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SYMPOSIUM

Blood Glucose Control in the Trauma Patient

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Abstract

Hyperglycemia can be a significant problem in the trauma population and has been shown to be associated with increased morbidity and mortality. Hyperglycemia in the trauma patient, as in other critically ill patients, is caused by a hypermetabolic response to stress and seems to be an entity of its own rather than simply a marker. Although several early studies in a mixed intensive care unit population indicated that insulin protocols aimed at strict glucose control improved outcome, later studies did not support this and, in fact, encountered increased complications due to hypoglycemia. More recent studies in the trauma population, while supporting the correlation between hyperglycemia and increased mortality, seemed to indicate that protocols aimed at moderate glucose control improved outcome while limiting the incidence of hypoglycemic complications.

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Introduction

The hypermetabolic response to stress that leads to hyperglycemia in critically ill patients is well known, with several studies demonstrating a relationship between admission hyperglycemia and poor outcome. This is more pronounced in patients with trauma than in critically ill patients without trauma.[1] Recent reports in trauma patients have attempted to ascertain whether strict glucose control beginning early in a patient's course can improve outcome.

The etiology of hyperglycemia in trauma patients is multifactorial, but is felt primarily to be the result of activation of the sympathoadrenal system with contributions from the hypothalamus and pituitary gland. In the injured patient, the stress response triggers increased levels of plasma catecholamines and glucocorticoids, which in turn lead to hyperglycemia. Additionally, glucagon has been shown to be a major factor, causing increased levels of hepatic gluconeogenesis and glycogenolysis.[2] Finally, insulin resistance and decreased insulin production have also been implicated.[3] Conventionally, this hyperglycemia was felt to be a compensatory mechanism by the body to cope with stress; however, it is now known to have a host of adverse effects. These include abnormal immune function, an increased infection rate, and other hemodynamic and electromyocardial disturbances.[2]

Multiple reports have shown an association between hyperglycemia and poor outcome in critically ill patients.[4–8] Other studies have also demonstrated a relationship between hyperglycemia and increased complications in trauma patients. In 2003, in a retrospective study, Yendamuri and colleagues[9] evaluated admission glucose as a prognostic indicator in trauma patients. Patients admitted to the

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Abbreviations: (GCS) Glasgow Coma Scale, (ICU) intensive care unit, (TBSA) total body surface area

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trauma intensive care unit (ICU) were divided into three groups based on admission glucose. The study found an increased mortality rate in patients who presented with moderate hyperglycemia (>200 mg/dl) and in those with mild hyperglycemia (>135 mg/dl) compared to patients admitted with normal (135 mg/dl) blood glucose. The authors also found that hospital and ICU lengths of stay were increased in these same groups. In 2004, Laird and associates[3] also evaluated the relationship between early hyperglycemia and mortality in trauma patients using conventional insulin therapy. The trauma ICU patients were separated into three groups based on the highest blood glucose recorded during the first 2 days. Results demonstrated that early hyperglycemia (>200 mg/dl) was an independent predictor of infection and mortality. Moreover, this finding was independent of the severity of injury or associated shock and showed that a glucose level >150 mg/dl was not a predictor of either mortality or infection.

Sung and colleagues[10] prospectively studied admission glucose and outcome in patients admitted to the trauma ICU using 200 mg/dl as the critical blood glucose value. Patients with blood glucose concentrations >200 mg/dl had a significantly increased number of ventilator days and length of stay, as well as increased infection and mortality rates. In 2005, Bochicchio and associates[11] evaluated whether preoperative hyperglycemia was associated with increased morbidity and mortality in trauma patients who underwent immediate surgical intervention. The procedures were primarily orthopedic, neurosurgical, and abdominal, and patients were stratified into two groups based on a blood glucose concentration of 200 mg/dl. The authors reported significantly increased infection and mortality rates in patients with a glucose value greater than 200 mg/dl on admission.

These studies addressed hyperglycemia on admission, or early in the hospital course. Bochicchio and colleagues[12] analyzed blood glucose during the first week in the hospital and its relationship to outcome, again in critically ill trauma patients. Over the first 7 days after admission, patients were assigned to one of three groups: low (0–139 mg/dl), medium (140–219 mg/dl), or high (≥220 mg/dl) blood glucose levels. Furthermore, patients were divided into groups based on the pattern of their glucose measurements as follows: all low, all moderate, all high, improving, worsening, and highly variable. In their study, all high, highly variable, and worsening blood glucose measurements were predictive of increased length of stay and mortality. This study was limited by lack of a standardized insulin protocol to manage glucose.

The same author published a similar study in 2007 that assessed blood glucose in the first 28 days for patients admitted to the trauma ICU.[13] In this study, the all high, all moderate, worsening, and highly variable groups in the first week had a significantly increased incidence of ventilator days, infection, hospital and ICU length of stay, and mortality. However, blood glucose in later weeks had no association with infection and only a weak association with mortality. The authors speculated that early euglycemia had a protective effect, perhaps because of a decreased inflammatory response and less insulin resistance.

In 2007, Scalea and colleagues[14] evaluated the impact of a tight glucose control regimen on outcome in critically injured trauma patients. Their experimental protocol included a 24-month period without strict blood glucose control (preintervention group) compared to a subsequent 24-month period with strict glycemic control (post-intervention group). Similar to the previous studies by Bochicchio and associates, glucose levels were stratified into low (≤150 mg/dl), medium (150–219 mg/dl), and high (≥220 mg/dl). The patients were further stratified into six blood glucose categories: all low, all moderate, all high, improving, worsening, and highly variable. In the postintervention phase, a strict insulin protocol was instituted with a target blood glucose level of 100–150 mg/dl. Mortality was significantly higher in the high, worsening, and highly variable groups during both time periods. More importantly, institution of the strict glucose control protocol nearly doubled the number of patients in the all low and improving groups, which translated to an overall morbidity and survival benefit. Although this study demonstrates a survival benefit associated with early tight glucose control in trauma patients, it is limited by its design: being neither prospective nor randomized. More importantly, the interrupted design leaves open the possibility that differences between the two groups are attributable to global improvements in care, not blood glucose control and intensive insulin therapy.

Blood Glucose Control in Traumatic Brain Injury

Like trauma in general, brain injury is associated with a sympathetic-adrenomedullary response that leads to increased levels of circulating norepinephrine, epinephrine, and dopamine with resultant hyperglycemia. Merguerian and colleagues[15] described an association between hyperglycemia (>270 mg/dl) and increased mortality in head-injured patients. Young and associates[16] looked at 59 consecutive brain-injured patients until

18 days after admission. All had a maximum Glasgow Coma Scale (GCS) of 4–10 in the first 24 hours and attempted to maintain blood glucose to a level <200 mg/dl. They found that patients with the highest peak admission glucose had the worst neurologic outcomes. There was a significant GCS improvement over the 18-day period in patients with a blood glucose ≤200 mg/dl compared to those with a blood glucose level of ≥200 mg/dl.

Secondary brain injury must be taken into account when considering strict glucose control in patients with traumatic brain injury. The injured brain is particularly susceptible to secondary insult as injured cells struggle to survive. In 2003, Jeremitsky and colleagues[17] evaluated 11 potential causes of secondary brain injury, including hyperglycemia (defined as glucose >200 mg/dl). Their results indicate that hyperglycemia, along with acidosis and late hypercapnia, is associated with a longer hospital stay. Moreover, hyperglycemia was associated with increased mortality (along with hypotension and hypothermia). Emphasis must be placed on strict monitoring of blood glucose knowing that hypoglycemia is also a potential cause of secondary brain injury, as neurons are generally insulin-independent cells whose glucose is supply driven.[18] The risks of hypoglycemia may limit the use of strict glucose control with intensive insulin therapy in patients with head injuries to a greater extent than those without and is a cause for institution of close glucose monitoring.

Glucose Control in Burn Injury Patients

The literature evaluating the utility of tight glucose control in patients with burns is sparse. Patients with burn injury require special consideration with respect to blood glucose control. More than any other trauma-related injury, patients with severe burn injury are profoundly hypermetabolic, leading to protein loss, decrease in lean body mass, and hyperglycemia through some of the same mechanisms as in other critically injured trauma patients.[19] This hypermetabolic state results in increased glucose availability for the body's glucose-dependent tissues, but in the end contributes to the same adverse effects as in the general trauma population, most notably immune dysfunction, sepsis, and multiple organ failure.

Gore and colleagues retrospectively studied 58 pediatric burn patients with >60% total body surface area (TBSA) burns. They divided patients into a poor glucose control group (defined as ≥40% of all plasma glucose values >140 mg/dl) and an adequate glucose control group (<40% of all values >140 mg/dl). They found that hyperglycemic patients had a greater incidence of positive blood cultures, a decreased percentage of skin graft "take," and an increased mortality.[20] Holm and associates[21] evaluated the association between early hyperglycemia and clinical outcome in 37 consecutive patients with greater than 25% TBSA burns. They targeted a blood glucose level of 180–200 mg/dl. The blood glucose values were significantly higher in nonsurvivors than in survivors, despite similar burn size.

In 2005, Pham and colleagues[22] evaluated an intensive insulin protocol with target glucose levels of 90–120 mg/dl in children with >30% burns and compared these to historical controls. Intensive insulin therapy was found to be safe and seemed to lower infection rates and improve survival, although the sample size was small. Cochran and colleagues[23] later evaluated an intensive insulin protocol (goal of maintaining glucose ≤120) in 30 patients, 17 of whom had burns and 13 of whom had soft tissue infections. The intensive insulin protocol seemed safe. Although there was a 5% per day rate of hypoglycemic episodes (<60 mg/dl), no patients suffered altered mental status, seizure, or death. Clearly, prospective randomized trials are needed to further confirm these findings.

Summary

In conclusion, hyperglycemia in the trauma population, including those with head injury and burns, is a significant problem. It is a result of the hypermetabolic response to stress. This seems to be more than simply a marker, but an entity of its own with a whole collection of adverse effects. Despite early promise from studies evaluating strict glucose control and their effect on mortality, the issue is not clear cut. Strict glucose control is associated with hypoglycemia, which has its own morbidity, especially in brain-injured patients. Several studies in the general trauma population seem to indicate that insulin protocols aiming for glucose levels in the moderate range (120–150 mg/dl), rather than the very strict range, may provide survival benefit and lower morbidity secondary to hypoglycemia. Although admission hyperglycemia has clearly been shown to have a negative effect in brain-injured and burn populations, evidence supporting strict insulin protocols is lacking. In all three patient populations, additional prospective, randomized, controlled trials are necessary to determine the optimal blood glucose range and the optimal sampling and treatment paradigm.

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