STATE OF THE ART

Hyperglycemia in acutely ill emergency patients — Cause or effect?

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ABSTRACT

Objectives: To clarify the benefits, risks and timing of glucose control and intensive insulin therapy in several groups, specifically the neurologic, cardiac and septic populations of patients, commonly seen in the emergency department.

Methods: Electronic search of MEDLINE (1966–2005; once with PubMed and once with Ovid) and Embase (1980–2005) using the terms insulin and glucose combined with emergency medicine, intensive care, cardiology and emergency department.

Results: There is considerable controversy in the literature surrounding the use of strict glucose control in cardiac, neurologic and septic patients. Much of this literature is non-randomized, and the timing of therapy is poorly investigated.

Conclusions: Hyperglycemia is associated with adverse outcomes in acutely ill neurologic, cardiac and septic patients, but it remains unclear whether this is a causative association. Glucose control and intensive insulin therapy may be useful in some patient subgroups; however, controlled trials of aggressive glycemic control have provided insufficient evidence to justify subjecting patients to the real risks of iatrogenic hypoglycemia. We recommend a cautious approach to the control of glucose levels in acutely ill emergency department patients, with a target glucose of below 8 to 9 mmol/L.

RÉSUMÉ

Key words: glucose; insulin; mortality; stroke; sepsis; myocardial infarction

Objectifs : Clarifier les avantages, les risques et le calendrier d'une thérapie de contrôle de la glycémie et d'une insulinothérapie intensive dans plusieurs groupes, et en particulier les populations de patients en neurologie et en cardiologie et les patients atteints de septicémie que l'on accueille couramment à l'urgence.

Méthodes : Recherche électronique effectuée dans MEDLINE (1966–2005; une fois avec PubMed et une fois avec Ovid) et Embase (1980–2005) en utilisant les termes insulin et glucose combinés avec Emergency Medicine, Intensive Care, Cardiology et Emergency Department.

Résultats : Les publications sur l'utilisation du contrôle rigoureux de la glycémie des patients en cardiologie, neurologie et atteints de septicémie soulèvent énormément de controverse. Beaucoup de ces études ne sont pas randomisées et l'on y étudie mal le calendrier de la thérapie.

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Conclusions : L'hyperglycémie est associée à des résultats défavorables chez les patients gravement malades en neurologie, en cardiologie et atteints de septicémie, mais on ne sait pas trop s'il s'agit d'un lien de cause à effet. Le contrôle de la glycémie et l'insulinothérapie intensive peuvent être utiles dans certains sous-groupes de patients, mais les études contrôlées portant sur un contrôle intensif de la glycémie n'ont pas produit suffisamment de données pour justifier de soumettre les patients aux risques réels que représente l'hypoglycémie iatrogène. Nous recommandons la prudence dans le contrôle de la glycémie chez les patients gravement malades à l'urgence et de viser une glycémie inférieure à 8 à 9 mmol/L.

Introduction

Stress induced hyperglycemia is a common finding in acute illness and is frequently seen in non-diabetic emergency department (ED) patients. Historically, patients with moderate hyperglycemia were treated using a strategy of benign neglect with the belief that higher glucose levels were a protective stress response in acute illness.[1] However, there is evidence that hyperglycemia, even at moderate levels and in non-diabetics, is associated with worse outcomes and increased mortality in several subgroups of ED patients.[2–9] In addition, there is equivocal evidence that strict glucose control offers significant benefit for these patients.[10–15] In view of the high volume of acutely ill patients seen in EDs, the often prolonged ED lengths of stay for critically ill patients, and evolving evidence regarding the value of early aggressive ED management, it is important for the emergency medicine community to be aware of the evidence and controversies surrounding the treatment of stress hyperglycemia, and to consider developing treatment protocols that are appropriate to our unique practice environment.

Neurological injury, acute myocardial ischemia and infection are 3 common reasons for ED admission. Many of the patients who ultimately die as a result of these conditions, do so from "downstream" complications and from multiple organ dysfunction syndrome (MODS).[16,17] MODS is characterized by the progressive decline in the function of 2 or more organ systems in critically ill patients, and is believed to be induced by inappropriate activation of the neuroendocrine system with the creation of a pro-inflammatory, procoagulant state.

During the ED phase of care, factors such as poor tissue perfusion, hemorrhage, blood transfusions, nosocomial infection, sepsis or potentially inappropriate forms of mechanical ventilation may aggravate ongoing tissue insult and result in the persistence of the abnormal metabolic response. This ongoing stress response creates a vicious cycle that may lead to further tissue injury, MODS and death. However, it may be possible to attenuate the subsequent neuroendocrine abnormalities responsible for MODS.

Stress hyperglycemia may be both a modifiable risk factor for MODS and for the development of abnormalities of cellular respiration, coagulation, inflammation and immune function. The question is this: By avoiding hyperglycemia, can we reduce downstream complications in our patients after they leave the ED? In this review, we will describe the causes of hyperglycemia in acutely ill patients and summarize the relevant observational and randomized trials of glucose control and insulin therapy in 3 specific ED patient populations: neurologic injury, acute myocardial infarction and sepsis.

Why does hyperglycemia occur in acute illness?

Stress hyperglycemia results from the excessive release of counterregulatory hormones and cytokines, such as glucagon, epinephrine, cortisol, growth hormone and insulin-like growth factor, and from the overproduction of inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), interleukin-1 and interleukin-6.[18]

Inflammatory mediators initiate the metabolic response to injury and can precipitate MODS. During acute illness there is an increase in the systemic inflammatory response that is characterized by increased production of pro-inflammatory cytokines, such as interleukin-1, interleukin-6, TNF-α and macrophage inhibitory factor,[19] and a decrease in the anti-inflammatory cytokines, interleukin-2, interleukin-4 and interleukin-10.[20,21] Acute hyperglycemia further upregulates the production of several of these inflammatory cytokines.[22]

High levels of extracellular glucose inhibit G6PD (glucose-6-phosphate dehydrogenase) and impair oxygen radical production in activated neutrophils.[23] In vivo, hyperglycemia could therefore impair microbial killing by neutrophils in a dose-dependent fashion. Neutrophil dysfunction[24] and impaired intracellular bactericidal activity[25] have been demonstrated when glucose concentrations are

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high. In an animal trauma model,[26] maintenance of normoglycemia enhanced innate immunity by preserving phagocytosis and the monocyte oxidative burst function.[27] These findings suggest that acute glucose control may lower the risk of infection that is so prevalent in our sickest patients.

Evidence from clinical studies

Stress-induced hyperglycemia is associated with worse clinical outcomes in several ED populations — notably neurologic, cardiac and septic patients.[2–15,28,29] In these groups, investigators have attempted to determine whether hyperglycemia is simply a marker of critical illness or a modifiable independent risk factor for adverse outcome. Results of these investigations have been ambiguous.

Neurological injury

A prospective study of patients with severe traumatic brain injury demonstrated that admission glucose levels >11.1 mmol/L were associated with increased mortality and poor neurologic outcomes.[2] In another study, admission or peak plasma glucose was inversely related to the Glasgow Coma Scale score and predicted both early and late mortality.[3] Similarly, elevated blood glucose on admission was associated with higher plasma levels of epinephrine and norepinephrine, and glucose levels >9.5 mmol/L mortality were linked to increased mortality.[4]

In a prospective cohort study of 750 non-diabetic patients with acute stroke, hyperglycemia independently predicted long-term morbidity and mortality.[5] A systematic review[6] of observational studies on hyperglycemia and stroke outcome also showed a higher risk of 30-day mortality when blood glucose levels were above 6–8 mmol/L. The relative risks were 3.07 (95% confidence interval [CI], 2.50–3.79) and 1.30 (95% CI, 0.49 to 3.43) in non-diabetic and diabetic patients, respectively. The National Institute of Neurological Disorders and Stroke Trial showed that hyperglycemia is an independent risk for hemorrhagic transformation after tPA administration.[7]

Acute coronary syndromes

Several studies have found that hyperglycemia is linked to poorer outcomes in patients with acute coronary syndromes. In one study of 1664 patients with acute myocardial infarction (AMI), Wahab and colleagues determined that admission blood glucose levels >11 mg/dL were associated with higher in-hospital and 1-year mortality — irrespective of any history of diabetes.[8] In a similar study of AMI patients, Norhammer and coworkers showed that elevated serum glucose levels were a risk factor for reinfarction, congestive heart failure and future cardiovascular events.[9]

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction trial[10–12] studied acute and chronic glycemic control in AMI patients who also had diabetes or hyperglycemia at the time of admission. Average follow-up was 3.4 years, during which a significant mortality benefit was realized in the insulin-treated group.

Subsequent to this analysis, the largest trial of glucose–insulin–potassium therapy in AMI patients was published.[10] The CREATE-ECLA trial enrolled 20 201 patients with ST-elevation myocardial infarction from 470 centres and found no significant effect on mortality, cardiac arrest or cardiogenic shock. This lack of effect was consistent in prespecified subgroups, including those with and without diabetes and those receiving and not receiving reperfusion therapy. The results of this large multicentre trial cast doubts on the outcomes of previous smaller trials (presented above) and on meta-analytic results derived from them, further increasing the uncertainty surrounding the benefit of insulin and glucose therapy in critically ill patients.

Sepsis and septic shock

In a 2001 study of critically ill intensive care unit (ICU) patients, Van den Berghe and associates demonstrated that aggressive insulin therapy to maintain blood glucose between 4.4 and 6.1 mmol/L reduced mortality from 8.0% with conventional treatment to 4.6%, a relative reduction of 42%.[13] Mortality reduction in the intensive insulin treatment group was attributed to lower rates of organ failure and bacteremia.

Although these results were promising, prospective observational cohort studies[28,29] and randomized trials[13,14] have provided conflicting results. Van den Berghe and associates have recently completed a single centre trial of strict glucose control in critically ill medical patients.[14] In this trial, an intention-to-treat analysis showed that in-hospital mortality was similar in patients receiving conventional treatment versus those receiving intensive insulin therapy (39.9% v. 37.2%; $p = 0.3$); however, after adjustment for baseline imbalances, the analysis showed a slight mortality reduction ($p = 0.05$) with strict glucose control. In the a priori subgroup of patients who required 3 days or more of ICU treatment, intensive insulin therapy reduced mortality from 52.5% to 43.0% ($p = 0.009$). Unfortunately, this benefit was offset by higher mortality in patients who spent <3 days in ICU, suggesting that it may have been a spurious finding.

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In a multi-centre randomized controlled trial comparing strict glucose control with conventional therapy in patients with severe sepsis and septic shock, the German Competence Network Sepsis trial (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP]) found no difference in 28 day (21.9% v. 21.6%; $p = 1.0$) and 90-day mortality (32.8% v. 29.5%; $p = 0.43$) but an increased risk of hypoglycemia (12.1% v. 2.1%) in the strict glucose control group versus conventional control, respectively.[15] Following a safety analysis, and in the absence of a mortality benefit, the trial was discontinued after enrolling 488 patients.

Timing and risks of aggressive glucose control in the emergency department

Although there is observational evidence that hyperglycemia is associated with adverse outcomes in acutely ill cardiac, neurologic and septic populations, the evidence from controlled trials is contradictory. Furthermore, if there is an optimal level of blood glucose, this level remains unclear. Although frank hyperglycemia (>10 mmol/L) appears to be deleterious in all of these populations, it is less obvious that strict euglycemia is of benefit. It is also unclear whether glucose control during the ED phase of care confers significant benefit.

Although there have been no ED trials of strict glucose management, data from other populations suggest that aggressive glucose control causes significant rates of hypoglycemia. Mackenzie and colleagues recently reported that when intensive glycemic control was managed by the bedside nurse, average morning glucose concentration was 7.0 ± 2.4 mmol/L, but 42% of patients suffered hypoglycemic episodes, defined as a serum glucose <2.2 mmol/L. Moreover, despite attempts to control blood glucoses within the target range of 4.4–6.1 mmol/L recommended by Van den Berghe and associates, patients spent 40% of each day with blood glucose concentrations >6.1 mmol/L.[30]

Overly aggressive glucose control may also pose more subtle risks to patients. Acute hypoglycemia can trigger counter-regulatory production of epinephrine and cortisol, with potentially deleterious effects on the immune and cardiovascular systems.[31] There is also evidence that acute hypoglycemia can cause prolonged alteration in subjects' ability to produce and regulate thyroid stimulating hormone, as well as adversely affecting the production of thyroid hormone itself.[32] Alterations in the regulation of these key hormones may represent under-appreciated adverse consequences of transient hypoglycemia and overly aggressive glucose control.

Many of the pathophysiologic processes by which hyperglycemia may exert cellular damage occur over a period of hours,[22,23,33] and it is reasonable to believe that strict glucose control within the first several hours of ED admission may be more beneficial than later treatment in modulating hyperglycemia-mediated inflammatory and coagulation abnormalities. However, there are no published human data that demonstrate a critical "cut-off" time and it is impossible to provide evidence-based ED "time to treatment" guidelines.

Despite the conflicting evidence surrounding strict glucose control in acutely ill patients, emergency physicians are faced with a decision — to treat hyperglycemia or not? One option is to wait for more conclusive evidence and continue to allow hyperglycemia. This would minimize the potential risks of iatrogenic hypoglycemia and it is the most easily implemented approach in today's busy EDs. Another option is to aggressively treat hyperglycemia in the hope of providing benefit. This approach is "ahead of the evidence," and has the potential to cause harm. Perhaps the most reasonable approach is to attempt to maintain glucose levels below 8–9 mmol/L in the ED. This is consistent with the results of most observational trials, as well as with the most recent controlled trials in critically ill intensive care patients. This "middle path" will present less risk of iatrogenic hypoglycemia than more aggressive control targets.

Conclusions

Hyperglycemia is associated with adverse outcomes in acutely ill neurologic, cardiac and septic patients, but it remains unclear whether this is a causative association. Glucose control and intensive insulin therapy may be useful in some patient subgroups; however, controlled trials of aggressive glycemic control have provided insufficient evidence to justify subjecting patients to the real risks of iatrogenic hypoglycemia. We recommend a cautious approach to the control of glucose levels in acutely ill ED patients, with a target glucose of <8–9 mmol/L.

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