

# First do no harm...Hypoglycemia or hyperglycemia?

*Dr. Van den Berghe has received a research grant from Novo Nordisk to the University of Leuven. Copyright © 2006 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins DOI: 10.1097/01.CCM.0000242913.88721.6E 2843 Crit Care Med 2006 Vol. 34, No. 11*

Hyperglycemia is common in intensive care unit (ICU) patients, and severity of hyperglycemia has been repeatedly associated with adverse outcome of a variety of illnesses including critical illness (1). Traditionally, insulin was not administered until blood glucose exceeded 180–200 mg/dL based on the rationale that such mild increases were not deleterious and tighter control might be complicated by life-threatening hypoglycemia.

In 2001, our large, randomized, controlled study revealed that intensive insulin therapy to maintain normal blood glucose levels (<110 mg/dL) saves lives and prevents debilitating and expensive complications in a predominantly surgical ICU population (2). The level of blood glucose control rather than the insulin dose explained the benefits (3). This study was followed by a publication by Krinsley (4), who reported that when intensive insulin therapy is implemented in real life intensive care, the benefits on morbidity and mortality can be largely reproduced.

Our subsequent randomized, controlled study of intensive insulin therapy in a very ill medical ICU population, with a high co-morbidity and a high risk of death, confirmed the morbidity benefits and, when blood glucose control is continued for at least a third day, also the reduced mortality (5). Furthermore, analysis of healthcare resource utilization clearly revealed substantial cost savings (6, 7). Hence, since the 2001 publication, and strongly encouraged by the Krinsley (4) article, many centers have started to implement blood glucose control in their ICUs.

Blood glucose control with insulin comes with risk of hypoglycemia. Despite this risk, tight blood glucose control is nowadays advised for all patients with diabetes, as it is clear that glucose toxicity plays a major role in diabetic complications (8, 9). Intensive insulin therapy in predominantly nondiabetic ICU patients also increased the risk of hypoglycemia, from 0.8% to 5.2% in the surgical Leuven study (2) and from 3.1% to 18.7% in the medical Leuven study (5). In both these studies, hypoglycemia occurred more in patients who did not survive. However, as hypoglycemia was associated with mortality in both insulin therapy groups, it remained unclear whether this association was casual or causal. More importantly, among hypoglycemic patients, mortality was lower in the intensive than in the conventional insulin therapy group (5). Fears of hypoglycemia and its imagined consequences, based on deeply rooted emotional belief rather than evidence, explain why hypoglycemia is often considered more dangerous than hyperglycemia in the critically ill.

Hypoglycemia is generally defined arbitrarily as blood glucose of <50 mg/dL with neuroglycopenic symptoms or of <40 mg/dL in the absence of symptoms. Clinically significant hypoglycemia is characterized by Whipple's triad: a) symptoms of neuroglycopenia, b) simultaneous blood glucose of <40 mg/dL, and c) relief of symptoms with the administration of glucose. All three criteria should be met to establish a diagnosis of hypoglycemia, at least outside the ICU, as a precipitous fall from hyperglycemia to euglycemia in diabetes can produce hypoglycemic symptoms (10) and because asymptomatic hypoglycemia with glucose levels as low as 30 mg/dL (1.7 mmol/L) can occur during fasting in normal women and during pregnancy (11). In the ICU, however, sedation may mask symptoms of neuroglycopenia and counter-regulatory responses may be impaired, which complicates the diagnosis of hypoglycemia in this setting.

Thus, the clinical relevance of a brief hypoglycemic episode, independent of the illness severity, remains unclear. Dr. Vriesendorp and colleagues (12) are to be congratulated for their elegant study in this issue of Critical Care Medicine, in which they assess the effect of incidental hypoglycemia on outcome of critically ill patients. This study was performed in a mixed medical/surgical ICU, where relatively strict blood glucose control with insulin, targeting blood glucose levels between 80 and 140 mg/dL, had become the standard of care. The risk of hypoglycemia with this regimen was 6.9%. They studied 302 patients using a nested case control design, which is the correct method for answering this question in a clinical setting. Matching of

cases and controls was done for age, sex, severity of illness, and duration of ICU stay before the hypoglycemic event. They found no association between hypoglycemia and early (within 5 days of the event) or late (hospital) mortality. These findings held after correcting for insulin therapy. Furthermore, seizures were observed in only one patient and hypoglycemic coma observed in two. The authors acknowledge that the small sample size does not allow to completely exclude harm of hypoglycemia, but the data are quite reassuring. First, “do no harm” is indeed the basis of medical ethics. It has also been a favorite one-liner for those opposing intensive insulin therapy in the ICU. The occurrence of biochemical hypoglycemia has been considered the “harm” that should be balanced against lives saved with intensive insulin therapy.

Hypoglycemia has also been the reason to stop one trial on intensive insulin therapy (13). The data of Dr. Vriesendorp and colleagues (12) now provide evidence against using risk of hypoglycemia as the reason not to apply intensive insulin therapy. Results of multiple-center trials on tight blood glucose control in the critically ill and of studies on the most optimal level of blood glucose for different patient populations are still lacking. While we await those results, the current evidence, largely provided by the two Leuven trials and the implementation study by Krinsley, is in favor of controlling blood glucose levels in the ICU. Indeed, these studies showed that many lives were saved with this intervention, despite a higher prevalence of hypoglycemia.

Hyperglycemia is deleterious for critically ill patients. Dr. Vriesendorp and colleagues (12) have now shown that incidental, brief episodes of hypoglycemia, when picked up rapidly and treated appropriately, are not likely to cause serious harm. To safely target normoglycemia in ICU patients, intensivists and ICU nurses alike anxiously await accurate continuous blood glucose sensors. This vital variable should be added to the bedside monitor, with appropriate alarms and trends facilitating safe implementation of insulin therapy. Ideally, a closed-loop computerized system, with an accurate continuous sensor and an insulin pump linked via an automated algorithm, will also safeguard precious nursing time. Such devices are not yet available, and systems that are commercially available and performing relatively well for patients with diabetes do not perform at all in critically ill patients. Hopefully, validated systems will become available soon and find their way to the ICU.

#### REFERENCES

1. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78:1471–1478
2. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
3. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med*, 2003; 31:359–366
4. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; 79:992–1000
5. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
6. Van den Berghe G, Wouters PJ, Kesteloot K, et al: Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. *Crit Care Med*, 2006; 34:612–616
7. Krinsley JS, Jones RL: Cost analysis of intensive glycemic control in critically ill adult patients. *Chest* 2006; 129:644–650
8. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977–986
9. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:837–853
10. Boyle PJ, Schwartz NS, Shah SD, et al: Plasma glucose concentration at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med* 1988; 318: 1487–1492
11. Merimee TJ, Tyson JE: Stabilization of plasma glucose during fasting: Normal variation in two separate studies. *N Engl J Med* 1974; 291:1275–1278
12. Vriesendorp TM, DeVries JH, van Santen S, et al: Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006; 34:2714–2718
13. Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP Trial). *ClinicalTrials.gov* Web site. Available at: <http://clinicaltrials.gov/ct/show/NCT00135473;jsessionid=F5B6FADAA1BDFED5C34D3803B4001814?order<9>. Accessed August 30, 2006