
ICU Volume 6 - Issue 3 - Autumn 2006 - Matrix Features

Tight Glycemic Control During Critical Illness: Overcoming the Obstacles

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Salient literature is reviewed describing the benefits and concerns of tight glycemic control in critically ill patients. Hypoglycemia and other pitfalls with implementation of an intensive insulin protocol are discussed.

Critically ill patients frequently develop hyperglycemia. Until recently, there have been few scientific reasons put forth for correcting this hyperglycemia.

Despite very little exploratory investigation to precede it, Van den Berghe and colleagues boldly embarked upon the Leuven study: a large prospective, randomized, surgical intensive care unit, controlled trial testing the hypothesis that strict euglycemic control using intensive insulin infusions could increase survival and reduce morbidity in a critical care population (Van den Berghe et al. 2001). They studied 1,548 surgical patients (62% post cardiac surgery), with the aim of maintaining a blood glucose range between 80 - 110 mg/dL (4.4 - 6.1 mmol/L). They observed a 42% reduction in risk of death and in various morbidities, particularly in the prolonged stay group of patients. Other comparative studies followed, in cardiac surgery (Finney et al. 2003; Lazar et al. 2004), trauma (Grey and Perdrizet 2004), mixed medical-surgical (Krinnsley 2004) and a large medical ICU population (Van den Berghe et al. 2006), reproducing the same signal in approximately 5,000 combined patients, i.e., that hyperglycemic management decreases mortality and morbidity.

A single, large German study (VISEP), as yet unpublished, failed to show benefit with intensive insulin in 537 patients with severe sepsis (Brunkhorst et al. 2005). However, the experimental design failed to exclude confounding variables by not controlling for conventional aspects of sepsis care (antibiotics, resuscitation, mechanical ventilation). Because the study was stopped prematurely due to potential but unrealized harm from hypoglycemia, it is not surprising that no conclusive observations related to benefit could be made.

Large multi-national studies ongoing in Europe (GLUControl) and in Australia/New Zealand and Canada (NICE-SUGAR) together will target some 8,000 patients and should elucidate the actual benefits of intensive insulin. However, results of a United States Veterans Affairs Medical Centers database investigation (announced at the June 2006 American Diabetes Association annual meeting) may have put the entire issue to rest. To wit, this study of 216,775 critically ill patients from 177 mixed ICUs demonstrated that each incremental increase in blood glucose above 6.1 mmol/L increased mortality. Survival with normoglycemia increased in medical and in septic patients, not just in patients with cardiovascular or surgical diseases (Falciglia American Diabetes Association, June 2006).

Management of hyperglycemia has become a top priority in the care of critically ill patients, with the Joint Commission on Accreditation of Healthcare Organization, the Institute of Healthcare Improvement, the American Diabetes Association and The Volunteer Hospital Association all strongly advocating for its implementation.

The chief obstacles to implementation of rigorous, tight glycemic control are twofold: nursing "pushback" and fear of hypoglycemia. Pushback occurs because intensive insulin treatment requires frequent, often hourly, blood glucose monitoring; this practice is inherently labor intensive, placing significant demands on the bedside nurse. Protocolizing euglycemic management is a means of insuring standardized care, reducing variability and increasing the likelihood of hitting the target blood glucose range in the earliest time possible. Even with protocolization, studies have shown that daily fluctuations in blood glucose are common and significant (Finney et al. 2003; Zimmerman et al. 2004).

Hypoglycemia, defined as a blood glucose < 40-60 mg/dL [2.2-3.3 mmol/L], is now recognized to be frequent (see figure 1) and often severe

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(Vriesendorp et al. 2006; Kanji et al. 2004). Few if any irreversible consequences of hypoglycaemia have been published in the setting of intensive insulin, but such consequences simply may have been unobserved or unreported. Renal failure, because it lengthens the duration of action of insulin, and the unadjusted discontinuation of nutrition/feedings without a decrease in concomitant insulin administration are the two most common risk factors associated with hypoglycemia. Additionally, recent evidence suggests that “fingerstick” capillary blood tested by bedside glucometer may be frequently inaccurate, particularly in the hypoglycemic range during which the true blood glucose is actually underestimated (Kanji et al. 2005).

Looking to the Future

Many questions remain to be answered. What is the proper blood glucose threshold that must be maintained? It may well be that different types of patients require different thresholds of blood glucose to achieve a benefit. How can intensive insulin therapy be provided in the least laborious, nurse-intensive fashion? There will have to be improvements in bedside blood glucose monitoring. The holy grail of device technology undoubtedly will be the ability to continuously monitor patient blood glucose concentrations, perhaps using fiberoptic or infrared technology (Krinsley et al. 2005). Continuous monitoring will provide multiple benefits: first, it will permit smoother, timelier adjustments in insulin infusions to more quickly achieve the blood glucose endpoint; and second, it will provide early warning to caregivers about incipient hypoglycemia. This latter concern has been a flashpoint of debate in intensive care units that are balancing strict euglycemia against safety concerns for the patient. Continuous monitoring will be pivotal not only in measuring absolute blood glucose values, but more importantly in signalling emerging trends over time.

Published on : Thu, 15 Aug 2013