

Refining Perioperative Glucose Management in Patients Experiencing, or at Risk for, Ischemic Brain Injury

ISCHEMIC brain injury is the third leading cause of death in the United States, and survivors of ischemic brain injury represent the leading cause of major disability. Most of these ischemic events begin outside the hospital. However, patients who enter the hospital neurologically intact may experience new-onset cerebral ischemia, *e.g.*, in association with cardiac or cerebrovascular surgery. Those who have experienced a single ischemic event (whether beginning outside or inside the hospital) are at risk for exacerbation of their injury during hospitalization due to secondary insults resulting from cardiac arrhythmias, systemic hypotension, surgical interventions, cerebral vasospasm, and other causes. During hospitalization, clinicians have many opportunities to lessen the risk of both primary and secondary ischemic injury. One such possibility is the disciplined monitoring and management of blood glucose concentrations. Although the issue of intensive insulin therapy and glycemic control is pertinent to critically ill patients in general, as addressed by Blasi-Ibanez *et al.*,[1] and reviewed by Lipshutz and Gropper[2] in last month's issue of ANESTHESIOLOGY, patients who have experienced or are at risk for ischemic brain injury represent a special population (for reasons we will later review). There is considerable, consistent evidence from animal models and human studies that outcome after a cerebral ischemic insult is partially modulated by blood and brain glucose concentrations. However, the current literature offers little guidance for the clinician on how to apply the existing data such that outcome can be optimized during the care of neurologically at-risk patients, particularly with respect to how rigidly glucose should be controlled and the magnitude of risk in executing such control. Two human studies reported in this issue of ANESTHESIOLOGY focused on this issue. Bilotta *et al.*[3] report on the challenges and pitfalls of glucose management in patients requiring intracranial surgical procedures. Likewise, Thiele *et al.*[4] report on the effect of institution of a strict blood glucose management protocol on outcome in critically ill patients with subarachnoid hemorrhage.

Glucose management in patients with cerebral insults-in-evolution may be problematic. Specifically, physiologic stress, use of corticosteroids or other drugs (*e.g.*, sympathomimetics), neuroendocrine disorders, nutritional support, and other factors may all combine to make the fine tuning of blood glucose concentrations difficult. Data from experiments in animal models inform us that modest changes in blood glucose concentrations, on the order of 40 mg/dl, are sufficient to modulate outcome after an ischemic insult.[5] Further, optimum neurologic outcome, based on animal and human research, will likely occur at blood glucose concentrations of 130 mg/dl or less.[6] However, it is unclear whether more rigorous glucose reduction is beneficial. Specifically, there is concern that hypoglycemia can cause irreversible brain injury and cardiovascular compromise independent of the presence of cerebral ischemia.

To address these challenges, Bilotta *et al.*[3] prospectively studied 483 patients presenting for elective or emergent intracranial procedures. Patients were randomized to either intensive (target blood glucose concentration = 80–110 mg/dl) or conventional (target blood glucose concentration < 215 mg/dl) glycemic management. The primary goal of this investigation was to compare the rates of hypoglycemic episodes (blood glucose < 50 mg/dl) between groups. Other outcome metrics evaluated were length of intensive care unit stay, infection rate, 6-month Glasgow Outcome Score, and mortality. A greater fraction of patients in the intensive glucose treatment group had hypoglycemic episodes (94% *vs.* 63% for conventional treatment; $P < 0.0001$), but they also had a lesser incidence of infections (26% *vs.* 39% for conventional therapy; $P = 0.002$) and a shorter median duration of intensive care unit stay (6 days *vs.* 8 days; $P < 0.0001$). Despite these differences, there was no difference in 6-month Glasgow Outcome Scores ($P = 0.984$) or mortality ($P = 0.689$) between groups.

A related study in this issue of ANESTHESIOLOGY retrospectively reported on an intensive glucose control protocol introduced at the University of Virginia Health System on January 1, 2002. Target blood glucose concentration was 90–120 mg/dl. Thiele *et al.*[4] compared clinical outcome in patients with subarachnoid hemorrhage managed before (1995–2001, n = 343) or after (2002–2007, n = 491) institution of the glucose-management protocol. Despite statistically positive results regarding glucose endpoints, the difference between preprotocol and postprotocol median blood glucose concentration was ex-

This Editorial View accompanies the following two articles: Thiele RH, Pouratian N, Zuo Z, Scalzo DC, Dobbs HA, Dumont AS, Kassell NF, Nemergut EC: Strict glucose control does not affect mortality after subarachnoid hemorrhage. Anesthesiology 2009; 110:603–10; and Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G: Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. ANESTHESIOLOGY 2009; 110:611–9.

Accepted for publication December 8, 2008. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

tremely small (121 mg/dl *vs.* 116 mg/dl, respectively; $P < 0.001$). There was, however, a large difference in median admission blood glucose concentration throughout the entire study period between survivors (135 mg/dl) and nonsurvivors (176 mg/dl; $P < 0.001$). It is unclear whether this association represents a cause-and-effect relationship between glucose concentration and injury or, instead, represents a stress response due to injury severity. Similar to Bilotta *et al.*, hypoglycemic episodes in the Thiele *et al.* research (blood glucose concentration < 60 mg/dl) were more common in the intensively managed group (7.1% *vs.*. 1.5%; $P < 0.001$). Thiele *et al.* also reported that hypoglycemia was independently associated with an increased risk of death (OR = 3.82; 95% CI = 1.40–10.44; $P = 0.009$); however, their research was unable to determine whether hypoglycemia contributed to death or whether patients who were more likely to die were also more vulnerable to developing hypoglycemia (*e.g.*, as a result of altered neuroendocrine function) during insulin treatment. Overall mortality during hospitalization was not influenced by glycemic management protocol ($P = 0.876$).

The studies of Bilotta *et al.*[3] and Thiele *et al.*[4] are similar to earlier studies of van den Berge,[7] Krinsley,[8] and Gandhi *et al.*,[9] that evaluated the feasibility of stringent glucose management in hospitalized patients. Endpoints of these three studies were some combination of death and the incidence of medical complications, *i.e.*, endpoints of most relevance to the type of *nonneurosurgical* patients being studied. Bilotta *et al.* and Thiele *et al.*, studied *neurosurgical* patients in their reports in ANESTHESIOLOGY, and (with the exception of assessing Glasgow Outcome Scores in the Bilotta *et al.* study) used endpoints similar to those of van den Berge *et al.*,[7] Krinsley,[8] and Gandhi *et al.*[9] Consistent with the earlier studies, Bilotta *et al.* and Thiele *et al.* report that a modest fraction of patients experienced hypoglycemia. Whereas Bilotta *et al.* and Thiele *et al.* provided information on some of the risks associated with aggressive glucose management in the neurosurgical patient population, meaningful advancement of our understanding of the risks *versus* benefits of strict glycemic management will require the application of more discriminating metrics of outcome, particularly neurologic outcome.

Recent research in cardiac and cerebral aneurysm surgery patients, *i.e.*, populations at high risk for additional or new-onset neurologic injury, has determined that neuropsychological changes, which require the use of highly sophisticated testing, are far more sensitive than the assessment of gross neurologic function, hospital stay data, or mortality rates in identifying brain injury.[10,11] In their recent retrospective analysis of data from 1000 patients entered into the Intraoperative Hypothermia for Aneurysm Surgery Trial database, Pasternak *et al.*[11] reported that aberrations of neuropsychological function were more common (*i.e.*, incidences of 18–70%, depending on the specific test being reported) than those of gross neurologic function (18–39%). Altered neuropsychological function occurred at a lesser glucose concentration (*i.e.*, ≥ 129 mg/dl) than gross neurologic function (*i.e.*, ≥ 152 mg/dl) based on the National Institutes of Health Stroke Scale. Of note, Glasgow Outcome Score data were insensitive to glucose modulation, and mortality rate was independent of blood glucose concentration ($P = 0.09$) in the Pasternak *et al.* investigation. Similarly, in their study of glucose control in 409 cardiac surgery patients, Gandhi *et al.*[5] determined that mortality rates alone were not influenced by glucose management, and only the composite of mortality rate and the overall rate of a medical complication identified a statistically significant result. Given these factors, it would seem that mortality rate is a crude, inadequate marker of glucose modulation of ischemic brain injury. Therefore, in terms of glucose modulation of outcome after an acute ischemic insult, future studies will be able to reach the strongest, most statistically clean and powerful, and most clinically relevant assessments when and only when they prospectively use formalized tests of gross neurologic function and neuropsychological function (and not some surrogates or mortality alone) to determine outcome.

Although the studies of Bilotta *et al.* and Thiele *et al.* address the feasibility of glucose management in patients experiencing or at risk for neurologic injury, neither assessed long-term outcome using the tests now demonstrated to quantify subtle glucose modulation of neurologic injury in neurosurgical patients (*i.e.*, neuropsychological testing, the National Institutes of Health Stroke Scale). As such, these investigators still leave unanswered one of the most important glucose-management issues of the day: What is the likelihood that glucose management can affect neuropsychological function and subtle sensorimotor function in those who survive a cerebral insult? These issues can only be addressed with prospective, appropriately powered study designs that employ appropriate tests of both sensorimotor function and neuropsychological function known to be associated with alterations in glucose concentrations. Given the incidences of hypoglycemia reported by Bilotta *et al.* and Theile *et al.* in neurosurgical patients, it is all the more important that future outcome investigations rigorously and prospectively evaluate both gross neurologic function and neuropsychological function in patient subjected to strict glucose control.

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