Hyperglycemia and neurological outcome in patients with head injury

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To examine the relationship between serum glucose and the outcome of patients suffering from head injury, the authors retrospectively reviewed the clinical course of 169 patients admitted for treatment to Harborview Medical Center (a regional trauma center). All patients underwent craniotomy for evacuation of intracranial hematoma and/or placement of a subarachnoid bolt for intracranial pressure monitoring under general anesthesia. Patients with a Glasgow Coma Scale (GCS) score of 8 or less had significantly higher serum glucose levels than patients with GCS scores of 12 to 15 (mean ± standard error of the mean 192 ± 7 mg/dl vs. 130 ± 8 mg/dl or 10.7 ± 0.4 mmol/liter vs. 7.2 ± 0.4 mmol/liter) (p < 0.0001). Patients who subsequently remained in a vegetative state or died had significantly higher glucose levels both on admission and postoperatively than patients who had good outcome or moderate disability (217 ± 12 mg/dl vs. 167 ± 6 mg/dl or 12.1 ± 0.7 mmol/liter vs. 9.3 ± 0.3 mmol/liter on admission, and 240 ± 16 mg/dl vs. 156 ± 5 mg/dl or 13.3 ± 0.9 mmol/liter vs. 8.9 ± 0.3 mmol/liter postoperatively) (p < 0.0001). Among the more severely injured patients (GCS score ≤ 8), a serum glucose level greater than 200 mg/dl (11.1 mmol/liter) postoperatively is associated with a significantly worse outcome (p < 0.01). The authors conclude that severely head-injured patients frequently develop hyperglycemia and the elevated serum glucose level may aggravate ischemic insults and worsen the neurological outcome in such patients.

KEY WORDS • glucose • head injury • hyperglycemia • cerebral ischemia

TRAUMATIC brain injury results in an increase in circulating catecholamines due to hypothalamic-adrenal activation. The increase in circulating catecholamines causes not only a hyperdynamic cardiovascular response but also a rise in blood glucose levels. Indeed, it has been demonstrated that blood glucose and lactate levels are frequently elevated in patients with severe head injury, and this may be accompanied by an elevated glucose concentration in the cerebrospinal fluid (CSF). Some investigators have suggested that hyperglycemia represents a stress response and reflects the extent of brain injury and, as such, has prognostic significance. On the other hand, it may have a direct impact on neurological outcome since hyperglycemia has been shown in both experimental and clinical studies to exacerbate the severity of brain injury during ischemic conditions.

The etiology of the increased neuronal injury caused by hyperglycemia is likely related to continuing anaerobic metabolism leading to intracellular acidosis and accumulation of lactate, particularly in the setting of transient focal ischemia which frequently occurs in severe head injury. In addition, anesthesia and surgical stress can cause an increase in cortisol levels, which may in turn cause an increase in serum glucose content. Despite these theoretical considerations, the relationship between hyperglycemia and outcome in patients with head injury, particularly those who have had the additional stress of surgical intervention, has not been well investigated. We therefore undertook a retrospective review of 169 consecutive patients with head injury to determine the association of serum glucose levels with neurological outcome.

Clinical Material and Methods

Case Material

The study was approved by the University of Washington Human Subjects Review Committee. We reviewed the charts of 169 consecutive patients admitted to Harborview Medical Center during 1988 who required the placement of a subarachnoid bolt for intra-
TABLE I

<table>
<thead>
<tr>
<th>Feature</th>
<th>GCS 12–15</th>
<th>GCS 9–11</th>
<th>GCS ≤ 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases†</td>
<td>23</td>
<td>29</td>
<td>109</td>
</tr>
<tr>
<td>GCS (mean ± SD)</td>
<td>13.6 ± 1.2</td>
<td>9.7 ± 0.8</td>
<td>5.2 ± 1.8</td>
</tr>
<tr>
<td>age in yrs (mean ± SD)</td>
<td>30 ± 20</td>
<td>28 ± 23</td>
<td>26 ± 17</td>
</tr>
<tr>
<td>sex (M/F)</td>
<td>17/6</td>
<td>20/9</td>
<td>84/25</td>
</tr>
<tr>
<td>admission glucose level in mg/dl</td>
<td>130 ± 5</td>
<td>166 ± 11‡</td>
<td>192 ± 7‡</td>
</tr>
<tr>
<td>postop glucose level in mg/dl</td>
<td>136 ± 6</td>
<td>164 ± 8‡</td>
<td>186 ± 8‡</td>
</tr>
<tr>
<td>diagnosis (%) of GCS group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diffuse brain swelling</td>
<td>74%</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td>epidural hematoma</td>
<td>17%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>4%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>intracerebral hematoma</td>
<td>4%</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>other</td>
<td>0%</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*GCS = Glasgow Coma Scale score; SD = standard deviation; SEM = standard error of the mean.
† In eight patients, GCS was not recorded on admission and their data were excluded.
‡ Significantly different from GCS 12–15, p < 0.01.

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cranial pressure (ICP) monitoring. All patients with a Glasgow Coma Scale29 (GCS) score of 8 or less were routinely monitored. Patients with GCS scores of greater than 8 but who were pharmacologically paralyzed as part of the initial resuscitation (and therefore could not be neurologically assessed) were frequently monitored as were patients with contusion/swelling on computerized tomography (CT) scans. All patients who required a craniotomy for evacuation of an intracranial hematoma also had placement of a subarachnoid bolt. It was our policy to place all subarachnoid bolts in the operating room under general anesthesia (usually an opioid with a low concentration of isoflurane and muscle relaxants). All patients were managed according to an aggressive protocol that included hyperventilation and administration of mannitol and diuretics when deemed appropriate. Hyperglycemia, however, was not treated with insulin.

The demographic data and the diagnoses of the patients reviewed are summarized in Table I. Thirty-three percent of the patients had long-bone fractures and 26% had chest/abdominal injuries. Steroids were administered to only 23 patients, who received dexamethasone (8 to 10 mg) prior to transfer to our hospital; 49 of these had GCS scores of less than 8. All patients received 5% dextrose solution as maintenance fluid at 75 to 100 ml/hr after admission but no glucose-containing solutions were given intraoperatively. There was no difference in the amount of 5% dextrose infused between the normoglycemic and the hyperglycemic groups, nor between patients with good outcome and patients with poor outcome. Not all patients had complete data; three did not have a serum glucose measurement on admission and two had no postoperative glucose measurement. These patients were excluded from data analysis.

Video Examined

Information retrieved included the admission GCS score, the Glasgow Outcome Scale1 (GOS) score (1 = good recovery; 2 = moderate disability; 3 = severe disability; 4 = persistent vegetative state; and 5 = death) at the end of 10 days, the serum glucose level on admission and 1 day postoperatively (usually 24 hours after admission), age, sex, CT diagnosis, surgical procedure, ICP, and medical treatment. Patients with diabetes who were not well controlled prior to the head injury were excluded.

Variables Examined

To assess the influence of head injury on serum glucose content, glucose levels on admission in patients with high GCS scores (12 to 15) were compared with those in patients with low GCS scores (≤ 8) using an unpaired t-test. Patients in the intermediate group (GCS scores 9 to 11) were not included in the analysis because the number was too small to yield any statistical significance. To determine the association of serum glucose value with outcome, the glucose levels in patients with a good outcome (GCS score 1 or 2) were compared with those of patients with a poor outcome (GCS score 4 or 5) using an unpaired t-test. Patients with a severe disability (GCS score 3) were not analyzed, not only because there were only 29 patients in this category, but also because we are primarily interested in the two extremes of the outcome spectrum. In patients with severe head injury (GCS score ≤ 8), we used chi-square analysis to examine the neurological outcome (GCS score 1/2 vs. 4/5) of patients whose serum glucose level was less than 200 mg/dl (11.1 mmol/liter) as compared to patients with a glucose value greater than 200 mg/dl. To further assess the prognostic value of an elevated serum glucose level, the same analysis was repeated using 150 mg/dl (8.3 mmol/liter) as the criterion. To
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![Graph showing the relationship between serum glucose levels and patient outcome](image)

**Fig. 2.** Outcome of patients with a Glasgow Coma Scale score of 8 or less categorized according to their postoperative glucose values (in mg/dl). Patients with postoperative glucose levels > 150 mg/dl or > 200 mg/dl (right) had significantly worse outcome than patients with lower values. There was a higher proportion of patients with poor outcome in both hyperglycemic groups. Numbers in bars denote the actual number of patients in that category.

evaluate the influence of surgical stress, in all analyses both admission and postoperative glucose values were examined. Relationships between the GCS score, GOS score, and serum glucose levels were assessed with multiple linear regression analysis. A p value of < 0.05 is considered to be significant.

**Results**

**GCS and Glucose Levels**

Patients with more severe head injury (GCS score ≤ 8) had significantly higher admission and postoperative glucose values than patients with mild injury (GCS scores 12 to 15) (Table 1). These differences were significant (p < 0.01).

**GOS and Glucose Levels**

As can be seen in Fig. 1, comparison of patients with a good outcome (GOS score 1/2) and patients in a vegetative state or dead (GOS score 4/5) demonstrated a significant difference in admission glucose value (p < 0.001). This difference was even more significant when the postoperative values were used (p < 0.0001). There was no significant difference in the patient ages with respect to outcome.

**GOS and Glucose Levels in Patients with GCS Scores ≤ 8**

In the severely injured patients (GCS scores ≤ 8), postoperative serum glucose levels greater than 200 mg/dl (11.1 mmol/liter) were associated with a poorer outcome (p < 0.05) (Fig. 2), but admission glucose levels greater than 200 mg/dl did not correlate with outcome (Fig. 3). However, patients with either admission or postoperative serum glucose levels greater than 150 mg/dl (8.3 mmol/liter) had a worse neurological outcome (p < 0.05) (Figs. 2 and 3). There was no significant difference in age between the patients with poor outcome versus good outcome in any subgroup. Since 200 mg/dl (11.1 mmol/liter) is conventionally accepted as significant hyperglycemia and represents a level at which treatment may be considered, we evaluated the criterion of a postoperative glucose level greater than 200 mg/dl as a prognostic test for poor neurological outcome in patients with a GCS score of 8 or less. This yielded a sensitivity of 49%, a specificity of 82%, a positive predictive value of 60%, and a negative predictive value of 75%.

**Influence of GCS Score and Glucose Levels on Outcome**

To assess the independent influence of glucose levels and GCS score on outcome, multiple linear regression analysis was used with both parameters as independent variables. When all patients were included for analysis, it yielded the following relationship: GOS score = 3.31 - 0.21 (GCS score) + 0.005 (glucose level), with p < 0.001 for both GCS score and glucose level. Evaluation of the standardized coefficients indicated that the independent influence of glucose levels on outcome was about half that of the GCS score. A similar relationship was also obtained when only patients with GCS scores of 8 or less were analyzed; GOS score = 4.36 - 0.4 (GCS score) + 0.004 (glucose level) with p < 0.01 for both GCS score and glucose level; the glucose level again influenced outcome independently with about half the impact of the GCS score.

**Influence of Change in Serum Glucose Level on Outcome**

To assess if a change in serum glucose status was associated with a similar change in neurological out-
come, we analyzed all patients according to their admission and subsequent postoperative glucose levels using 200 mg/dl (11.1 mmol/liter) as the criterion. Patients were first separated into two groups: Group I, with an admission glucose level greater than 200 mg/dl and Group II, with an admission glucose level less than 200 mg/dl. Groups I and II were then subcategorized according to their postoperative glucose values. The neurological outcome (GOS score 1/2 vs. 4/5) of these patients in absolute numbers and percentages is displayed in Table 2. As can be seen, when evaluated as a group without stratification according to their GCS score, Group I patients had a relatively poor outcome compared to Group II patients (p < 0.05). However, within Group I, a better neurological outcome was observed in patients whose postoperative glucose level declined to less than 200 mg/dl. Similarly, Group II patients who subsequently developed hyperglycemia had a significantly worse outcome than patients who continued to have glucose levels below 200 mg/dl in the postoperative period (p < 0.001). The subsequent course of both subsets (postoperative glucose levels > 200 and ≤ 200 mg/dl) were also significantly different from that of the parent group (Group II) (p < 0.05).

Discussion

In this study, we have demonstrated that patients with severe head injury frequently have elevated serum glucose levels and patients with poor neurological outcome have a much higher serum glucose value than patients with good outcome. When patients were stratified according to their admission GCS score, a postoperative serum glucose level greater than 200 mg/dl (11.1 mmol/liter) was associated with a worse neurological outcome in the severely head-injured patients.

Hyperglycemia, Acidosis, and Neurological Injury

The correlation of hyperglycemia with severity of head injury is not surprising and is consistent with several previous studies with smaller numbers of patients. However, the fact that hyperglycemia may aggravate neurological outcome in severely head-injured patients has not been addressed and has important therapeutic implications. Numerous studies in animal models of focal ischemia have demonstrated an increase in neurological deficits and/or size of infarct with hyperglycemia. Although the mechanism is not entirely clear and, in some studies of permanent focal ischemia, even beneficial effects of hyperglycemia have been demonstrated, it is generally agreed that an abundant supply of glucose substrate during ischemic conditions allows continuation of anaerobic metabolism with accumulation of lactate and hydrogen ions. The resultant intracellular acidosis triggers a cascade that may involve activation of calcium entry into the cells, lipolysis, release of cytotoxic fatty acids and the glutamates, and eventual destruction of neurons. Indeed, Kraig, et al., have demonstrated that cerebral lactic acidosis can cause brain-tissue necrosis in a pattern resembling that seen in ischemic brain infarctions. This typically occurs at a pH of about 5.3, which is a level of acidity that can be easily achieved during complete ischemia under hyperglycemic conditions.

Stress Response

In the clinical mode, it has been observed that hyperglycemic patients who were successfully resuscitated after a cardiac arrest had a worse neurological outcome than normoglycemic patients. Similarly, hyperglycemic patients who suffered a stroke had a worse outcome than patients with normoglycemia. A cause and effect...
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Incidence of good outcome (GOS 1/2) and poor outcome (GOS 4/5) according to admission and postoperative glucose levels*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group &amp; Glucose Level</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>Group I patients</td>
<td></td>
</tr>
<tr>
<td>200 mg/dl on admission</td>
<td>53</td>
</tr>
<tr>
<td>&gt;200 mg/dl postop†</td>
<td>14</td>
</tr>
<tr>
<td>&lt;200 mg/dl postop†</td>
<td>35</td>
</tr>
<tr>
<td>Group II patients</td>
<td></td>
</tr>
<tr>
<td>&lt;200 mg/dl on admission‡</td>
<td>111</td>
</tr>
<tr>
<td>&gt;200 mg/dl postop§</td>
<td>26</td>
</tr>
<tr>
<td>&lt;200 mg/dl postop§</td>
<td>85</td>
</tr>
</tbody>
</table>

* In Group I (admission glucose level > 200 mg/dl), patients with persistent hyperglycemia had worse outcome than patients with normalized glucose levels (< 200 mg/dl) postoperatively. In Group II (admission glucose < 200 mg/dl), patients who developed hyperglycemia postoperatively did worse than those who did not. GOS = Glasgow Outcome Scale score.
† Difference in outcome significantly different from each other (p < 0.05).
‡ Significantly different from all patients with glucose levels > 200 mg/dl on admission (p < 0.05).
§ Difference in outcome significantly different from each other (p < 0.001).

In the present study, we found that patients with poor neurological outcome had a significantly higher serum glucose value than did patients with a good neurological outcome, suggesting that hyperglycemia may indeed increase neurological deficit. Although it is difficult to differentiate an association from a cause-effect relationship, a detailed examination of our analysis of the most severely injured group (GCS scores ≤ 8) strongly suggests that it is more than an association. In this relatively homogeneous group, patients with postoperative serum glucose levels greater than 200 mg/dl had a significantly worse outcome than patients with a lower glucose level.

We also examined the effects of mild hyperglycemia (> 150 mg/dl) versus moderate hyperglycemia (> 200 mg/dl), and surprisingly the findings indicated that patients with glucose levels lower than 150 mg/dl did better than patients with glucose levels lower than 200 mg/dl (Figs. 2 and 3). The fact that even a small reduction in glucose level from moderate to mild hyperglycemia is also associated with an improvement in neurological outcome strengthens the argument that, in addition to being a stress response, hyperglycemia may directly influence outcome. Moreover, results from multiple linear regression analysis suggest that, after controlling for the influence of the GCS score, glucose levels had an independent effect on outcome.

Our findings are similar to those of Young, et al.,31 who found in a smaller series of patients that a peak 24-hour glucose level greater than 200 mg/dl is associated with a significantly worse neurological outcome. In contrast, Parish and Webb32 were unable to find any association between hyperglycemia and prognosis in a small series of pediatric patients. However, they used a serum glucose level greater than 270 mg/dl as the definition for hyperglycemia, a value that may be too high and therefore insensitive to detect any potential difference in neurological outcome between the normoglycemic and the hyperglycemic groups. More recently, Kushner, et al.,33 have documented the association of high serum glucose levels with poor clinical findings as well as metabolic brain abnormalities seen on positron emission tomography in 39 patients suffering ischemic cerebral infarction.

Although our findings suggest a cause-effect relationship between hyperglycemia and poor neurological outcome in head injury, the present data do not prove the relationship. Nevertheless, the observations that patients with persistent hyperglycemia did not fare as well as patients who had normalized postoperative glucose levels (< 200 mg/dl) and that patients with admission glucose levels less than 200 mg/dl who subsequently developed hyperglycemia had worse outcome have two important implications: 1) they strengthen the theory that indeed the relationship between hyperglycemia and poor neurological outcome is more than an association phenomenon, and 2) they support the existence of a therapeutic time window during which treatment of hyperglycemia may improve neurological outcome.
Added to the recent evidence from animal studies demonstrating a beneficial effect of insulin therapy in cerebral ischemia, it is clear that these observations argue strongly in favor of aggressive treatment of hyperglycemia in head-injured patients, although hypoglycemia must not be allowed to occur since this is equally detrimental. The definitive proof of the therapeutic value of such treatment, however, can only come from a randomized clinical trial.

Retrospective Analysis

Due to the retrospective nature of this study, many variables and sources of potential bias could not be controlled. To the extent that it was not part of the routine practice to treat hyperglycemia in nondiabetic patients and that patients who are known diabetics were excluded, no bias was introduced in the grouping of the patients prior to their head injury. By examining the group with the most severe injury (a GCS score ≤ 8), we sought to minimize the potential bias inherent in a retrospective study. The nature of the intravenous infusion was not controlled, but all patients received a 5% dextrose and 0.2% saline infusion as maintenance fluid in the intensive care unit and lactated Ringer’s solution or normal saline for replenishment of intravascular volume. The more severely injured patients did not receive additional glucose-containing solutions.

We studied data obtained after the 10-day outcome instead of the conventional 6-month outcome because we were more interested in the immediate impact of hyperglycemia rather than the long-term effects. Moreover, the high percentage of poor outcomes (dead or vegetative) in the group with GCS scores of 8 or less suggests that the results are unlikely to be altered by a change in evaluation time.

Conclusions

We have demonstrated that hyperglycemia is frequently present in head-injured patients and the presence of hyperglycemia correlates with the extent of the initial injury. We also found that, in severely head-injured patients (GCS score ≤ 8), an elevated glucose level greater than 200 mg/dl (11.1 mmol/liter) in the first 24 hours is highly predictive of poor outcome. The results suggest a causal relationship between hyperglycemia and poor outcome.

References


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