Demographics and outcome variables stratified according to patient's blood glucose levels.

| | BS < 200 N = 135 | BS > 200 N = 85 | P-VALUE |
|-----|---------------------|--------------------|---------|
| Age | 41.56 ± 14.3 | 39.1 ± 17.33 | 0.333 |
| ISS | 19.23 ± 4.25 | 26.6 ± 3.16 | 0.041* |
| HLS | 24.33 ± 15.23 | 16.67 ± 9.23 | 0.012* |
| ILS | 9.24 ± 5.13 | 15.34 ± 7.45 | 0.022* |

Note: * $P < 0.05$ shows significant difference.

Abbreviations: HLS, hospital length of stay (days); ILS, intensive care unit length of stay (days); ISS, injury severity score; BS, blood sugar (glucose) level (mg/dL).

Results

Overall, 220 patients were included in the study. Men accounted for the greater part of the study population ($N = 149$, 67.7%). The mean age of the study population was 41.38 ± 19.07 years, with no considerable dissimilarity among the two study groups. The mean ISS showed significant variance between the two study groups. Table 1 shows the additional variables considered in both groups. Nearly 39% ($n = 85$) of patients were admitted with hyperglycemia during the study period. According to Table 1, HLS was 16.67 ± 9.23 days in the group with glucose ≥ 200 mg/dL compared to 24.33 ± 15.23 in the group with glucose <200 mg/dL ($P \leq 0.012$). Moreover, ILS was 15.34 ± 7.45 days in the group with glucose ≥ 200 mg/dL compared to 9.24 ± 5.13 days in the group with glucose <200 mg/dL ($P \leq 0.022$).

The mortality rate in patients as a result of hyperglycemia was 65.8% ($N = 56$) against 23.7% ($N = 32$) within the group with glucose <200 mg/dL, showing that mortality increases as blood glucose level increases ($\chi^2 = 5.033$; $P = 0.014$).

The association of mortality with hyperglycemia appears to be linear and is shown in Figure 1.

In addition, we compared the surviving and deceased patients across a range of ISS, HLS, and ILS values and blood glucose ranges (Table 2). Thus, HLS was 14.09 ± 12.36 days

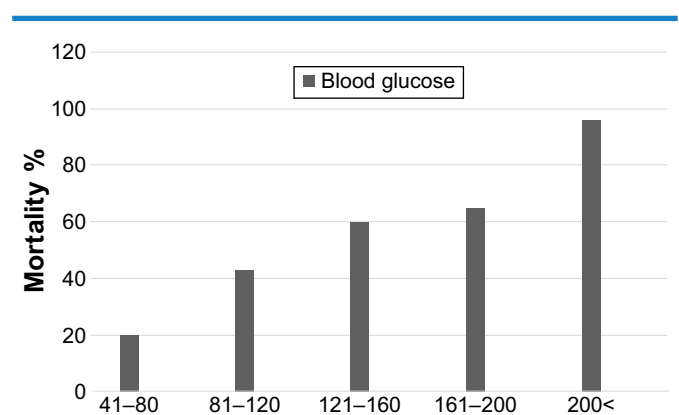


Figure 1. The relationship between blood glucose level in the first 24 hours in ICU and mortality.

Abbreviation: ICU, intensive care unit.

**Table 2.** Demographics and outcome variables according to patient's mortality.

| | DEAD (N = 88) | ALIVE (N = 132) | P-VALUE |
|---------------------|----------------|-----------------|---------|
| Age | 40.23 ± 16.54 | 36.22 ± 14.23 | 0.34 |
| ISS | 24.19 ± 5.04 | 20.23 ± 6.43 | 0.042* |
| HLS | 14.09 ± 12.36 | 24.78 ± 18.33 | 0.005* |
| ILS | 10.11 ± 9.23 | 17.56 ± 11.43 | 0.01* |
| Admission BG (mean) | 256.34 ± 88.43 | 165.52 ± 56.61 | 0.003* |
| 72 hour BG | 278.22 ± 78.45 | 168.44 ± 44.33 | 0.003* |

Note: * $P < 0.05$ shows significant difference.

Abbreviations: HLS, hospital length of stay (days); ILS, intensive care unit length of stay (days); ISS, injury severity score; BG, blood glucose level (mg/dL).

in dead patients compared to 24.78 ± 18.33 days in alive patients ($P \leq 0.005$); ILS was 10.11 ± 9.23 days in dead patients compared to 17.56 ± 11.43 days in alive patients ($P \leq 0.01$).

Discussion

The development of hyperglycemia itself might contribute to morbidity and mortality via generating a noxious cellular environment, causing electrolyte irregularities, and depressing immune efficacy.^{15,16} Catecholamines increase glucagon secretion and inhibit insulin secretion following damage and stress.¹⁷ Clinical reports on trauma patients have mainly paid attention to patients with traumatic brain injuries in whom there is a positive association between blood glucose levels and mortality rates. Krinsley showed that a modest amount of hyperglycemia leading to ICU admission was related to a significant increase in hospital death in patients with a wide variety of medical and surgical findings.^{18,26} A huge prospective randomized experimental trial showed that control of blood glucose level by means of a rigorous insulin administration procedure improved the clinical outcome and decreased mortality by 42%.¹⁹ A study by Sung et al showed that admission hyperglycemia is an autonomous prognosticator of outcomes and infection in trauma patients.¹⁹ In this study, we established that the mortality rate among patients with blood glucose levels ≥ 200 mg/dL was considerably greater than that in patients with levels < 200 mg/dL. This decision is in accordance with the majority of other studies,^{7,20} except that we were not able to demonstrate a statistically considerable association between higher glucose levels and the length of hospital/ICU stay. Most recently, Yendamari et al⁷ retrospectively studied the influence of admission hyperglycemia in 738 trauma patients. The authors determined that hyperglycemia on admission separately predicted increases in ILS and HLS. Furthermore, there was also an increase in mortality, along with morbidity, caused by infectious disease courses. Shorter HLS is a consequence of the elevated mortality rate in patients with higher blood glucose levels (ie, ≥ 200 mg/dL). We conclude that admission

hyperglycemia is accompanied by increased mortality rate in head injury patients; however, it is still uncertain whether it causes longer HLS and ILS.

On the basis of the results of this study, although the HLS of patients in the blood sugar < 200 mg/dL group was higher than that in the hyperglycemic group, these patients were discharged from the ICU earlier than the hyperglycemic group, and perhaps those with blood sugar > 200 mg/dL had a higher mortality rate during the ICU admission.

The mechanisms by which blood glucose causes a harmful effect on the outcome after head injury are uncertain. Some researchers^{20,21} believe that hyperglycemia is purely a likeness of the stress response to injury. The metabolic appearance of the stress response is characterized by hyperglycemia mediated by a number of neural and hormonal mechanisms.²¹ In the head-injured patient, plasma noradrenalin levels are associated with the GCS score^{22,23} and outcome.^{24,25} Serum cortisol has similarly been linked with mortality after head injury.²⁶ Additionally, serum insulin levels correlate with the degree of coma after head injury.²⁷

Clearly, enhancements in clinical management could reduce the severity of hyperglycemia, in addition to decreasing the incidence of other complications such as multiple organ failure.²⁷ With reference to severe head injury, a randomized controlled study is needed to elucidate the precise relationship between blood glucose level and outcome. If hyperglycemia does cause secondary brain injury, there are several treatment decisions that could be adopted and that might reduce both mortality and neurological morbidity.

Finally, because the prevalence of diabetes is increasing in society, the higher the blood glucose level, the greater its impact will be in patients hospitalized for trauma. Thus, after proving the necessity of screening for patients with diabetes in study designs, we believe that we have been able to exclude the confounding effects of diabetes in our traumatic patients more accurately than did previous studies because we determined the HbA1c level as the basic principle of our study.

Conclusions

We conclude that admission hyperglycemia is related with increased death rate in head injury patients; moreover, it can also be a cause of mortality in the ICU.

Key Points

- Hyperglycemia is linked with amplified mortality rate in head injury patients.
- Shorter hospital length of stay is a consequence of the elevated mortality rate in patients with higher blood glucose levels (ie, ≥ 200 mg/dL).
- Comprehensive treatment of hyperglycemia can improve the outcome of severe head injury patients.

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Author Contributions

Conceived and designed the experiments: AQ, KH, LA. Contributed to the writing of the manuscript: SBK, LA. Agree with manuscript results and conclusions: SBK, KA, AQ, LA, KH. Jointly developed the structure and arguments for the paper: SBK, KA, AQ, LA, KH. Made critical revisions and approved final version: KH. All authors reviewed and approved of the final manuscript.

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