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Intensive Insulin in Intensive Care

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Among the critically ill, elevations in blood glucose, a marker previously ignored or described as adaptive, became a major therapeutic target after a 2001 study indicated a mortality benefit of intensive insulin therapy among patients in a surgical intensive care unit (ICU).[1] Concern has arisen about that study because of the relatively high mortality in relation to the severity of illness among patients in the control group; the frequent administration of parenteral calories to critically ill patients, a practice that is uncommon at other centers; a preponderance of patients who had cardiac surgery in the single center where the study was performed; and the fact that in such studies blinding of the investigators is nearly impossible.[2] Despite these concerns, aggressive control of blood sugar levels became widely accepted and, to some extent, a benchmark for the quality of ICU care. In this issue of the *Journal*, the same authors who reported on the use of intensive insulin therapy in the surgical ICU report on a trial of this therapy in a medical ICU[3]; the results are somewhat surprising.

Both the previous study in a surgical ICU and the present study, in a medical ICU, were essentially unblinded. In both studies, the majority of the patients received substantial amounts of parenteral calories. The new study was designed so that all 1200 patients who underwent randomization were predicted to stay in the ICU for at least three days. Although the study must be considered negative on the basis of the intention-to-treat analysis (rate of death during intensive care, 26.8 percent in the conventional-treatment group vs. 24.2 percent in the intensive-treatment group; P=0.30), the subgroup analyses are interesting. The greatest benefit was seen among the 767 patients who actually remained in the medical ICU for at least three days — a finding similar to the benefit in the previous study. Notably, among patients whose stays in the ICU were shorter (that is, those who were predicted to need but did not actually require three days of intensive care), there was an apparent increase in mortality among those receiving intensive insulin therapy (56 deaths), as compared with those in the conventional-treatment group (42 deaths). Unfortunately, there is no easy way to predict the duration of a patient's stay in the ICU; therefore, it remains unclear which patients should receive intensive insulin therapy as they enter the ICU.

Imbalances were present at randomization, and statistical adjustments for mortality may not fully account for differences in the severity of illness because of residual confounding. However, if the poor outcome among patients staying in the ICU less than three days is reproducible, there are several potential explanations. Insulin has pluripotent effects and may induce deleterious consequences not just from hypoglycemia but also through other biologic actions.[4,5] Indeed, hypoglycemia was an independent predictor of death in the present study; thus, the theory of short-term, adaptive elevations in blood sugar levels, as described historically, may actually have some merit. A probable explanation is that intensive insulin therapy itself might act as a type of metabolic stress test. If one adopts this view, then the development of hypoglycemia could be taken to reflect a failure of the secretion of counterregulatory hormones, such as epinephrine, glucagon, cortisol, and growth hormone, which could prevent hypoglycemia.[6,7] Lack of physiological reserve in various hormonal

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systems probably portends a poor prognosis, as with relative adrenocortical insufficiency in sepsis.[8,9] Thus, the effect of intensive insulin therapy may have been to unmask patients in whom counterregulatory hormones such as catecholamines could not be released (i.e., those with autonomic failure), rather than demonstrating a harmful effect of intensive insulin therapy or hypoglycemia itself.

The potential issue of hypoglycemia deserves attention. Because the use of aggressive parenteral nutrition varies among ICUs, one could predict that hypoglycemia would be more common in ICUs that use less aggressive nutritional support. Although episodes of hypoglycemia (defined by the authors as a level of 40 mg per deciliter [2.2 mmol per liter] or less) did not result in seizures, the implications of such episodes and of more moderate hypoglycemia for long-term neurocognitive functioning have not been assessed adequately in patients who are critically ill.[10]

Although an APACHE II (Acute Physiology and Chronic Health Evaluation) score is far from an ideal marker of the severity of illness, the mortality of 53 percent among control patients in the conventional-treatment group seems to be high for the apparent severity of illness. Some skeptics have suggested that parenteral nutrition produces substantial morbidity and that intensive insulin may serve, in part, to offset some of this associated risk. However, a review of the literature on total parenteral nutrition suggests that a large proportion of the apparent morbidity is mediated by hyperglycemia. Although total parenteral nutrition has been implicated in yeast infection, some data suggest that the best predictor of nosocomial candidemia is the presence of hyperglycemia, not the use of total parenteral nutrition.[5] Thus, one could logically argue that, in an era of tight glycemic control, total parenteral nutrition deserves a reappraisal. Although enteral nutrition has been assumed to be superior to parenteral nutrition, credible data supporting this assumption are sparse.[11] In fact, some recent data suggest important complications, including those that result from aspiration, with the provision of early enteral nutrition.[12] Thus, metabolic support, by both safely providing adequate calories and controlling sugars, may be the most appropriate strategy in the treatment of the critically ill.

More optimistically, Van den Berghe and colleagues have shown the potential for a statistically significant improvement in morbidity, including such outcomes as renal failure, with tight glycemic control among all patients who underwent randomization.[3] As clinicians struggle to understand the best way to manage blood glucose levels in the ICU, one thing is clear: the days of ignoring blood sugar levels or tolerating marked hyperglycemia in the ICU (which was commonplace even five years ago) are over. As we await the outcome of ongoing large-scale, multicenter, randomized trials examining the issue of glycemic control in the ICU (the Glucontrol study and the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation [NICE-SUGAR] study[2]), physicians will need to interpret the available data in the context of their clinical practices.

One option would be to withhold intensive insulin therapy until conclusive data are available. Another would be to administer intensive insulin therapy to all critically ill patients on the assumption that more patients will benefit than will be harmed. In my opinion, a reasonable approach would be to provide adequate exogenous insulin to achieve target glucose values of less than 150 mg per deciliter (8.3 mmol per liter), at least during the first three days in the ICU. If critical illness persists beyond three days despite the provision of other proven therapies and resuscitation, a goal of normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) could then be considered, to maximize the potential benefits. This approach would allow time for a gradual increase in calories in enteral feedings, which should minimize hypoglycemic complications. According to this approach, on the one hand, patients whose stay in the ICU is short, such as those who might have been harmed in the study by Van den Berghe and

colleagues, would not receive aggressive glucose control unnecessarily. On the other hand, those staying longer in the ICU would eventually attain euglycemia, which appears to be necessary to achieve the maximum benefit of intensive insulin therapy.[1] Although this approach requires further study, it would seem to be a reasonable strategy that incorporates the best available evidence until more definitive data emerge.

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