

Glucose Control in the Intensive Care Unit: A Roller Coaster Ride or a Swinging Pendulum?

Richard J. Comi, MD

Many studies of tight control of blood glucose in critically ill patients are associated with poor outcomes. However, randomized studies of tight glucose control in patients admitted to coronary care or surgical intensive care units showed a reduction in mortality rates; supported by recommendations from professional organizations, many intensive care units implemented protocols for tight glucose control. More recent studies in medical intensive care units did not confirm the benefits of tight control, however, and the most recent study suggests that tight control increases mortality

rates. Furthermore, tight control significantly increases episodes of hypoglycemia. The sum of the recent literature suggests that a degree of glucose control lies between the extremes of the adverse outcomes related to poor glucose control and those related to overly aggressive glucose control.

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For author affiliation, see end of text.

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Practice guidelines for some conditions seem to be on a roller coaster. The guidelines recommend a practice, but within a few years the evidence changes, and then they recommend against the practice. The sudden shift in clinical practice away from the use of hormone replacement therapy in postmenopausal women after the report of the Women's Health Initiative randomized trial is a case in point (1). In fact, the evidence base does change rapidly. A study of 100 quantitative systematic reviews showed that the evidence changed enough to alter the conclusions of a review at a median 5.7 years after its publication (2).

The evidence base for tight glucose control in the intensive care unit (ICU) is also changing rapidly. The situation seems similar to the postmenopausal hormone replacement example. Common features include plenty of circumstantial evidence, a firmly entrenched assumption that an intervention is valid and easily implemented, and reputable guidelines that recommend the intervention. However, the evidence base for glucose control in ICU patients better resembles a swinging pendulum rather than a roller coaster. In this commentary, I will develop the case that the evidence is oscillating—and approaching—a “sweet spot.”

The circumstantial evidence for tight glucose control in the ICU seems compelling (3). Pathophysiologically, glucose can be seen as a marker of the function of overall metabolism and the anabolic effects of insulin. A long-held belief is that increased catabolism is detrimental to severely ill patients (4). Glucose concentrations, whether on admission or in the postoperative period, or the mean glucose concentration in the hospitalized patient, are directly associated with adverse outcomes, such as longer stay, readmission, and mortality (5–7). Moreover, elevated glucose concentrations at the time of a severe illness are associated with worse long-term outcomes, such as risk for mortality and congestive heart failure at 1 year after myocardial infarction, or degree of disability after stroke (8, 9). No evidence suggests that elevated concentrations are a salutary response to severe illness. Efforts to control blood glucose after cardiac surgery markedly reduced sternal wound infections compared with historical controls (10). Taken together,

the evidence, although circumstantial, suggested that blood glucose control in the hospital might significantly improve outcomes. It was a short leap to imagine that the sickest patients—those in the ICU—would have the greatest benefit.

Randomized clinical trials on glucose control in critically ill patients were first reported in 1995. These studies were done at a time when physicians did not place a high priority on glucose control in hospitalized patients. Physicians used a sliding scale to calculate insulin doses (the true purpose of the sliding scale is not to control glucose but to provide a contingency plan for insulin dosing so that nurses could decide the dose without needing to call the physician, which the sliding scale does admirably). Patients in the ICU with blood glucose concentrations over 11.1 mmol/L (200 mg/dL) were common. Few protocols tried to match insulin dose to nutritional intake, and no one tried to assess the effectiveness of these dosing schemes.

The DIGAMI (Diabetes Insulin-Glucose in Acute Myocardial Infarction) study was the first clinical trial of tight glucose control in the hospital. This randomized study compared intravenous insulin followed by multiple-dose insulin therapy versus standard care for patients with diabetes and acute myocardial infarction (8). Although the authors did not define their protocol, attentive control of blood glucose from the time of admission to the post-discharge period reduced mortality at 1 year by 26%. In 2001, a Belgian group performed the first large randomized trial of tight glucose control in critically ill patients in a surgical intensive care unit. Most patients were recovering from coronary artery bypass surgery (11). The authors enrolled anyone with elevated glucose concentrations, not just patients with diabetes. Tight control dramatically re-

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duced the mortality rate from 8% in the control group (in which the glucose control target was 10.0 mmol/L [<180 mg/dL]) to 4.6% in the normal glucose-control group (in which the glucose control target was 6.1 mmol/L [<110 mg/L]). Of note, the glucose control targets for all patients—diabetic or nondiabetic—were those typically set for nondiabetic patients. Although most diabetologists believed that tight glucose control would help, they were surprised by magnitude of the benefit. At that point, the pendulum was at its apogee on the side of tight glucose control, and major organizations issued guidelines endorsing tight glucose control in the ICU.

However, when the Belgian group applied their glucose-control protocol to medical ICU patients, the results were very different. The mortality rate in the tight control group was lower in patients who stayed in the ICU for 3 or more days but higher in those who stayed in the ICU less than 3 days (12). Furthermore, the benefit was much smaller than that seen in the Belgian group's study of patients in the surgical ICU: a 6% reduction in mortality in patients with longer stays in the ICU rather than the 42% reduction seen in the surgical ICU. In a study of tight glucose control in patients with sepsis, the authors followed the Belgian study's protocol for glucose control, achieved lower glucose concentrations in intensively treated patients, and found no decrease in the mortality rate (13). A meta-analysis of studies of tight glucose control in ICUs found little benefit and an increased risk for hypoglycemia (14). With this meta-analysis, one could envision the pendulum swinging past the neutral point between tight control and usual control. However, the next study—NICE-SUGAR (the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation)—gave the pendulum a strong push toward the case against tight glucose control.

The NICE-SUGAR trial was a very large (6104 patients) multicenter trial (15). In theory, a multicenter trial provides a realistic appraisal of the effects of a glucose control protocol in the real world of practice, because implementation will inevitably vary from site to site. The NICE-SUGAR trial compared the outcomes of 2 strategies for patients in the medical ICU: keeping blood glucose concentrations below 6.7 mmol/L [120 mg/dL] versus keeping them in the range of 7.8 to 10.0 mmol/L [140 to 180 mg/dL]. The protocol achieved substantially lower glucose concentrations in the intensive control group, and tight control did not improve outcomes. In fact, mortality was slightly but statistically significantly higher in patients treated with tighter glucose control (27.5% vs. 24.9%). The authors wisely did not speculate about why the study showed net harm but identified some key hypotheses to test. In an editorial that accompanied the publication of this trial, Inzucchi and Seymour (16) point out that the control group in this study had an average glucose concentration of 7.8 to 10.0 mmol/L [140 to 180 mg/dL], not the concentrations of 10.0 to 11.1 mmol/L [180 to 200 mg/dL]

in previous studies (16). They speculated that better glucose control in the control groups might have improved outcomes to a point at which it was impossible to measure a significant benefit from even tighter control. They also point to other differences in the NICE-SUGAR trial compared with previous studies that may have affected outcome, such as early nutritional support provided to patients in the Belgian studies. The authors acknowledged the ongoing debate about the importance of tight control in sick patients but argued that we should not retreat to conventional wisdom of the 1980s that control of glucose was not important.

Those who seek guidance from these trials—with their disparate results about benefits of tight glucose control—should examine what was found about the harms of tight control. All recent studies of tight control have reported increased rates of significant hypoglycemia. These studies defined hypoglycemia as blood glucose concentrations less than 40 mg/dL. The rate of hypoglycemia in the tight control groups in the ICU-based studies varied from 7% to 20%; the rate in the control groups has been as low as 0.5%. Severe hypoglycemia increases stress hormone levels in relatively healthy patients. We don't know whether hypoglycemia has the same effect in severely ill persons who already have increased levels of epinephrine, cortisol, and growth hormone. Increases in these hormones or, conversely, failure to increase these hormones in response to additional stress, might cause adverse events in desperately ill patients. From such studies as ACCORD (Action to Control Cardiovascular Risk in Diabetes), we are learning that increased rates of severe hypoglycemia events are associated with increased mortality in patients with significant cardiac disease (17), but these studies cannot show that hypoglycemia precipitates the adverse event. Until more definitive analyses of the relationship of hypoglycemia and adverse outcomes in ill patients are available, I believe that we must avoid tight control protocols that cause increased rates of hypoglycemia. This approach leaves open the possibility of reinvestigating the benefit of very tight control when and if improved technology can promise safety from hypoglycemia.

I believe that this literature is telling us that there is a glycemically "sweet spot," in which the patient is safe from harm of hypoglycemia and protected from the danger of severely deranged metabolism during illness. Of course, we have no proof that it exists. We lack definitive evidence that hypoglycemia causes increased mortality and that reducing blood glucose concentrations improves outcomes. However, both of these suppositions are testable. Indeed, the NICE-SUGAR trial sets a good standard for glucose control: maintenance of glucose concentrations below 10.0 mmol/L [180 mg/dL] with a 0.5% incidence of hypoglycemia. The Belgian studies suggest that keeping the average blood glucose concentration near 11.1 mmol/L [200 mg/dL] increases the risk for adverse outcomes more than tighter control does. We do not know whether keeping blood

glucose concentrations below such targets as 8.3 mmol/L [150 mg/dL] improves outcomes compared with targets less than 10.0 mmol/L [180 mg/dL], but the hypothesis is safely testable. We also do not know whether the presence, severity, and duration of diabetes affect the benefit that we can expect from tight control.

Although this commentary may appear to be a cautionary tale, it really is a tale of the medical literature and its real-time impact on clinical practice. The Belgian study results staked out the extreme therapeutic position—near-normoglycemia in the ICU in diabetic and nondiabetic patients—and subsequent trials have refined the clinical debate and softened the therapeutic targets. We now have a better idea of the safety limits of our current technology for glucose control in the community (ACCORD) and the ICU. The pendulum is now suspended between the indifference to glucose control of the 1980s and the extreme tight control position of the 1990s. In the future, we can expect the amplitude of the pendulum's excursions to decrease steadily as we approach the glycemic “sweet spot.”

From Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire.

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Requests for Single Reprints: Richard J. Comi, MD, Dartmouth Hitchcock Medical Center, Hitchcock Clinic, 1 Medical Center Drive, Lebanon, NH 03756.

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