Glycemic Control in the Critically Ill and in Brain Injury

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GLYCEMIC CONTROL IN THE CRITICALLY ILL: OVERVIEW

The publication in 2001 of the now famous Leuven I trial (Van Den Berghe et al., 2001) showed that tight glycemic control in a population of surgical critically ill patients could improve survival, reduce multiple organ failure and nosocomial infection. This past decade as witnessed a great deal research dedicated to confirming these initial findings.

Leuven I (Van Den Berghe et al., 2001) unleashed a torrent of skepticism, excitement and investigation into tight glycemic control. Google searches of “tight glycemic control” and “intensive insulin” produce 80,900 and 334,000 results, respectively. After entering a new decade, where are we? There is a great deal that we do not know, in part, because this field of discovery has been disadvantaged by inconsistencies in research methodology. Among differences in the studies are casetype selection, targeted ranges of blood glucose, inconsistency in the frequency of blood glucose monitoring, variability in the accuracy of glucometer devices used, in the methods used to define euglycemia, whether insulin dosing was driven by paper protocol or software algorithm and nonstandardization in caloric intake. Starting with Leuven I, all of the prospective studies conducted to date are vulnerable to significant methodologic criticisms (Nasraway Jr. and Rattan, 2010). We also really have no conclusive understanding on the biologic plausibility to explain how intensive insulin would decrease death or organ failure or nosocomial infection. Is it through anti-inflammatory pathways, because insulin is a vasodilator that may increase microperfusion, or by other unrealized mechanisms of action? In some ways, the scientific evolution of this field resembles that of Sepsis research from 1985-2005, in which the study of anti-inflammatory compounds was severely hindered by lack of standardization in the total treatment for patients with severe sepsis, with too many confounding and uncontrolled variables (Nasraway Jr., 1999).

After all of these studies, what do we actually know? What are the consistent threads? This is what we know with certainty:

1. Hyperglycemia is bad. Falciglia (2009) convincingly showed in an analysis of 259,040 ICU patients that hyperglycemia (glucose > 110 mg/dL) was associated with mortality independent of illness severity, type of ICU or length of stay. Consistent with the findings of others, the two-thirds of patients who are nondiabetic benefit more from insulin than do diabetics.

2. Hypoglycemia is bad. An incidental and constant observation from many studies is that severe hypoglycemia (glucose < 40 mg/dL) in a population of patients by logistic regression is associated with a 6-fold increase in death (Griesdale et al., 2009). It would not be surprising to find with additional study that even mild hypoglycemia has long lasting but subtle neurologic consequences that are not clinically evident or

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measured. Hypoglycemia is particularly detrimental to the brain, which neither pro-
duces nor stores glucose, but is entirely dependent upon cerebral glucose delivery.

3. Critically ill patients typically sustain large swings in blood glucose, even with insulin administration (Finney et al., 2003). Sustaining the blood glucose within a target range in a hypermetabolic patient with changing gluconeogenic drivers in a 24 hour day is enormously challenging, frequently outstripping the crude tools used at the bedside to measure blood glucose and respond to its variation in concentration.

4. Software-driven insulin dosing is better than paper-driven insulin protocols. Software integrates all of the glucose measurements and all of the previous insulin adjustments to determine the next best insulin dose. Software appears to reduce glucose variability and sustain glucose within the target range for prolonged periods of time (Juneja et al., 2009). There are now many software programs tested and/or available.

5. Handheld blood glucometers, originally intended for use by Type I diabetic outpa-
tients in the 1980s, are not accurate enough in the ICU environment (Kanji et al., 2005), and are very laborious to use. In the USA, the Food and Drug Administration in March of 2010 hosted a public inquiry into glucose meters, after which it is redefin-
ing what it will accept in the way of accuracy by blood glucose measurement de-
vices in the hospital setting going forward (2010). It has asked the international stan-
dards body to reset its limits for accuracy for glucometers. Current generation
handheld devices now in use will not make the cut.

6. The more frequent the blood glucose measurement, even with handheld glucometers, the less hypoglycemia experienced by patients and the tighter the glycemic control (Cook et al., 2008b). Frequency is crucial, however laborious it may be.

**What can we expect going forward?**

We can expect that the world will continue to use intensive insulin, but that the range that defines “tight” will be narrowed as it becomes more achievable. We can expect that there will be more emphasis on defining hypoglycemia, and in avoiding it with greater rigor. We can expect a movement towards insulin-dosing software, as the development of many programs appears to be simple, and competition will force down the cost of purchase and use. Software-insulin dosing has hidden advantages: it forces more blood glucose monitoring and also provides an instant database for analysis. We will someday be using glucometers that are engineered to be more accurate, especially in the hypoglycemic range, avoiding pitfalls in today’s instruments due to chemical interferences and specific disease conditions. Importantly, these devices will be continuous or near continuous, and by their nature will be less arduous. At the same time, manufacturers will need to make these devices affordable, or their uptake will be slowed. The frequency of blood glucose measurements by these devices will dramatically make safer the continuous administra-
tion of insulin.

Improving the accuracy of blood glucose measurements and standardizing the determination of insulin dosing with better methods will produce better quality research, synergizing global convergence on tight glycemic control, reduced glucose variability and better patient out-
comes.
GLYCEMIC CONTROL IN ACUTE BRAIN INJURY

Research into blood glucose management for patients with acute brain injury has been a representative microcosm of the larger field of glycemic control in the critically ill. Numerous studies have demonstrated that hyperglycemia in patients after stroke or other forms of acute brain injury is deleterious and worsens outcome (Bilotta et al., 2009; Cook et al., 2008a). Van den Berghe and colleagues (2005) retrospectively analyzed 63 patients from their original study; these patients had sustained isolated brain injury. Patients who had been randomized to intensive insulin therapy sustained decreases in the mean and maximal intracranial pressure. This, in turn, was associated with improved long-term recovery in comparison with those patients who had received conventional glycemic management.

However, a very important study examined the effects of tight glycemic control on cerebral glucose metabolism after severe brain injury. Tight glycemic control, even without systemic hypoglycemia, was associated with decreased brain glucose and increase in brain energy crises (Oddo et al., 2008). The latter was associated with an increased in death. The study has raised questions about the value of very tight glycemic control.

There have since then for prospective randomized controlled trials examining the benefits of intensive insulin in patients with subarachnoid hemorrhage (Bilotta et al., 2007), traumatic brain injury (Bilotta et al., 2008; Coester et al., 2010), or in a heterogeneous group of mechanically ventilated critically ill neurologic patients (Green et al., 2010). Overall, there were no differences in the rates of infection, neurologic recovery, or in mortality rate. The results of these studies have frustrated advocates for very tight glycemic control.

It is clear that severe hyperglycemia in patients with acute brain injury is deleterious. However blood glucose concentrations which are normal, but tightly regulated, may also be deleterious with a reduction in brain glucose availability. As a result the best overall recommendation has been to achieve a broader range of glycemic control while avoiding hypoglycemia in this especially sensitive population. Bilotta et al (2009) have suggested a blood glucose concentration target range of 80-155 mg/dL.
REFERENCES


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