Effects of Hyperglycemia on Neurologic Outcome in Stroke Patients

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Abstract: *Hyperglycemia in acute stroke patients increases cerebral infarct size and worsens neurologic outcome with and without preexisting diabetes mellitus. Hyperglycemia results from metabolic alterations in glucose metabolism, and is most common in patients with acute illness such as stroke. Strict control of hyperglycemia with intensive insulin therapy has been shown to dramatically decrease hospital morbidity and mortality, inpatient stays, hospital costs, and, most importantly, neurologic injury. Insulin treatment protocols developed and implemented by multidisciplinary teams allow for rapid and effective control of hyperglycemia. Nurses who know about hyperglycemia's often-neglected and detrimental effects can play a vital role in influencing outcomes in stroke patients.*

Case Study

A 67-year-old woman presented to the emergency department with an acute onset of left arm weakness and difficulty with walking and speech. Her medical history was significant for hypertension and cardiovascular disease. A physical exam revealed a blood pressure of 194/108 mm Hg, dysarthric speech, and decreased strength in the left upper and lower extremities. Laboratory values revealed mild electrolyte abnormalities and an elevated serum glucose of 268 mg/dL. Computed tomography (CT) of the head demonstrated early findings consistent with acute ischemic stroke.

The woman was admitted to the neuroscience intensive care unit (ICU) for acute stroke care and a diagnostic work-up. She was placed on standard stroke protocol admission orders, with bedside fingerstick glucose monitoring every 6 hours. A sliding-scale regular insulin regimen also was in place to treat blood glucose higher than 150 mg/dL, as needed. Throughout the evening of admission and the following day, her blood glucose level remained higher than 200 mg/dL despite sliding-scale coverage. A hemoglobin A1C was ordered to check for diabetes mellitus (DM). No changes were made in the sliding scale or monitoring frequency.

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On day 2 after admission, the patient's neurologic status declined further. A clinical exam revealed forced eye deviation, left-sided paralysis, and declining mental status. She required intubation and full mechanical support for severe aspiration pneumonia.

Magnetic resonance imaging (MRI) of the brain revealed an evolving large ischemic stroke in the right middle cerebral artery distribution with significant brain edema. She eventually required tracheostomy and gastrostromy tube placements for long-term management because of her poor neurologic condition. She was discharged to a skilled nursing home after 1 month of hospitalization.

Introduction

Hyperglycemia in critically ill patients has been described as a "toxic metabolic milieu" that slowly and insidiously results in increased morbidity and mortality. The presence of hyperglycemia in acute stroke increases cerebral infarct size and subsequently worsens neurologic outcome (Parsons et al., 2002). Hyperglycemia is a common problem in the stroke population. It is estimated that 20%–50% of acute stroke patients—even those without preexisting DM—present with a concurrent diagnosis of hyperglycemia (Alvarez-Sabín et al., 2003). Controlling hyperglycemia with a continuous insulin infusion to reach euglycemic levels has been shown to decrease morbidity and mortality. This article reviews the pathophysiology of hyperglycemia, its effects on injured brain tissue, and overall neurologic outcome. Hyperglycemic treatment strategies also are discussed, as well as issues with which neuroscience nurses should be familiar to provide optimal care for stroke patients with hyperglycemia.

Hyperglycemia Pathophysiology

Overview of Postprandial Glucose Metabolism

In healthy individuals without DM, the regulation of blood glucose concentration is maintained through hormonal, neural, and hepatic autoregulatory mechanisms (Robinson & van Soeren, 2004). Under normal circumstances, a postprandial increase in blood glucose concentration stimulates the release of insulin from the pancreas, specifically the b-cells. Insulin mediates peripheral glucose disposal and suppresses glucogenesis in the liver. This process maintains blood glucose homeostasis. After uptake into the skeletal muscle, glucose either is directed to glucagon formation (pathway for carbohydrate storage) or glycolysis (used in the Kreb's cycle,

Table 1. Risk Factors for the Development of Stress Hyperglycemia in Critical Illness

Factor	Major mechanism
Preexisting diabetes mellitus	Insulin deficiency (relative or absolute)
Infusion of catecholamine pressor (i.e., epinephrine and norepinephrine)	Insulin resistance
Glucocorticoid therapy	Insulin resistance
Obesity	Insulin resistance
Increasing Acute Physiology and Chronic Health Evaluation (APACHE) score	Higher counterregulatory hormone levels
Older age	Insulin deficiency
Sepsis	Insulin resistance
Hypothermia	Insulin deficiency
Hypoxemia	Insulin deficiency
Uremia	Insulin resistance
Cirrhosis	Insulin resistance

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resulting in energy production). Excess glucose also can be stored in the liver or converted to fatty acids for storage in adipose tissue.

Altered Glucose Metabolism in Critical Illness

Critical illness induces a number of adaptive changes in human physiology; the most prominent are changes in the neuroendocrine function (Ferrando, 1999). An increase in counterregulatory hormones, such as glucagons, epinephrine, norepinephrine, and growth hormone, results in increased hepatic glucose production and decreased peripheral glucose uptake, subsequently inducing a hyperglycemic state (Montori, Bistrian, & McMahon, 2002). In addition, critical illness exacerbates the circulation of abnormal levels of cytokines—particularly tumor necrosis factor, alpha, and interleukin— further elevating serum glucose (McCowen, Malhotra, & Bistrian, 2001). Patients with DM exhibit a greater response to counterregulatory hormones, and may not increase insulin secretion as a compensatory response to needed levels, resulting in even higher glucose levels (Montori et al., 2002).

Effects of Exogenous Insulin

Hyperglycemic treatment with exogenous insulin alters the metabolic abnormalities seen in hyperglycemia (American Association of Clinical Endocrinologists [AACE], 2003). Improved outcomes from insulin administration in critically ill people may be due to favorable alterations in myocardial and skeletal muscle metabolism, oxidative glycolisis, and increased nitric oxide production that results in arterial vasodilatation. Insulin inhibits both lipolysis and inflammatory growth factors that have been associated with poor outcomes in patients with cardiac arrhythmias and acute myocardial infarction (AACE, 2003).

In global ischemia (e.g., anoxic brain injury and encephalopathy), insulin acts directly on brain parenchyma to reduce neuronal necrosis in the brain cortex, striatum, and hippocampus (Auer, 1998). Animal data indicate that the direct mechanism is mediated by insulin-like growth factor-1 receptors. The direct effect appears to predominate in global ischemia. In focal ischemia, unlike global ischemia, the effect of insulin is predominantly via peripheral hypoglycemia because neuroprotection largely is annulled by coadministration of glucose (Auer, 1998). Insulin also has been shown to improve cell membrane stability, assisting with cerebral edema resolution (American Association of Clinical Endocrinologists, 2003).

Hyperglycemia Risk Factors

Hyperglycemia as a manifestation of the stress response is most evident after an ICU admission and may resolve as the underlying catabolic illness subsides (McCowen et al. 2001). Multiple factors have been associated with an increased risk of hyperglycemia in critical illness, including frequent administration of exogenous dextrose through intravenous drip, intravenous medications and antibiotics in dextrose solutions, glucocorticoid medication, catecholamine vasopressors, total parenteral nutrition administration (TPN), as well as increased age and prolonged bed rest. Table 1 lists the risk factors associated with the development of hyperglycemia in acute, critical illness. Some patients, particularly those with an untreated underlying process such as infection or ongoing injury, may demonstrate persistent metabolic disregulation and continued hyperglycemia (McCowen et al., 2001).

Bed rest alone in the absence of critical illness is associated with reduced skeletal muscle insulin sensitivity (McCowen et al., 2001). Stuart, Shangraw, Prince, Peters, & Wolfe (1988) found that 6 days of strict bed rest in healthy volunteers resulted in moderate deterioration in oral glucose tolerance and increased fasting plasma insulin concentration and insulin response to oral glucose challenge by more than than 40%.

Aging is associated with a higher incidence of stress hyperglycemia (McCowen et al., 2001). It is suggested that elderly people mount an inadequate response to the

insulin resistance of critical illness, which is produced by the actions of increased counterregulatory hormones and cytokines (McCowen et al., 2001). In a study by Frankenfield, Cooney, Smith, & Rowe (2000), trauma patients older than 60 years of age had a 38% incidence of hyperglycemia, compared with a 0% incidence in younger patients with similar carbohydrate intake.

An often-overlooked risk factor for hyperglycemia in critically ill patients is the use of dextrose in excess amounts. High concentrations of dextrose are found in multiple sources in hospitals, such as in dialysis solutions, intravenous medications, and TPN. In an analysis of stress hyperglycemia in nondiabetic patients receiving TPN, participants who received dextrose at rates higher than 4 mg/kg/min had a 50% chance of developing hyperglycemia (Schloerb & Henning, 1998).

Hyperglycemic Effects on the Injured Brain

The effects of hyperglycemia on the injured brain have been studied in both animals and humans. Hyperglycemia has been associated with increased cerebral lactate resulting in local brain tissue acidosis (Kagansky, Levy, & Knobler, 2001). Brain tissue acidosis worsens mitochondrial function in the penumbra, the moderately ischemic tissue of the brain surrounding the injured core, and increases cerebral infarct size (Alvarez-Sabín et al., 2003). In a study of 63 patients with sudden-onset focal neurological deficit consistent with hemispherical ischemic stroke who received serial MRI, hyperglycemia was shown to reduce penumbral salvage, resulting in greater final infarct size (Parsons et al., 2002).

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Hyperglycemia also adversely affects the ischemic brain by disrupting the blood-brain barrier and promoting cerebral edema. In their study of rats with hemorrhagic stroke and hyperglycemia, Song et al. (2003) found that hyperglycemia-induced brain injury resulted in increased free radical formation. In turn, the increased amount of free radical formation increased blood-brain barrier permeability and brain edema. The authors hypothesized that elevated glucose levels aggravated brain edema, which culminated in cell death surrounding hemorrhagic stroke tissue.

Hyperglycemia also is thought to play a role in negative outcomes in stroke patients treated with early reperfusion therapy. Research indicates that elevated glucose levels impair cerebrovascular reactivity in the microvasculature (Alvarez-Sabín et al., 2003). As a result, there is decreased reperfusion after tissue plasmogin activator (tPA)-induced recanalization, contributing to a worsened neurologic outcome (Kawai, Keep, & Benz, 1997). It has also been suggested that hyperglycemia may be an important risk factor for hemorrhagic conversion of stroke after tPA. Alvarez-Sabín et al. (2003) found that elevated blood glucose before reperfusion partly offsets the benefit of early restoration of blood flow, translating into decreased neurologic improvement, greater infarct size, and worsened outcomes in hyperglycemic patients. The PROACT II stroke thrombolysis trial (Kase et al., 2001) also found conclusive evidence that hyperglycemia is a significant risk factor for symptomatic hemorrhagic conversion of an ischemic stroke. When serum glucose was stratified into categories of increasing levels of hyperglycemia, subjects with values higher than 200 mg/dL had a 36% risk of symptomatic intracerebral hemorrhage (ICH).

Hyperglycemic Effects on Neurologic Patient Outcomes

For two decades, researchers have studied the effects of hyperglycemia on clinical outcomes of patients with neurologic injury (Jeremitsky, Omert, Dunham, Protetch, & Rodriguez, 2003). Hyperglycemia associated with DM is a well-established risk factor for vascular disease. However, the effects of acute hyperglycemia on neurologic outcome, whether related to DM or in response to stress during acute illness, are not well understood.

The effect of hyperglycemia at hospital admission on stroke outcome is of great interest to the neurologic research community. Williams et al. (2002) found that in a study of 656 patients with acute ischemic stroke, those with hyperglycemia upon hospital admission had a significantly higher risk for death at 30 days, 1 year, and 6 years following stroke. They also noted that patients with admission hyperglycemia had longer hospital stays and incurred higher hospital costs. In a systematic overview of 32 studies, Capes, Hunt, Malmberg, Pathak, and Gerstein (2001) concluded that stress hyperglycemia upon hospital admission was associated with poor functional recovery. Patients with no history of DM who had an ischemic stroke and moderately elevated glucose levels also had a threefold higher risk of short-term mortality and an increased risk of poor functional recovery compared with patients with lower glucose levels.

Persistent hyperglycemia throughout hospitalization also may play an important role in poor neurologic outcomes. Baird et al. (2003) studied 25 patients who underwent serial glucose testing for 72 hours following the onset of stroke symptoms. MRI was obtained at 15 hours, 5 days, and 85 days after the onset of stroke symptoms. It was found that persistent hyperglycemia influenced stroke evolution, and was a significant indicator of infarct progression and negative clinical and functional outcomes.

Hyperglycemia also has been studied as an important outcome indicator in other types of neurologic injury. In a study of 81 patients diagnosed with traumatic brain injury, Jeremitsky et al. (2003), found that hyperglycemia was associated with increased mortality and longer hospital stays. In another study of traumatic brain-injured patients, high admission glucose levels were associated with worsened neurologic outcome (Young, Ott, Dempsey, Haack, & Tibbs, 1989).

Hyperglycemic Management

Lowering serum glucose to near-normoglycemic levels reduces morbidity and mortality regardless of patients' DM history (AACE, 2003). In years past, apathy often reigned when strict inpatient glycemic control was suggested because implementing this strategy had not been closely analyzed (McCowen et al., 2001). Recent data, however, have shown that it is safe, feasible and prudent to further lower glucose levels with a continuous insulin infusion or sliding-scale regimen (Van den Berghe et al., 2001).

The strict means of glycemic control has sparked interest. Van den Berghe et al. (2001) found that patients with blood glucose levels maintained at less than 110 mg/dL with a continuous infusion had a 32% reduction in morality and shorter ICU stays. In a metaanalysis of 26 studies, Capes et al. (2001) found that patients with blood glucose levels of 110–126 mg/dL had a higher risk of in-hospital mortality than those who maintained levels lower than 110 mg/dL. Krinsley (2003) also found that mortality was lowest among patients with mean serum glucose values between 80 and 99 mg/dL, but increased significantly and progressively as mean serum glucose values exceeded this range. Table 2 features the recommended glucose target levels from the AACE.

Strict glycemic control in the ICU can be achieved with a continuous insulin infusion or a sliding-scale regimen. A continuous insulin infusion is considered superior to a sliding-scale regimen because it allows for an immediate response to a specific blood glucose level, with potential for frequent adjustments. Serum glucose levels are required every 1–2 hours when using a continuous insulin infusion, promoting tighter control of glycemic levels. In contrast, the sliding-scale method allows only for a retrospective assessment of glucose requirements, and the arbitrary scale cutoff points may not be relevant to patients. Consequently, a sliding scale may result in overall higher glycemic levels (Brown & Dodek, 2001). Van den Berghe et al. (2003) determined that blood glucose levels lower than 110 mg/dL could be reached effectively and safely within 24 hours of ICU admission, and maintained throughout the ICU stay with a continuous insulin infusion using a titration algorithm. Fig 1 lists the conditions for which intravenous insulin therapy is indicated.

Table 2. Upper Limits for Glycemic Target to Promote Improved Outcomes

Care Unit	Blood Glucose Level
Critical care unit	110 mg/dL
Noncritical care unit	110 mg/dL preprandial 180 mg/dL maximal glucose

Source: (AACE, 2003)

- Critical illness
- Prolonged NPO status in patients who are insulin-deficient in perioperative period
- After organ transplantation
- Receiving total parenteral nutrition therapy
- Glucose exacerbated by high-dose glucocorticoid therapy
- Stroke
- Labor and delivery
- As a dose-finding strategy before conversion to subcutaneous (SQ) insulin therapy
- Other illnesses requiring prompt glucose control

**List is not all-inclusive.*
Source: (AACE, 2003)

Fig 1. *Indications for intravenous insulin therapy**

The most common complication of insulin therapy, either with sliding-scale or continuous infusion, is hypoglycemia. Symptoms of hypoglycemia include palpitations, anxiety, weakness, fatigue, confusion, behavioral changes, loss of consciousness, and seizures. Van den Berghe et al. (2003) found that hypoglycemia, while uncommon, occurred more often in the patients receiving intensive insulin therapy to maintain blood glucose level lower than 110 mg/dL. Van den Berghe et al. (2003) concluded the risk of hypoglycemia was outweighed by the benefits of intensive insulin therapy and tighter glycemic control.

Hyperglycemia Treatment Protocols

The use of standardized protocols developed by multidisciplinary teams is associated with improved glycemic control and lower rates of hypoglycemia (AACE, 2003). Such protocols allow for faster and more effective control of hyperglycemia (Brown & Dodek, 2001). Protocols should specify the frequency of blood glucose checks and insulin dosage based on glucose level. Guidelines for preventing, identifying, and treating hypoglycemia, as well as recommendations for insulin drip adjustments based on patient conditions, should be clearly defined. Fig 2 provides an example of a protocol for continuous insulin infusion.

Nurses should participate actively in the development of insulin drip protocols. Bedside nurses play an important role in monitoring the efficacy of the protocol and recognizing steps that should be added to or deleted

1. Bedside blood glucose (BG) monitoring Q 1 hour until patient is within target range on two consecutive readings, and then obtain BG Q 2 h. If the BG falls above or below the targeted range, resume Q 1 h readings.
2. If initial BG > 150 mg/dL, give IV regular insulin bolus: Dose _____ units. (Dose 0.1 Units/kg body weight)
3. Insulin drip: 125 units of regular insulin in 250 ml 0.9% normal saline (1 ml of solution = 0.5 units of Insulin)
4. Target BG range on Insulin Drip: ____mg/dL to _____ mg/dl. (Suggested 80-110 for ICU patients)
5. For each BG value, recalculate drip rate and disregard previous rate of infusion.
6. Calculate insulin drip rate: (BG – 60) x _____ (multiplier) = Units of insulin per hour (x2 to determine cc's/hour)
7. Typical starting multiplier 0.02, but varies by insulin sensitivity
   Adjusting multiplier:
   - BG > target range: Increase multiplier by 0.01
   - BG within target range: No change in multiplier
   - BG < target range: Decrease multiplier by 0.01
8. Treating hypoglycemia:
   - (a) BG 60-80: Give 50% dextrose in water (D50W) using formula: (100 – BG) x 0.3 = ml D50W IV Push
   - (b) BG < 60: Give D50W using formula: (100 – BG) x 0.3 = ml D50W IV Push and decrease insulin drip to 50% of current infusion rate

   Recheck BG in 30 minutes:
   - BG > 80: Decrease multiplier by 0.01 and then return to step 5 formula
   - BG 60–80: Repeat step 8a
   - BG < 60: Notify physician and repeat step 8b
9. Special considerations:
   - Tube feeding/total parenteral nutrition (TPN) adjustments: Notify physician to determine if they would like to adjust the insulin when the patient has a discontinue (DC) or hold order for tube feedings/TPN (e.g., NPO 8 h for a procedure) or when tube feedings/TPN are interrupted for any other reasons (e.g., "residuals," loss of access, etc.).
   - Patient is traveling to procedures requiring insulin drip to be held (ex. radiology): If BG > target range, treat immediately before to leaving nursing unit with regular insulin subcutaneous (SC) and then stop infusion. Calculate the SC insulin dose as ½ current infusion rate. (Example: Insulin infusion is 10 units/h, give 5 units regular insulin SC and stop infusion immediately before leaving the unit.) Upon return to unit, check BG; follow protocol above resuming the regular insulin infusion at previous rate (ex. 10 uits/h).

Fig 2. *Example of intravenous (IV) insulin infusion protocol*

from the protocol. The team should discuss their observations and suggestions frequently. Finding out what does and does not work is part of the learning process that will lead to optimal care.

Nursing Considerations

Strict glycemic control in the ICU requires a collaborative effort from the entire medical team. Nurses play an important role in this process by identifying patients at risk for prolonged hyperglycemia. They must evaluate admission serum glucose levels and closely monitor elevated bedside glycemic levels when caring for critically ill patients, especially neurological patients. Prompt reporting of worrisome observations to the medical team can significantly improve outcomes.

Nursing responsibilities for patients receiving insulin include proper administration, assessment of patient response to insulin therapy, and education of patients and their families about insulin's administration, adjustment, and side effects (Lewis, Heitkemper, & Dirksen, 2000). ICU nurses also must report deviations from accepted parameters or the proactive approach to intravenous insulin therapy.

Nurses must educate themselves and their peers about hyperglycemia and its profound negative influence on outcomes. Resistance to improved therapies and new protocols or techniques usually stems from a fear of change or a lack of understanding. Newly developed plans of care often are viewed as laborious "busy work," with no clear recognition of the evidence-based approach. Educational speakers and in-services that address the importance of hyperglycemic management can help nurses improve the continuity and quality of care.

If glycemic levels remain elevated throughout the acute illness phase, patients should be transitioned to an oral or long-acting subcutaneous antihyperglycemic regimen. Patient education at this point is extremely valuable, especially when combined with outpatient resources and endocrinology referrals. Stroke patients requiring rehabilitation benefit from early nursing discharge planning and maintained glycemic management planning.

Recommendations for Research

Further research regarding hyperglycemia's effects on all disease entities is of great importance. There are many research opportunities regarding the role of insulin in glycemic control in the neuroscience arena. Most currently available data reflect the effect of hyperglycemia on ischemic stroke patients. Neuroscience illnesses that are affected by hyperglycemia deserve the same attention. Future clinical trials are needed to address the effects of hyperglycemia on diagnoses such as intracranial hemorrhage, subarachnoid hemorrhage, encephalitis, global anoxia, and spinal trauma.

Projects intended to improve and tailor insulin protocols to specific disease states also are important. For

example, studying the effects of insulin therapy on patients with spinal cord injury who are receiving a steroid infusion may provide beneficial information for the staff. Documenting the benefits of early and aggressive hyperglycemic control will determine patient outcome and hospital resource utilization benefits.

Summary

The adverse effects of hyperglycemia on neurological outcomes for stroke patients are significant. Controlling hyperglycemia in acute illness is critical if nurses are to improve patient morbidity and mortality. Neuroscience nurses play an important role in recognizing hyperglycemia and taking the necessary interventions to control glucose levels and positively affect patient outcome.

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