Extolling the Virtues of Euglycemia

Reviewed by Meeta Sharma, MD

STUDY

van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in critically ill patients. *N Engl J Med* 345:1359–1367, 2001

SUMMARY

Design. A prospective, randomized, controlled trial, involving adults receiving mechanical ventilation who were admitted to the surgical intensive care unit.

Methods. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose between 80 and 110 mg/dl) or conventional treatment (infusion of insulin only if blood glucose exceeded 215 mg/dl and maintenance of glucose between 180 and 200 mg/dl). In the intensive treatment group, the insulin drip dose was adjusted according to a strict algorithm by a team of intensive care nurses assisted by a study physician who was not involved in the clinical care of the patients.

Subjects. By the end of a 1-year enrollment period, 1,548 patients were included in the study. All were adults receiving mechanical ventilation and admitted to the surgical intensive care unit. Patients with do-not-resuscitate orders were excluded from the study. Thirteen percent of the subjects had a history of diabetes, and 5% were receiving treatment with insulin. On admission, 75% had blood glucose levels exceeding the upper limit of the normal range (110 mg/dl) after an overnight fast. Twelve percent had blood glucose levels in the nonfasting diabetic range (>200 mg/dl).

Hypothesis. Hyperglycemia or relative insulin deficiency (or both) during critical illness predisposes patients to complications such as severe infections, polyneuropathy, multiple organ failure, and death. Attaining euglycemia through intensive insulin therapy will reduce mortality and morbidity among critically ill patients.

Results. The study was terminated early because of the impressiveness of the results. Intensive insulin therapy reduced mortality during intensive care from 8% with conventional therapy to 4.6% ($P < 0.04$, with adjustment for sequential analyses). The reduction in mortality was particularly striking among patients who remained in the surgical intensive care for more than 5 days. For these patients, the mortality rate fell from 20.2% with conventional treatment to 10.6% with intensive insulin therapy. The greatest reduction in mortality was for deaths caused by multiple organ failure with a proven septic focus.

Intensive insulin therapy also reduced:

- overall in-hospital mortality by 34%;
- bloodstream infections by 46%;
- acute renal failure requiring dialysis or hemofiltration by 41%;
- the median number of red cell transfusions by 50%; and
- critical illness polyneuropathy by 44%.

Patients receiving intensive therapy were also less likely to require prolonged mechanical ventilation and intensive care.

Conclusion. In a surgical intensive care unit, intensive insulin therapy to maintain blood glucose at or below 110 mg/dl reduced morbidity and mortality among critically ill patients.

COMMENTARY

Hyperglycemia associated with insulin resistance is commonly seen in critically ill patients—even in those without a history of diabetes.[1–3] The well-defined pathophysiology of the effects of intercurrent illness and surgery on carbohydrate metabolism can lead to hyperglycemia.[4]

Hyperglycemia in critically ill patients has been reported to lead to complications such as increased susceptibility to infections, critical illness polyneuropathy, and failure of vital organs, although data from controlled trials are incomplete. In nondiabetic patients with ongoing critical illnesses, high serum levels of insulin-like growth factor 1, which reflect an impaired response of hepatocytes to insulin, increase the risk of death.[5]

The study by van den Berghe shows that tight glucose control affects both morbidity and mortality in the surgical intensive care unit. These impressive results led researchers to terminate the study early.

One of the study's limitations was that it was not blinded because insulin dose adjustments required blood glucose monitoring. Additionally, the patient population was limited to those undergoing surgery (most frequently cardiac surgery) at a single institution. Therefore, it would be unwise to extrapolate the results to patients in medical intensive care units or to those with other types of

critical illness.

As noted above, mortality in the intensive insulin therapy group was significantly lower than in the group receiving conventional therapy. This benefit was greatest among patients who remained in the surgical intensive care setting for more than 5 days and was achieved primarily through a reduction in multiple organ failure with a proven septic focus. Overall in-hospital mortality was one-third lower in the intensive treatment group. Morbidity (such as renal dysfunction and the need for red cell transfusion) was also lower in this group.

There are multiple possible reasons why euglycemia is associated with such a bonanza of benefits. The authors of the study hypothesize that insulin resistance and hyperglycemia are directly related to adverse outcomes. Earlier studies with recombinant human growth hormone in critically ill patients were a miserable failure; this therapy resulted in a doubling of the mortality rate in these patients.[6] Growth hormone is well known to aggravate insulin resistance and hyperglycemia. Hyperglycemia has deleterious effects on macrophage and neutrophil function. Additionally, there are insulin-induced trophic effects on mucosal and skin barriers. Not surprisingly, the patients in the intensive insulin therapy group had fewer episodes of septicemia and a decreased need for prolonged antibiotic therapy. Other studies involving nondiabetic patients have found that plasma glucose level on admission is an independent predictor of prognosis after myocardial infarction[7] or of the need for coronary-artery bypass grafting.[8]

For busy clinicians, this study yields a few important take-home points:

- Therapeutic interventions aimed at improving the metabolic derangements associated with critical illness, specifically hyperglycemia, are beneficial and cost-effective in the surgical intensive care unit.
- Tight glycemic control can be attained easily with an insulin drip, which can be titrated by a group of well-trained nurses following a rigid algorithm, and with minimal adverse effects to patients (and health care providers!).
- Further studies are necessary to determine whether intensive insulin therapy in patients with hyperglycemia in a *medical* intensive care setting will have a similar positive effect on both morbidity and mortality.

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