Relationship of Early Hyperglycemia to Mortality in Trauma Patients

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Introduction: **Recent randomized prospective data suggest that early hyperglycemia is associated with excess mortality in critically ill patients, and tight glucose control leads to improved outcome. This concept has not been carefully examined in trauma patients, and the relationship of early hyperglycemia to mortality from sepsis in this population is unclear. The objective of this study was to determine the relationship different levels of early blood glucose elevation to outcome in a trauma ICU population.**

Methods: **The records of all patients admitted to the ICU over a 2-year period at a Level I trauma center were reviewed for age, injury severity scores (ISS), admission Glasgow Coma Scale (GCS) score, base deficit (BD), blood glucose, and mortality. Three possible cutoffs in defining hyperglycemia were examined (glucose ≥110 mg/dL, ≥150 mg/dL, ≥200 mg/dL) in relation to infection and mortality. Early hyperglycemia was defined as elevated blood glucose on hospital days 1 or 2. Those with diabetes mellitus were excluded.**

Results: **From 1/00–12/01, 516 eligible patients were admitted to the ICU after injury. Early hyperglycemia occurred in 483 at the ≥110 mg/dL level, 311 at the ≥150 mg/dL level, and 90 patients at the ≥200 mg/dL level. Univariate logistic regression demonstrated a significant relationship between ISS and subsequent infection($p = 0.02$) and a trend toward such a relationship in GCS score, glucose ≥150 mg/dL, and glucose ≥200 mg/dL ($p = 0.06$, 0.12, and 0.06). A similar analysis for the relationship of these variables to eventual mortality showed a significant correlation with all examined variables except glucose ≥110 mg/dL. Multiple logistic regression to control for the effect of age, ISS, GCS score, and BD found early glucose ≥200 mg/dL to be an independent predictor of both infection and mortality while no such relationship was found with ≥110 mg/dL or ≥150 mg/dL.**

Conclusions: **Early hyperglycemia as defined by glucose ≥200 mg/dL is associated with significantly higher infection and mortality rates in trauma patients independent of injury characteristics. This was not true at the cutoffs of ≥110 mg/dL or ≥150 mg/dL. These data support the need for a prospective analysis of tight glucose control, keeping serum glucose <200 mg/dL in critically ill trauma patients. However, aggressive maintenance of levels <110 mg/dL as reported by others may not be necessary.**

Key Words:

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Hyperglycemia is a common problem in critically ill patients. Hyperglycemia secondary to metabolic stress is manifested early in the hospital course of patients in the intensive care unit and resolves as the catabolic response subsides. Furthermore, hyperglycemia is associated with similar complications as uncontrolled diabetes, including an increased mortality, an increased number of infectious complications, and poor wound healing.[1] The presence of elevated blood glucose also impedes normal host defenses against infection and impairs the normal inflammatory response.[2,3]

Hyperglycemia is noted after injury in diabetics and non-diabetics.[4,5] There are multiple factors that explain this phenomenon. During stress states, there is a catecholamine excess stimulating glycogenolysis and increasing glycogen levels.[6] Additionally, there is a depression of insulin production[5] and peripheral insulin resistance.[7] The overall result is increased gluconeogenesis via cortisol and glucagon, increased glycogenolysis via epinephrine, and peripheral insulin resistance via glucagon and epinephrine. A persistent elevation of the blood glucose has been noted in injured patients, and the severity of injury seems to correlate with the level of hyperglycemia.[8]

Recent randomized prospective data have demonstrated a relationship between intensive insulin therapy and a reduction in morbidity and mortality in surgical ICU patients.[9] Although it has been shown that trauma ICU patients are hyperglycemic during the acute phase of their injury, the correlation between the degree of hyperglycemia and mortality and complications is not clear. The goal of this study was to determine the relationship between early hyperglycemia and outcome in trauma patients and to define the an appropriate level of glucose control for future prospective studies.

METHODS

Patients and Definitions

The records of all patients admitted to the intensive care unit were identified from the trauma registry of a Level I

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trauma center over a 2-year period. These patient records were reviewed for age, plasma glucose level, base deficit (BD), Glasgow Coma Scale (GCS) score, Injury Severity Score (ISS), and outcome. Diabetic patients were excluded. Patients with hyperglycemia were not treated by a strict protocol. Hyperglycemia generally was managed using both continuous intravenous insulin infusion and intermittent dosing and was initiated with plasma glucose values >200 mg/dL. Patients with glucose <200 do not receive insulin.

While in the intensive care unit, patients are monitored daily for the presence of systemic inflammatory response syndrome (SIRS) as defined by Bone et al.[10] Patients with SIRS and C-reactive protein >17mcg/dL undergo a systematic search for the source of possible infection. If the patient has a new or changing infiltrate on chest radiograph, this search includes bronchoalveolar lavage (BAL). Pneumonia was defined as $\geq 10^5$ cfu/mL on BAL. Line sepsis was diagnosed using sonicated catheter cultures with >1,000 cfu/mL being significant. Bacteremia was defined as any pathogenic organism noted on blood culture. Wound infection was diagnosed by presence of erythema, induration, fluctuance, or purulent drainage. The effect of hyperglycemia was examined at three different levels, >110 mg/dL, >150 mg/dL, and >200 mg/dL. Early hyperglycemia was defined as plasma glucose values exceeding these ranges on ICU days 1 or 2. The blood glucose values selected were single episodes occurring on day 1 at admission and day 2 at the first lab draw of the day.

Statistics

Statistical analysis was performed using Statview 5.0 (SAS Institute Inc., Cary, NC). Dichotomous variables were compared using χ^2 or Fisher's exact test where appropriate. Continuous variables were compared using Student's t test. The relationship of studied variables to eventual infection and death was examined using logistic regression analysis. Significance is defined as $p < 0.05$.

RESULTS

Patients

From 1/1/2000 through 12/31/2001, 556 patients were admitted to the trauma intensive care unit at Wake Forest University Baptist Medical Center. Of these, 516 did not have diabetes mellitus, and this group makes up the study population. The mean age of this group was 42 ± 19 years, mean injury ISS 24 ± 13, and the mean admission BD was −7.2 ± 7 mEq/L. Three hundred and sixty-one patients were male, and 155 were female. Overall rate of infection (pneumonia, line sepsis, bacteremia, wound infection, abscess) was 24% (127), and mortality was 19% (98). The majority of infected patients had pneumonia (93). Sixteen patients had pneumonia in addition to another infection site (bacteremia-13, line sepsis-2, wound infection-1). Eighteen patients had other varied sources of infection (bacteremia-7, line sepsis-5, intra-abdominal abscess-3, endocarditis-1, meningitis-1, line sepsis combined with wound infection-1).

Hyperglycemia

The incidence of hyperglycemia at three different levels was examined and the characteristics of the groups evaluated at each level. Four hundred and eighty-three patients had a blood glucose of ≥110 mg/dL on hospital day 1 or 2. The injury severity and characteristics of those above and below this cutoff are shown in Table 1. The two groups were similar with respect to age, injury severity, shock, and mortality. Rate of infection was higher in the group ≥110 mg/dL.

Similar analyses were performed where hyperglycemia is defined first as ≥150 mg/dL, and then ≥200 mg/dL. These comparisons are shown in Tables 2 and 3. Early hyperglycemia occurred in 60% (311) of patients at the ≥150 mg/dL level and in 17% (90) at the ≥200 mg/dL level. While early hyperglycemia is associated with infection and mortality at

Table 1 Comparison of Patients with and without Early Glucose Measurements of ≥110 mg/dL

	≥110 (n = 483)	<110 (n = 33)	p
Age	42	38	0.59
ISS	24	18	0.19
GCS score	11	12	0.75
Adm BD (mg/dL)	−7.2	−4.5	0.30
Infection	122 (25%)	2 (6%)	0.01
Mortality	82 (17%)	3 (9%)	0.33

ISS, injury severity score; GCS, Glasgow Coma Scale; Adm BD, admission base deficit.

Table 2 Comparison of Patients with and without Early Glucose Measurements of ≥150 mg/dL

	≥150 (n = 311)	<150 (n = 205)	p
Age	44	38	<0.0001
ISS	26	19	<0.0001
GCS score	11	12	0.19
Adm BD (mg/dL)	−7.3	−7.0	0.68
Infection	96 (31%)	28 (14%)	<0.0001
Mortality	70 (13%)	15 (7%)	<0.0001

ISS, injury severity score; GCS, Glasgow Coma Scale; Adm BD, admission base deficit.

Table 3 Comparison of Patients with and without Early Glucose Measurements of ≥200 mg/dL

	≥200 (n = 90)	<200 (n = 426)	p
Age	42	41	0.50
ISS	24	23	0.75
GCS score	11	12	0.05
Adm BD (mg/dL)	−6.8	−7.4	0.46
Infection	29 (32%)	96 (22%)	0.04
Mortality	31 (34%)	54 (13%)	<0.0001

ISS, injury severity score; GCS, Glasgow Coma Scale; Adm BD, admission base deficit.

both the ≥150 mg/dL and ≥200 mg/dL levels, differences in age and injury severity at the ≥150 mg/dL cutoff and GCS score at the ≥200 mg/dL cutoff may confound any inferences made about the relationship of hyperglycemia to infection overall mortality.

Relationship of Hyperglycemia to Infection

For this reason, logistic regression analysis was performed to determine the effect of each examined variable on infection. These analyses are shown in Table 4. Univariate logistic regression identified a significant association between higher ISS and infection. There was a trend toward higher infection rates with lower GCS scores as well as early hyperglycemia at both the ≥150 mg/dL and ≥200 mg/dL levels but not the ≥110 mg/dL level. Multivariate logistic regression incorporating variables with a p value of <0.2 was then performed to determine the relative contribution of each variable to infection. Hyperglycemia cutoffs of ≥150 mg/dL and ≥200 mg/dL were evaluated separately to avoid problems of co-linearity. Of these parameters, only hyperglycemia at the ≥200 mg/dL level proved to be an independent predictor of subsequent infection ($p = 0.02$).

Relationship of Hyperglycemia to Mortality

Univariate logistic regression analysis of the relationship of age ISS, GCS score, BD, and hyperglycemia (≥110 mg/dL, ≥150 mg/dL, and ≥200 mg/dL) to mortality showed significant relationships between all variables and eventual death except the ≥110 mg/dL glucose level (Table 4).

Multivariate logistic regression, again incorporating those variables with $p < 0.2$ identifies glucose ≥200 mg/dL, age, ISS, GCS score, and BD as independent predictors of mortality ($p = 0.04$, <0.0001, <0.0001, <0.006, and 0.03 respectively) while ≥150 mg/dL is not ($p = 0.29$).

DISCUSSION

Critically ill patients frequently are found to be hyperglycemic, and there is evidence that such hyperglycemia may lead to worse outcomes.[1] There is little information available to indicate that this relationship is true in trauma patients, however. These data demonstrate that early hyperglycemia as defined by plasma glucose >200 mg/dL is associated with higher rates of infection and mortality in severely injured patients. Furthermore, this effect appears to be independent of the severity of injury or associated shock. This may have important implications for both outcome prediction and glucose management in the trauma intensive care unit.

Table 4 Relationship to Age, Severity of Injury, Shock, and Elevated Glucose to Subsequent Infection and Mortality on Univariate Logistic Regression

Variable	p Value (Infection)	p Value (Mortality)
Age (years)	0.39	<0.0001
ISS	0.02	<0.0001
GCS score	0.06	<0.0001
BD (mg/dL)	0.79	0.01
Glucose ≥110 mg/dL	0.37	0.97
Glucose ≥150 mg/dL	0.12	<0.0001
Glucose ≥200 mg/dL	0.06	<0.0001

ISS, injury severity score; GCS, Glasgow Coma Scale; BD, base deficit.

Stress-induced hyperglycemia is a significant problem in injured patients.[4,5] Hyperglycemia is associated with excess mortality, as shown by several previous investigators. Derangements in glucose control are associated with an increased mortality and poorer neurologic recovery after stroke regardless of whether the patient was diabetic or nondiabetic.[11] This same relationship holds true for patients with severe head injuries, again demonstrating worse neurologic outcome and higher mortality.[12] In patients hospitalized after acute myocardial infarction, hyperglycemia is associated with higher mortality and the development of cardiogenic shock and congestive heart failure.[13] In a population of burn patients, associations between hyperglycemia and infection rates, reduced skin graft take, and increased mortality are demonstrated.[14] Data are only now beginning to emerge connecting hyperglycemia with outcome in the general trauma population, however. This report solidifies this concept, but the mechanism of influence remains debated.

Diabetic patients have similar responses with higher rates of infection, and it appears that elevated glucose may play a role in this. Those with diabetes undergoing coronary artery bypass grafting who had high preoperative blood glucose levels had higher rates of infection including mediastinitis, wound infection, lung infection, and urinary tract infection.[15] Hyperglycemia in this case is associated with a depressed response to invasive infection with a reduction in neutrophil chemotaxis, adherence to vascular endothelium, phagocytosis, and cell-mediated immunity.[2] Controlling glucose lowers the risk of infection, as shown by Zerr et al. They found that maintaining plasma glucose <200 mg/dL led to a significant reduction in infection rate in diabetics undergoing open-heart operations.[16]

Alternatively, elevated glucose may simply be associated with more severe injuries and thus poorer outcome. Hyperglycemia occurs as a result of injury.[4] There is a relationship between severity of injury and magnitude of hyperglycemia.[8] The presence of hyperglycemia can be explained by a number of factors. Catecholamine excess occurs as a component of the stress response, resulting in glycogenolysis and increased hepatic glucose production. Catecholamines are the initial mediators of hyperglycemia via this mechanism. Epinephrine stimulates glucagon release and glycogenolysis and interferes with insulin-mediated glucose uptake.[6] During the early days after injury, insulin levels rise yet patients are hyperglycemic, possibly indicating that tissues are resistant to insulin. Injury is associated with glucose intolerance from peripheral insulin resistance and with decreased pancreatic insulin production.[5,7] Insulin resistance occurs in the setting of stress, although the exact mechanism of this is unknown.[7] Prospective

work by Gore et al. evaluating protein catabolism in groups of burn patients with hyperglycemia revealed severe persistent hyperglycemia despite administration of insulin in patients with severe hyperglycemia (glucose >200). This work suggests that insulin resistance has a role in continued hyperglycemia and protein catabolism.[18]

Glucagon production is stimulated by epinephrine, resulting in hyperglycemia.[17] High, nonsuppressible levels of glucagon appear after injury and are associated with increased gluconeogenesis. Hyperglycemia results from increased glucose production mediated by hyperglucagonemia rather than decreased glucose utilization. In burn injury, for example, glucagon is the primary stimulant of excessive glucose production. This response is exaggerated relative to the normal response. Additionally, worse base deficits, lower GCS scores, and higher ISS all reflect more severe injury and expected higher plasma glucose. Advanced age also is associated with an increased plasma glucose.[19] However, after controlling for such potential confounders, glucose >200 mg/dL is associated with higher infection rates and mortality independent of these factors.

Given that early hyperglycemia is associated with poor outcome, it becomes logical to ask whether aggressive glucose control will improve outcome in these patients. Recent randomized prospective data by Van den Berghe et al. suggest that this is the case. They found that tight glucose control (≤110 mg/dL) led to a significant reduction in overall mortality and decreased complications associated with a prolonged ICU admission such as renal failure, time on the ventilator, and rates of infection.[9] Indeed, initiating therapy with insulin may play a key role in the regulation of the inflammatory response. Studies suggest that both insulin and glucose can affect the systemic inflammatory response. Administration of glucose and insulin enhances the inflammatory response against a noxious stimulus. Hyperinsulinemia indirectly amplifies components of inflammatory and stress responses to infection.[3] Hyperglycemia also may inactivate immunoglobulins and contribute to the risk of infection.[20] Insulin also plays a role in protein metabolism. Subjects given an infusion of stress hormones (hydrocortisone, epinephrine, and glucagons) and somatostatin to suppress insulin demonstrate an accentuated nitrogen loss and skeletal muscle protein breakdown.[21] Insulin therapy through these mechanisms may reduce mortality and complications associated with prolonged ICU stay.[9] Although treatment appears to influence outcome in other data sets, we cannot make inferences about causality or the possible effects of treatment in the current study due to its retrospective nature.

The optimal level at which aggressive glucose control should be considered remains undefined. Three levels of hyperglycemia were examined in the current work. We examined injury characteristics and mortality and related them to a plasma glucose of >110 mg/dL, >150 mg/dL, and >200 mg/dL. The first level of >110 mg/dL was chosen because this is the upper limit of normal in our hospital laboratory. This was also the goal for intensive treatment in the study by Van den Berghe et al.[9] Next, we examined plasma glucose >150 mg/dL. This was the mean glucose in patients with worse outcome in the Van den Berghe study.[9] The final value of >200 mg/dL was chosen because a relationship between hyperglycemia and worse outcome has been demonstrated in another group of ICU patients.[12]

Our data indicate that, of these possible cutoffs, only blood glucose in excess of 200 mg/dL is independently associated with worse clinical outcome. Earlier randomized prospective data would suggest otherwise, and that tight glucose control keeping plasma glucose less than 110 mg/dL reduces mortality and complications associated with critical illness.[9] Further prospective data from Van den Berghe et al. revealed poorer outcomes with respect to mortality, bacteremia, need for blood transfusion, and critical illness polyneuropathy in a group of surgical ICU patients with blood glucose of 110–150 mg/dL. That work suggested that goals for treatment of hyperglycemia should be stricter, aiming to keep blood glucose from 80–110 mg/dL.[22] This data set, while retrospective, indicates that such control may be overly aggressive in the injured population, and further work is needed investigating this relationship in trauma patients.

In conclusion, these data demonstrate that serum glucose >200 mg/dL early after injury is associated with higher rates of infection as well as mortality in the trauma population independent of severity of injury or shock. This is not true of lower levels of hyperglycemia (110 mg/dL or 150 mg/dL). These data support the need for a randomized prospective trial to investigate the need for insulin therapy in this population. However the intensity of glucose control needed must be carefully examined and may not need to be as tight as suggested by some previous investigators.

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