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Intensive Insulin Therapy for Critically Ill Patients

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OBJECTIVE: To evaluate the clinical outcomes of glycemic control of intensive insulin therapy and recommend its place in the management of critically ill patients.

DATA SOURCES: Searches of MEDLINE (1966–March 2004) and Cochrane Library, as well as an extensive manual review of abstracts were performed using the key search terms hyperglycemia, insulin, intensive care unit, critically ill, outcomes, and guidelines and algorithms.

STUDY SELECTION AND DATA EXTRACTION: All articles identified from the data sources were evaluated and deemed relevant if they included and assessed clinical outcomes.

DATA SYNTHESIS: Mortality among patients with prolonged critical illness exceeds 20%, and most deaths are attributable to sepsis and multisystem organ failure. Hyperglycemia is common in critically ill patients, even in those with no history of diabetes mellitus. Maintaining normoglycemia with insulin in critically ill patients has been shown to improve neurologic, cardiovascular, and infectious outcomes. Most importantly, morbidity and mortality are reduced with aggressive insulin therapy. This information can be implemented into protocols to maintain strict control of glucose.

CONCLUSIONS: Use of insulin protocols in critically ill patients improves blood glucose control and reduces morbidity and mortality in critically ill populations. Glucose levels in critically ill patients should be controlled through implementation of insulin protocols with the goal to achieve normoglycemia, regardless of a history of diabetes. Frequent monitoring is imperative to avoid hypoglycemia.

KEY WORDS: hyperglycemia, insulin infusions, intensive care unit.

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There is a pressing need to improve patient outcomes in intensive care units (ICUs). ICUs comprise 3–5% of hospital beds; however, a disproportionate amount of hospital resources (20–30%) are consumed there.¹ Pharmaceuticals contribute substantially to the total costs, particularly as expensive new biotechnology drugs are approved for use.² The search continues for optimal low-cost therapies. Until recently, no single drug has significantly impacted survival above that afforded by aggressive hemodynamic support, ventilation, and appropriate antibiotics. Although one recently approved agent, drotrecogin alfa, may reduce

mortality in severe sepsis, the clinical benefit is associated with considerable acquisition costs.³ Overall, ICU mortality remains >20% despite our best efforts.⁴

Hyperglycemia is common in critically ill patients with and without diabetes.⁵ Elevated blood glucose (BG) concentrations are associated with increased morbidity and mortality after burns,⁶ surgery,⁷ stroke, myocardial infarction (MI), and head trauma.^{8–13} Hyperglycemia is believed to increase infarct size in both MI and stroke.^{9,11,12} Admission BG concentration is an independent predictor for mortality in women undergoing coronary artery bypass surgery.¹⁴ In addition, there is evidence that hyperglycemia increases the risk of nosocomial infections and may be a causal factor.¹⁵

Author information provided at the end of the text.

While the aforementioned outcomes data describe association, not cause, aggressive treatment of hyperglycemia positively impacts outcomes in critically ill patients. The technology to deliver tight glycemic control in the critical care setting is widely available; implementing a safe and effective program is necessary. The purpose of this paper is to review the pathophysiology and clinical outcomes of hyperglycemia in various populations of critically ill patients and discuss the impact of strict glucose control on clinical outcomes, as well as to recommend the role of insulin protocols in the ICU.

Data Sources

Searches of MEDLINE (1966–March 2004) and Cochrane Library, as well as an extensive manual review of abstracts were performed using the key search terms hyperglycemia, insulin, intensive care unit, critically ill, outcomes, and guidelines and algorithms. All articles identified from the data sources were evaluated and deemed relevant if they included and assessed clinical outcomes.

Pathophysiology of Hyperglycemia in Critical Illness

The concept of stress-induced hyperglycemia, typically defined as BG concentrations >200 mg/dL, has been described for almost 150 years. Hyperglycemia in critical illness is associated with infection, medications, and other conditions.

Stress associated with acute illness increases the concentration of counterregulatory hormones and cytokines (Table 1). Epinephrine mediates stress hyperglycemia by altering postreceptor signaling, resulting in insulin resistance. In addition, epinephrine increases gluconeogenesis and directly suppresses insulin secretion. Glucagon increases gluconeogenesis and hepatic glycogenolysis. Studies have demonstrated that hyperglycemia after trauma is primarily caused by increased hepatic glucose production and insulin resistance rather than impaired glucose clearance.^{16–20} In early studies, infusing epinephrine, glucagon, and cortisol resulted in a 60–80% increase in BG, as well as a 100% increase in gluconeogenesis despite hyperinsulinemia. The combination of hormone infusions resulted in a threefold greater increase in BG compared with responses to individual hormones.^{21,22} Similar results are reported in animal models, where net hepatic glucose production was significantly increased but peripheral glucose clearance was unchanged despite a threefold increase in insulin concentration. Gluconeogenesis accounted for the vast majority of hyperglycemia occurrences.²³ In burn injury, glucagon is the primary stimulant of excessive glucose production.²⁴ Glucose may remain elevated for weeks, resulting in hyperglycemia.²⁵

Severely ill patients have increased production of various cytokines, particularly tumor necrosis factor- α (TNF- α), interleukin (IL)-1, and IL-6, which leads to stress-induced hyperglycemia. Surgery and critical illness promote

the release of these inflammatory mediators from mononuclear cells, contributing to insulin resistance and hyperglycemia. TNF- α causes insulin resistance in both liver and skeletal muscle via modification of signaling properties of insulin receptor substrates.²⁶

Medications frequently administered in the ICU or operating room may cause hyperglycemia. Exogenously administered epinephrine and norepinephrine exacerbate hyperglycemia via their α -adrenergic effects.^{27,28} Other therapies that can result in hyperglycemia include corticosteroids, other sympathomimetics, and immunosuppressants (eg, cyclosporine, tacrolimus).²⁹

The influence of corticosteroids on glucose can be observed in the transplant population. Hepatic glucose production is increased in both steroid-treated insulin-dependent diabetes mellitus (IDDM) patients who have received a renal transplant and IDDM patients without nephropathy compared with nondiabetic renal graft recipients and healthy controls ($p < 0.01$).³⁰ Insulin-stimulated glucose disposal was reduced in patients with IDDM regardless of whether they had undergone renal transplantation and in nondiabetic patients who received transplants versus healthy controls ($p < 0.05$). This reduction was mainly due to impairment in nonoxidative glucose metabolism (ie, glycogen synthesis). IDDM patients without nephropathy show both hepatic and peripheral insulin resistance; further increases in insulin resistance are caused by corticosteroids and can be corrected by increasing insulin doses. Interestingly, nondiabetic, steroid-treated renal graft recipients show insulin resistance comparable to that of IDDM patients.

Hyperglycemia can result from parenteral and enteral nutrition and from dextrose solutions used for drug or fluid administration. Nondiabetic hospitalized patients who receive dextrose solutions at rates >4 g/kg/min (eg, total par-

Table 1. Counterregulatory Hormones Involved in the Hyperglycemic Response to Critical Illness

Hormone	Mechanism
Epinephrine	skeletal muscle insulin resistance via altered postreceptor signaling increased gluconeogenesis increased skeletal muscle and hepatic glycogenolysis increased lipolysis; increased free fatty acids direct suppression of insulin secretion
Glucagon	increased gluconeogenesis increased hepatic glycogenolysis
Glucocorticoids	skeletal muscle insulin resistance increased lipolysis increased gluconeogenesis
Growth hormone	skeletal muscle insulin resistance increased lipolysis increased gluconeogenesis
Norepinephrine	increased lipolysis increased gluconeogenesis; marked hyperglycemia only at high concentrations
Tumor necrosis factor	skeletal muscle insulin resistance via altered postreceptor signaling hepatic insulin resistance

enteral nutrition solutions) have a 50% chance of developing hyperglycemia.³¹ Dialysis solutions are a hidden source of glucose; systemic absorption of 80 g/day has been reported.^{19,32,33} The hyperglycemic response to surgery can also be altered by the anesthetic technique. For example, epidural analgesia with local anesthetic established before surgery inhibits the increase in BG concentration during abdominal surgery compared with inhaled anesthesia.^{34,35} Furthermore, intravenous anesthesia with large or moderate doses of opioids attenuates the hyperglycemic response to surgery.^{36,37} In contrast, isoflurane anesthesia results in both impaired glucose clearance and increased glucose production.³⁸ Hypothermia induced by cardioplegia solutions during coronary artery bypass surgery also inhibits insulin responses to hyperglycemia.³⁹

Surgical animal models reveal that insulin resistance is the key mechanism for releasing glucose into the circulation, thereby increasing intravascular volume.¹⁷ Surgery produces insulin resistance in both skeletal muscle and adipose tissue.^{18,19} Insulin resistance develops in proportion to the duration of surgery and may persist for weeks.¹⁸ Studies of thermal-induced trauma demonstrate that serum insulin levels remain significantly high 3 weeks after injury, consistent with the presence of an insulin-resistant state, resulting in increased glucose concentrations.¹⁶ In contrast, studies of septic and thermal injury-induced insulin resistance differ in that peripheral glucose uptake in sepsis is refractory to insulin stimulation, whereas nonseptic burn injury is not.⁴⁰ Hyperglycemia associated with insulin resistance has also been demonstrated in critically ill patients with no history of diabetes.⁴¹

Physiologic Beneficial Effects of Insulin

In addition to its hypoglycemic action, insulin promotes muscle protein synthesis⁴² and inhibits lipolysis.⁴³ Insulin also produces a variety of antiinflammatory responses. Intensive insulin therapy significantly reduces C-reactive protein levels ($p < 0.02$) and increases mannose-binding lectin ($p < 0.02$) from baseline in patients requiring ICU care for >5 days.⁴⁴ It suppresses nuclear factor κ - β expression and free radical generation, and enhances endothelial nitric oxide production.⁴⁵ Although glucose has proinflammatory properties that result in production of TNF- α and other cytokines, insulin may have a cardioprotective effect as it reduces thromboxane A₂ production and plasma plasminogen activator inhibitor-1 activity, thereby decreasing platelet aggregation and increasing fibrinolysis.⁴⁶⁻⁴⁸ TNF causes endothelial dysfunction and apoptosis, triggers procoagulant activity and fibrin deposition, and enhances nitric oxide synthesis in a variety of cells. Administration of exogenous insulin suppresses TNF production in a dose-dependent manner.⁴⁹ These effects may explain the increased mortality and incidence of cardiogenic shock in patients who have experienced acute MI and developed stress hyperglycemia, even though they are not diabetic.⁹ Insulin has been shown to stimulate the activity of enzymes essential in the formation of prostaglandin E₁ and I₂

precursors, which are potent vasodilators and inhibitors of platelet aggregation.⁵⁰ These precursors suppress the synthesis and production of TNF and IL-2 by human T cells.

Outcomes

NEUROLOGY

Changes in BG concentrations in critically ill patients have various effects on neurologic function. Hyperglycemia has been reported to augment ischemic brain injury and worsen outcomes in many animal and human studies.^{10,11,13,51} One study evaluated 267 nondiabetic patients with nonpenetrating head injuries.⁵² A significant relationship was found between postoperative BG concentrations, pupillary reaction, and maximal intracranial pressure during the first 24 hours. Among patients with more severe head injury, BG levels >200 mg/dL were associated with worse outcomes. The postoperative BG concentration was an independent predictor of outcomes at 6 months. Elevated brain glucose concentrations resulting from hyperglycemia, in conjunction with an ischemia-induced shift to anaerobic glycolysis, led to more severe elevations of brain lactic acid concentrations and more profound acidosis.

There are conflicting results concerning the effects of hyperglycemia on focal brain ischemia^{53,54}; however, when restricting analysis to reversible ischemia models, there is a consistent association between higher BG concentrations and larger infarct size.⁵⁵⁻⁵⁷ Possible mechanisms of this effect include increased brain tissue acidosis, which may contribute to progressing infarction, increased blood-brain barrier permeability, and increased hemorrhagic transformation of the infarct.⁵⁸⁻⁶⁰ Negative neurologic outcomes associated with hyperglycemia include the evolution of hypoperfused tissue, greater infarct size, and worse functional outcome in patients with acute ischemic stroke,^{10,61} longer hospital stays, and higher hospital charges.^{13,61}

Hyperglycemia is also independently associated with increased mortality at 30 days, one year, and 6 years after stroke.¹³ Parsons et al.¹⁰ prospectively studied 63 acute stroke patients. Acute and subacute magnetic resonance spectroscopy was performed to assess the relationship between acute BG and lactate production in the ischemic region. BG concentrations >130 mg/dL were present in 40% of admissions of the patients evaluated and remained high throughout the patient's hospital stay (mean 206 mg/dL). Longer hospital stays (7 vs 6 days; $p = 0.01$) and higher inpatient charges (\$6600 vs \$5200; $p < 0.01$) were noted in the hyperglycemia group.

Hypoglycemia causes alterations in brain electrical activity ranging from cortical slowing, burst suppression with associated seizure activity, to isoelectricity.⁶² Hypoglycemia evokes a centrally mediated stress counterregulatory response characterized by increased serum concentrations of epinephrine and norepinephrine. This response is seen even with minor changes in BG levels. Severe hypoglycemia with associated electroencephalographic flattening is accompanied by large increases in cerebral blood

flow; however, changes in cerebral blood flow are more variable in less severe hypoglycemia. Decreased cerebral glucose uptake is seen during various degrees of hypoglycemia. Finally, hypoglycemia causes metabolic disturbances involving neuronal protein synthesis, amino acid metabolism, and pH homeostasis, along with neuronal necrosis and permanent neurologic damage in the most severe form of hypoglycemia. Due to the poor outcomes associated with glucose fluctuations, a microdialysis probe for monitoring glucose and lactate concentrations in the cerebral cortex has been studied in the neurosurgical population.⁶³

There is some evidence that administering insulin during cerebral ischemia is beneficial; however, the detrimental effects of hypoglycemia such as brain damage must be considered. The safety of glucose-insulin-potassium (GIK) infusion was evaluated in 25 patients within 24 hours of ictus with hyperglycemia (127–309 mg/dL). Only one patient required treatment for symptomatic hypoglycemia.⁶⁴ When hyperglycemia is present before an ischemic or anoxic event, neurologic damage is worse.⁶² These findings are more consistent in cases of global versus focal ischemia. Since hyperglycemia is clearly associated with poor neurologic outcome during cerebral ischemia, perhaps glucose-containing solutions should be withheld. However, as of May 24, 2004, there are no published studies evaluating the effects of elevated BG values on neurologic morbidity and mortality, and the role of insulin is not fully known.

CARDIOVASCULAR

Hyperglycemia has several effects on the myocardium resulting in oxidative stress and increased superoxide production in the mitochondria. Oxygen free radical formation may scavenge endogenous nitric oxide, increasing electrical instability of the heart and peripheral vascular tone. High sympathetic activity during an MI leads to increased production of free fatty acids, which increases myocardial oxygen requirements and decreases contractility.^{65,66} It is believed that patients with inadequate insulin response to hyperglycemia have impaired glucose oxidation in both ischemic and nonischemic areas of the myocardium, which increases oxygen-consuming fatty acid metabolism, thus increasing the risk of ischemia, decreased myocardial contraction, and arrhythmias.⁶⁷ The administration of glucose GIK infusions suppresses free fatty acid oxidation in MI patients, providing support for this theory.⁶⁸ The main effect of GIK therapy is believed to be administration of glucose to the ischemic myocardium.⁶⁹ Insulin itself may have a cardioprotective effect, as it reduces thromboxane A₂ production and plasma plasminogen activator inhibitor-1 activity, thereby decreasing platelet aggregation and increasing fibrinolysis.⁴⁶⁻⁴⁸ A recent study in post-MI patients receiving standard therapy including thrombolytics and GIK infusions corroborates the evidence that insulin has anti-inflammatory and profibrinolytic effects.⁷⁰ Patients receiving GIK therapy had significantly lower C-reactive protein, serum amyloid A, and plasminogen activator in-

hibitor-1 levels. Insulin may also be a coronary vasodilator through the nitric oxide pathway in healthy individuals, as well as in patients with type 1 diabetes, obesity, and coronary artery disease.⁷¹

Reports of using GIK to support the failing heart after MI date back to the 1960s.^{72,73} Despite that long history, results from trials employing GIK in MI and cardiac surgery are often inconclusive due to small sample sizes and differences of study design and GIK infusions.⁷⁴ The dose shown to suppress free fatty acid uptake in the myocardium is 30 g of glucose, 50 units of insulin, and 80 mmol of potassium chloride per liter at 1.5 mL/kg/h.⁶⁸ A meta-analysis of randomized clinical trials involving GIK infusions in MI indicated a significant reduction in inpatient mortality for patients receiving GIK compared with conventional treatment.⁴ Major criticisms in the majority of trials include defective study design and concomitant therapies with predated thrombolytic and β -blocker therapies.⁷⁴

Contemporary studies continue to show conflicting results with GIK infusions. In 1998, a study including 407 MI patients randomized to GIK or control showed a 66% reduction of in-hospital mortality when GIK was added to reperfusion therapy.^{75,76} The absolute mortality risk decreased from 15.2% in the control group to 5.2% in the GIK group. In 2003, GIK was studied in 940 MI patients receiving primary angioplasty.⁶⁹ The infusion was titrated to maintain a BG level of 127–200 mg/dL for 8–12 hours. Thirty-day mortality revealed a nonsignificant reduction between GIK therapy and placebo (4.8% vs 5.8%, respectively). The only significant decrease in mortality occurred in patients without signs of heart failure (Killip class 1), from 4.2% in the control group to 1.2% in the GIK group. In the control group, 67% of deaths were due to development of heart failure.⁷⁶ There was no significant difference in mortality in patients with heart failure (Killip class ≥ 2) receiving GIK.

The benefit of GIK therapy may be attributed to an improvement in ventricular function. A study of 37 MI patients with primary angioplasty randomized to receive GIK or placebo revealed that GIK significantly increased left-ventricular ejection fraction from mean \pm SD, 39% \pm 12% at baseline to 51% \pm 13% at 3 months, while the placebo group increase was not significant (from 44% \pm 13% to 49% \pm 14%).⁷⁷ Larger studies are needed to confirm these findings.

The benefit of glucose and insulin therapy has been studied in diabetic patients experiencing an MI. In the DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) trial, 620 diabetic patients were randomized to receive insulin and glucose infusion until the BG level was 128–199 mg/dL. Subcutaneous injections of insulin were continued for 3 months.⁷⁸ Results at one year showed a statistically significant reduction in mortality from 26.1% in the conventional treatment group to 18.6% in the insulin group ($p = 0.027$). The benefit was sustained for 3.5 years, with an 11% absolute risk reduction in mortality.⁷⁹ The most pronounced reduction in mortality was in diabetic patients with a low cardiac risk profile who had received no previous insulin administration.

GIK therapy remains controversial and not widely adopted due to conflicting reports.⁸⁰ One explanation for the inconsistent findings may be the varying target BG concentrations in the clinical trials, from 120 to 200 mg/dL. Recent studies raise the question of the most appropriate BG concentration in patients after an MI has occurred. A meta-analysis including >6000 patients revealed that stress hyperglycemia occurs in 71% of nondiabetic and 84% of diabetic patients experiencing an MI.⁹ The nondiabetic patients with BG concentrations ≥ 110 mg/dL had a 3.9-fold higher risk of death than patients with lower BG concentrations. Nondiabetic patients with admission BG concentrations >145–181 mg/dL were at higher risk of congestive heart failure or cardiogenic shock. A recent study reconfirms that nonsurviving cardiac medical patients have significantly higher initial, mean, and maximum BG concentrations compared with survivors in the ICU.⁸¹ This trial supports further investigation into intensive glucose control with GIK therapy targeting BG concentrations <110 mg/dL to improve outcomes in patients with MI.

POSTOPERATIVE INFECTIONS

Increasing evidence suggests that hyperglycemia impedes normal physiologic responses to infection.^{82–85} In vitro and in vivo studies report substantial impairment in immune function and wound healing associated with hyperglycemia.^{86–93} Mechanisms include complement inactivation,^{87,89} irregularities in granulocyte adherence,^{92,93} impaired phagocytosis,^{91,94} delayed chemotaxis and oxidative burst,^{95,96} and decreased bactericidal activity.^{94,97} Collagen deposition is impaired, possibly due to decreased fibroblast proliferation.⁸⁶ The degree of leukocyte abnormalities varies directly with BG concentrations^{98–100}; impaired phagocytic function occurs with BG levels as low as 200 mg/dL.¹⁵

Although numerous in vitro studies of the influence of hyperglycemia on immune function have been reported, few were conducted in a clinical setting.^{101–103} A prospective cohort study assessed the correlation between perioperative glucose control and the subsequent risk of infectious complications in 411 diabetic patients undergoing coronary artery surgery.¹⁰¹ Hyperglycemia was an independent predictor of short-term infectious complications. After adjusting for confounding variables, patients with mean BG concentrations >200 mg/dL following surgery had higher rates of leg and chest wound infections, pneumonia, and urinary tract infections.

Zerr et al.¹⁰² evaluated the impact of an insulin protocol targeted at maintaining BG concentrations <200 mg/dL. A retrospective chart review was conducted including 9000 postoperative cardiac surgery patients, 18% of whom were diabetic. Elevated BG concentrations on the first and second postoperative days were associated with a higher incidence of deep sternal wound infections. BG concentrations >200 mg/dL at 48 hours were significantly associated with increased risk of deep wound infection ($p = 0.002$). The rate of deep sternal wound infections in diabetic patients decreased from 2.8% prior to implementation of the in-

sulin protocol to 0.74% the third year after implementation ($p = 0.14$). In nondiabetic patients, the rate decreased from 0.4% to 0.31%.

Similar results have been reported. In a prospective study of 2500 diabetic patients who underwent cardiac surgery, the impact of sliding scale insulin compared with continuous insulin infusions titrated to maintain BG concentrations at 150–200 mg/dL was evaluated.¹⁰³ A significant reduction in the incidence of deep sternal wound infections (0.8% vs 2%; $p = 0.01$) was observed in the continuous-infusion group. Hyperglycemia in the immediate postoperative period was an independent predictor of infections.

CRITICALLY ILL PATIENT POPULATION

van den Berghe et al.¹⁰⁴ investigated the value of insulin therapy directed at maintaining strict glucose control in 1500 patients admitted to the ICU. This study included both diabetic and nondiabetic patients, and the majority (63%) had undergone cardiac bypass surgery. Patients were randomized to receive intensive insulin therapy (continuous infusions to maintain BG concentrations at 80–110 mg/dL) or conventional insulin therapy. Conventionally treated patients received continuous insulin infusions only if their BG concentration exceeded 215 mg/dL and the glucose target level was 180–200 mg/dL. Interim analysis at one year demonstrated a significant reduction in ICU mortality (4.6 vs 8.0%; $p = 0.036$) with continuous infusion; the study was then terminated prematurely. The mortality benefit was especially evident among patients requiring intensive care for >5 days (10.6 vs 20.2%; $p = 0.005$) and was achieved primarily through a reduced incidence of multisystem organ failure with a proven septic focus.

These findings were significant regardless of whether patients had a history of diabetes. Overall, in-hospital mortality was lower in the intensive insulin group. Intensive insulin treatment also reduced the risk of bloodstream infections and sepsis by 46% ($p = 0.003$), renal dysfunction, and the need for red blood cell transfusions.

Similar results were reported in a retrospective review of >1800 critically ill medical and surgical patients (22.4% diabetics).⁸¹ The lowest hospital mortality (9.6%) occurred in patients with mean glucose concentrations between 80 and 99 mg/dL. Mortality increased progressively with increases in mean glucose concentrations, and the highest mortality (42.5%) was noted in patients with mean BG concentrations >300 mg/dL ($p < 0.001$). Importantly, these observations were consistent among all patient subgroups; there was no difference in mortality based on the presence or absence of diabetes.

Clinical studies demonstrate that GIK solutions improve outcomes in thermal injury and sepsis. Bronsveld et al.¹⁰⁵ studied the effects of GIK (1 g/kg of glucose 50%; insulin 1.5 units/kg; potassium chloride 10 mEq) in 15 patients with septic shock who, despite volume replacement and vasopressors, had persistent hypotension and lactic acidosis. GIK infusion increased cardiac index, but it was only significant for patients with a lower cardiac index at base-

line ($p < 0.01$). Mean arterial and pulmonary artery pressures did not change. The observation period was only 30 minutes after GIK infusion. Another study evaluated the effect of GIK as adjunctive treatment in 17 early burn patients.¹⁰⁶ GIK infusions for 15 minutes (100 mL of glucose 50%; insulin 75 units; potassium chloride 10 mEq) resulted in significant increases in cardiac index ($p < 0.01$), stroke volume ($p < 0.05$), left-ventricular stroke work ($p < 0.05$), and decreased systemic vascular resistance ($p < 0.05$) compared with baseline values. The urine volume also increased after GIK therapy compared with the baseline volume ($p < 0.01$). Although these investigators administered insulin, they did not use a goal-directed insulin infusion algorithm to achieve preset BG concentrations.

It is uncertain whether euglycemia or the protective effects of insulin confer the reported morbidity and mortality benefits. Two recent studies provide insight into this controversy. One study attempted to define the factors that determine insulin requirements and establish whether reductions in mortality and morbidity were a result of insulin infusion or prevention of hyperglycemia.¹⁰⁷ In this study, insulin requirements were highest and most variable during the first 6 hours of intensive care. Multivariate logistic regression analysis indicated that lowered BG concentrations rather than insulin dose corresponded to decreased mortality ($p < 0.0001$), critical illness polyneuropathy ($p < 0.0001$), bacteremia ($p = 0.02$), and inflammation ($p = 0.0006$), but not to prevention of renal failure. The insulin dose was an independent determinant in prevention of renal failure ($p = 0.03$). Among the relevant findings in those investigators' original study¹⁰⁴ was the significant reduction in the incidence of acute renal failure requiring renal replacement therapy in the treatment group. These beneficial clinical effects could be explained by the antiinflammatory properties of insulin and the recent finding that insulin has potent anti-apoptotic effects.¹⁰⁸ In contrast, high glucose concentrations produce apoptotic effects in tubular epithelial cells.¹⁰⁹ Thus, insulin may minimize the damage associated with cytokine-induced cellular dysfunction and cell death and may have an important role in prevention of renal failure.

A recent prospective observational study demonstrated that it is the control of BG concentrations, not insulin administration, that is associated with reduced mortality and morbidity in ICU patients.¹¹⁰ Relationship between ICU outcome and degree of BG control and insulin administration was modeled using multivariate logistic regression. At prevailing BG concentrations of 111–144 mg/dL, increased insulin administration was positively and significantly associated with ICU mortality. This was observed in both diabetic and nondiabetic patients.

POTENTIAL FOR HYPOGLYCEMIA

Hypoglycemia is a serious consequence of insulin therapy that could lead to neurologic sequelae. The definition of hypoglycemia differs in insulin therapy trials, making it difficult to compare rates of hypoglycemia. Van den Berghe et al.¹⁰⁷ reported that the incidence of hypoglycemia, de-

defined as a BG level ≤ 40 mg/dL, was 5.2% in intensive insulin-treated patients versus 0.8% in conventionally treated patients. In a national survey, Cohen et al.¹¹¹ found that 11% of serious medication errors resulted from insulin misadministration. The Joint Commission on Accreditation of Healthcare Organizations mandates that efforts made to improve the safety of using high-alert medications (eg, insulin) are documented. Proactive planning to reduce insulin misadministration includes spelling rather than abbreviating dosage units to avoid potential for an overdose. Although time consuming, a check system for infusion pump rates and concentration settings should be instituted to avoid infusion-pump programming errors. Hypoglycemic episodes can be prevented with proactive systematic changes and avid monitoring.

Summary

The patient population in the van den Berghe et al.¹⁰⁴ trial was limited to those undergoing surgery, mostly cardiac surgery; these results cannot be extrapolated to patients in nonsurgical ICUs or to those with other types of critical illness. A recent study of intensive insulin therapy to maintain normoglycemia resulted in significant reductions in morbidity and mortality in a more heterogeneous population of medical and surgical critically ill patients.⁸¹ Similar to the van den Berghe et al. trial, these authors demonstrated that even a modest elevation of BG to >99 mg/dL during ICU stay was associated with increased hospital mortality. This study included almost twice as many diabetics as did the van den Berghe et al. trial. Based on available literature, it appears that control of BG concentration—not insulin administration—confers the mortality benefit. Optimal benefits appear to be achieved with maintenance of BG concentrations <100 – 110 mg/dL. Furthermore, it seems prudent to control glucose, regardless of a history of diabetes.

Prospective, randomized controlled studies of sufficient sample size to provide a power analysis for evaluation of critically ill patient subsets are needed in adult and pediatric patients to compare conventional methods of glucose control with normoglycemia in a broad patient population. The potential for improvement in ICU patient outcomes, combined with the economics of implementing therapy with a low-cost drug, make intensive insulin therapy an attractive option.

Implementing protocols that optimize target BG concentrations has great potential for positively improving patient outcomes in the ICU. These protocols should be updated as needed based on evolving literature on the topic. Future studies are needed in other ICU populations in order to evaluate both the clinical and economic impact of these guidelines.

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EXTRACTO

OBJETIVO: Evaluar los resultados clínicos en cuanto al control glucémico relacionado a la terapia intensiva de insulina y recomendar su lugar en el manejo de pacientes con enfermedades aguda críticas.

FUENTES DE INFORMACIÓN: Se realizó búsquedas en el banco de datos de MEDLINE (1966 a marzo del 2004), la Biblioteca de Cochrane, y un repaso manual extensivo de los extractos usando términos claves tales como hiperglucemia, insulina, unidad de cuidado intensivo, enfermedades aguda críticas, resultados clínicos, y guías e algoritmos.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Todos los artículos identificados de las fuentes de información fueron evaluados y juzgados ser relevantes si incluyeron y determinaron resultados clínicos.

SÍNTESIS DE DATOS: La mortalidad entre pacientes con enfermedades aguda críticas prolongadas excede un 20%, y la mayoría de las muertes han sido atribuidas al sepsis y falla orgánica multisistémica. La hiperglucemia es común en pacientes con enfermedades aguda críticas, aun en aquellos sin un historial de diabetes mellitus. El mantenimiento de la normoglucemia con el uso de insulina en pacientes con enfermedades aguda críticas ha producido mejoras en los resultados neurológicos, cardiovasculares, e infecciosos. Sobre todo, se puede reducir la morbilidad y la mortalidad con el uso de la terapia agresiva de insulina. La implantación de esta información en protocolos para mantener el control estricto de glucosa ha sido bien recibida y segura.

CONCLUSIONES: El uso de protocolos de insulina en pacientes críticamente enfermos puede mejorar el control sanguíneo de glucosa y reducir la morbilidad y mortalidad en esta población. Se recomienda la introducción de protocolos de insulina para controlar los niveles de glucosa con el propósito de obtener un estado de euglucemia, independientemente del historial diabético. Se requiere una supervisión frecuente e imprescindible para evitar la hipoglucemia.

Carlos C da Camara

RÉSUMÉ

OBJECTIF: Évaluer les bénéfices cliniques associés au contrôle de la glycémie avec une insulinothérapie intensive et recommander son utilisation chez les patients de soins intensifs.

REVUE DE LITTÉRATURE: Une recherche dans les bases MEDLINE (1966 à mars 2004) et Cochrane ainsi qu'un dépouillement manuel extensif de résumés ont été effectués en utilisant les mots clés suivants: hyperglycémie, insuline, unité de soins intensifs, patients de soins intensifs, lignes directrices, et algorithmes. Tous les articles ont été évalués et jugés pertinents s'ils traitaient d'issues cliniques.

RÉSUMÉ: Le taux de mortalité chez les patients effectuant un séjour prolongé aux soins intensifs dépasse les 20% et la plupart des décès est attribuable à la septicémie et à l'insuffisance multi-organique. L'hyperglycémie est fréquente chez ces patients, même chez ceux sans histoire de diabète sucré. Le maintien d'une glycémie normale avec l'insuline s'est révélé efficace pour améliorer les issues neurologiques, cardiovasculaires, et infectieuses. La morbidité et la mortalité sont diminuées par l'utilisation d'une insulinothérapie intensive.

CONCLUSIONS: L'utilisation de protocoles d'insuline chez les patients de soins intensifs améliore le contrôle de la glycémie et réduit la morbidité et la mortalité. La mise en place de protocoles d'insuline visant la normalisation de la glycémie chez les patients de soins intensifs est recommandée et ce peu importe la présence ou non de diabète sucré dans les antécédents du patient. Une surveillance étroite de la glycémie est nécessaire afin d'éviter l'hypoglycémie.

Alain Marcot