EDITORIALS

Glucose Control in the ICU — How Tight Is Too Tight?

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For the past decade, hospitals have focused on the inpatient management of hyperglycemia, particularly in the intensive care unit (ICU). Extensive observational data have shown a consistent, almost linear relationship between blood glucose levels in hospitalized patients and adverse clinical outcomes, even in patients without established diabetes.[1] It has never been entirely clear, however, whether glycemia serves as a mediator of these outcomes or merely as a marker of the sickest patients, who present with the well-known counterregulatory stress response to illness. Several early studies suggested a clinical benefit from strict glucose control during critical care but were weakened by a retrospective design or other methodologic concerns.[2] In the *Journal* in 2001, in a study from a single center in Leuven, Belgium, Van den Berghe et al.[3] reported a dramatic 42% relative reduction in mortality in the surgical ICU when blood glucose was normalized to 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter) by means of insulin infusion in a prospective, randomized fashion (Table 1). Five years later, the same investigators reported findings from their medical ICU, revealing no mortality benefit from intensive glucose control, except in a subgroup requiring critical care for 3 or more days.[4]

Predominantly on the basis of the first of these two trials, many hospitals identified an opportunity to improve the quality of care and sought to institute intensive glucose control measures. Key stakeholders were identified, protocols and algorithms created, working groups appointed, educational programs developed, and consensus conferences held.[8] Professional organizations joined in this new, apparent mandate to reduce glucose levels not just in the critically ill, but in all hospitalized patients.[8] Even the Joint Commission offered commendation to hospitals demonstrating success in certain process-performance measures involving the care of inpatients with diabetes.[9]

Recently, two multicenter studies called into question the Leuven findings.[5,6] Both reported unacceptably high rates of hypoglycemia, and one trial was prematurely terminated for this reason.[6] By this time, an increasingly vocal chorus of critics had emerged, raising concerns about how stringent glucose targets actually needed to be.[10] Two meta-analyses on the subject reached disparate conclusions.[11,12]

Into this controversy comes the multinational Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (ClinicalTrials.gov number, NCT00220987), reported on in this issue of the *Journal*.[7] Intensive and conventional glycemic control were compared in a randomized, unblinded fashion in 6104 patients in the ICU, involving the use of intravenous insulin to achieve a blood glucose level of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter) or a level of 144 to 180 mg per deciliter (8.0 to 10.0 mmol per liter), respectively. The two treatment groups showed good glycemic separation, with a mean absolute difference of 29 mg per deciliter in overall blood glucose levels (not as widely separated as in the Leuven studies [47 mg per deciliter]).[13] The results of NICE-SUGAR contrast starkly with those of preceding trials, with an absolute increase in the rate of the primary end point, death at 90 days, with intensive glucose control (27.5%, vs. 24.9% with conventional control; odds ratio, 1.14; $P=0.02$). Not surprisingly, severe hypoglycemia occurred in more patients in the intensive-control group than in the conventional-control group (6.8% vs. 0.5%, $P<0.001$).

The strengths of the NICE-SUGAR trial include its large, multicenter framework, robust statistical analysis, use of a uniform and validated insulin protocol applied consistently across sites with resultant low rates of hypoglycemia, the broad and probably representative spectrum of critically ill patients, and use of a precise and clinically meaningful primary outcome — death — that is resistant to the vagaries of adjudication. The trial's weaknesses include its understandably open-label design and a small imbalance between groups with respect to receipt of corticosteroid therapy. In addition, 10% of patients randomly assigned to undergo intensive glucose control had study treatment discontinued prematurely. Because they were analyzed in the customary intention-to-treat fashion, the extent to which these patients, essentially crossovers, contributed to the difference in mortality between the two groups is as yet unclear. An additional unexplained and somewhat puzzling aspect of the results of the NICE-SUGAR study is the lack of any significant differences in the lengths of stay in the ICU or hospital or in organ-dysfunction rates between the two groups, despite the higher mortality in the intensive-control group.

The many differences between the Leuven trials[3,4] and the NICE-SUGAR trial may begin to explain their divergent conclusions. In contrast to the current multinational study, the Belgian investigations were performed from a single center, raising the possibility that local features of that population of patients or the approach to care might have influenced outcomes in ways that could not be replicated elsewhere. For example, parenteral hyperalimentation was the rule in Leuven, whereas enteral nutrition predominated in the NICE-SUGAR study. Perhaps more importantly, the Belgian studies compared intensive glycemic management to standard management at the time — reduction of glucose level only if the level is markedly elevated (>215 mg per deciliter [11.9 mmol per liter]). In contrast, the glucose level in the conventional-control group of the NICE-SUGAR trial was targeted at only a mildly elevated range — 144 to 180 mg per deciliter — and more than two thirds of these patients still received intravenous insulin to accomplish this goal.

Accepting these differences, how might we explain the surprising finding of a possible risk of death from intensive insulin therapy? Could insulin itself have direct deleterious effects (sym-

Table 1. Summary Data from Randomized Clinical Trials of Intensive Insulin Therapy in Critically Ill Patients.*

Trial Name (Source)†	No. of Patients	Type of ICU	Blood Glucose Level Targeted		Blood Glucose Level Achieved‡		Primary Outcome	Rate of Outcome		Odds Ratio (95% CI)
			Intensive Glucose Control	Conventional Glucose Control	Intensive Glucose Control	Conventional Glucose Control		Intensive Glucose Control	Conventional Glucose Control	
			milligrams per deciliter					*percent*		
Leuven 1 (Van den Berghe et al.[3])	1548	Surgical	80–110	180–200	103	153	Death in ICU	4.6	8.0	0.58 (0.38–0.78)
Leuven 2 (Van den Berghe et al.[4])	1200	Medical	80–110	180–200	111	153	Death in hospital	37.3	40.0	0.94 (0.84–1.06)
Glucontrol (Devos et al.,[5] Preiser J.C.: personal communication)	1101	General	80–110	140–180	118	144	Death in ICU	16.7	15.2	1.10 (0.84–1.44)
VISEP (Brunkhorst et al.[6])§	537	General	80–110	180–200	112	151	Death at 28 days	24.7	26.0	Not reported
NICE-SUGAR[7]	6104	General	81–108	144–180	118	145	Death at 90 days	27.5	24.9	1.14 (1.02–1.28)

* To convert the values for blood glucose to millimoles per liter, multiply by 0.05551. ICU denotes intensive care unit.
† ClinicalTrials.gov numbers are NCT00115479 for the Leuven 2 study, NCT00135473 for the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, NCT00107601 for the Glucontrol study, and NCT00220987 for the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study. The Leuven 1 study was not registered.
‡ The achieved blood glucose levels reported are the mean morning levels, except for those for the Glucontrol study, which are mean overall blood glucose levels.
§ The patients in the VISEP study were patients with sepsis. Although the odds ratio was not reported, it was reported that the two groups did not differ significantly in the rate of death at 28 days ($P=0.74$).

pathetic activation, sodium retention, or mitogenic actions)? Was the increased mortality simply related to hypoglycemia and resultant neuroglycopenia, which is difficult to detect in patients who are intubated and sedated? Did the well-recognized complexities of intensive management of glucose distract from other, ostensibly more important management practices in the ICU? Is stress hyperglycemia the body's proper response to illness, an attempt to shunt energy from temporarily unessential skeletal muscle to critical organs? Do all measured biologic perturbations due to illness require medical correction? For example, attempts to rectify elevated blood carbon dioxide levels in patients with certain forms of respiratory failure may actually increase the risk of adverse outcomes. This realization led to the now-widely-adopted therapeutic concept of permissive hypercapnia.[14]

The answer to these important questions must await post hoc analyses that the NICE-SUGAR study investigators are now obliged to conduct. Further exploration of the precise causes of death in the patients may be helpful. A per-protocol analysis (vs. intention-to-treat analysis) would be of great interest. Data inquiries stratified according to the development of hypoglycemia, duration of euglycemia, mean insulin dose received, and length of stay in the ICU may shed further light on the provocative results of the NICE-SUGAR study. Moreover, which subgroups of patients, if any, might still benefit from the more stringent levels of glycemic control will most likely require further study.

Clinicians, particularly those involved in critical care, are now left in something of a quandary. At many institutions, an infrastructure has emerged that facilitates the automatic and seamless use of insulin infusion in patients in the ICU. Should these efforts now be abandoned? Until further evidence becomes available, it would seem reasonable to continue our attempts to optimize the management of blood glucose in our hospitalized patients, especially to avert the extremes of hyperglycemia (which have acute effects on renal function, hemodynamics, and immune defenses) and also hypoglycemia (with its own, often more immediate and serious, consequences).

In retrospect, it may turn out that we have been overly enthusiastic in our attempts to attain euglycemia during critical care. (Similar and well-intentioned exuberance for rigid glucose targets in outpatient care was challenged this past summer by the jarring results from the Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial [NCT00000620].[15]) However, we would caution against any overreaction to the NICE-SUGAR findings. As noted, many hospitals have implemented refined insulin-infusion protocols and are achieving exemplary glucose control and clinical outcomes in their ICUs. The NICE-SUGAR study simply tells us that in cohorts of patients such as those studied, there is no additional benefit from the lowering of blood glucose levels below the range of approximately 140 to 180 mg per deciliter; indeed, for unclear reasons, there may be some risk that remains to be elucidated. Notwithstanding, it would be a disservice to our critically ill patients to infer from the NICE-SUGAR data that neglectful glycemic control involving haphazard therapeutic approaches (e.g., use of insulin "sliding scales") — all too common a decade ago — is again acceptable practice in our ICUs.

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1. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. Circulation 2005;111:3078-86.
2. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999;67:352-62.
3. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
4. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-61.
5. Devos P, Preiser JC, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the Glucontrol study. Intensive Care Med 2007;33:Suppl 2:S189.
6. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.
7. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.
8. ACE/ADA Task Force on Inpatient Diabetes. American College of Endocrinology and American Diabetes Association consensus statement on inpatient diabetes and glycemic control. Endocr Pract 2006;12:458-68.
9. Inpatient diabetes certification. Oakbrook Terrace, IL: The

Joint Commission. (Accessed March 6, 2009, at http://www.jointcommission.org/CertificationPrograms/Inpatient+Diabetes/.)
10. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA 2003;290:2041-7.
11. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials. Arch Intern Med 2004;164:2005-11.
12. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933-44.
13. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefits versus harm. Diabetes 2006;55:3151-9.
14. O'Croinin D, Ni Chonghaile M, Higgins B, Laffey JG. Bench-to-bedside review: permissive hypercapnia. Crit Care 2005;9:51-9.
15. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.

Prevention of Viral Sexually Transmitted Infections — Foreskin at the Forefront

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Three landmark randomized, controlled trials conducted in South Africa, Uganda, and Kenya from 2005 through 2007 demonstrated that adult male circumcision reduced the acquisition of human immunodeficiency virus (HIV) by 50 to 60%.[1-3] Complications associated with the procedure were rare and almost uniformly minor.[4] These findings were largely consistent with those of observational and ecologic studies in which adult male circumcision was associated with a lower HIV risk at both individual and population levels,[5] and mathematical models suggest that widespread circumcision could substantially reduce the HIV epidemic in high-prevalence heterosexual populations.[6] In 2007, the World Health Organization and the United Nations Programme on HIV/AIDS recommended that circumcision be promoted in areas with a high prevalence of heterosexually transmitted HIV, and donor agencies are now funding male circumcision programs in Africa.

In this issue of the *Journal,* Tobian et al.[7] report findings from the Ugandan trial on the effect of circumcision on the prevalence of human papillomavirus (HPV) infection and the incidence of herpes simplex virus type 2 (HSV-2) infection and syphilis. They found that adult male circumcision decreased the prevalence of HPV by 35%, reduced HSV-2 acquisition by 25%, and had no effect on the incidence of syphilis (which probably reflected a limited power to detect an effect). In previous reports from this trial, the Ugandan team reported that male circumcision reduced the occurrence of genital ulcers in men and genital ulcers, bacterial vaginosis, and trichomoniasis in female partners.[8,9] These findings agree with two recent studies from South Africa showing that circumcision reduced the prevalence of high-risk HPV and the incidence of HSV-2 by one third.[10,11] The results are also biologically plausible, since the foreskin may increase susceptibility to microabrasion and allows prolonged contact time between pathogens and nonkeratinized skin. These new data should prompt a major reassessment of the role of male circumcision, not only in HIV prevention but also in the prevention of other sexually transmitted infections.

Both HPV and HSV-2 infections are global health problems that far outstrip HIV infection in frequency and result in substantial morbidity and mortality. Roughly three quarters of U.S. adults have had at least one HPV infection. High-risk HPV types cause cervical cancer, the second most common cause of cancer deaths in women globally. In 2002, a total of 273,000 women worldwide died of cervical cancer, including 6500 in North America. Furthermore, approximately 536 million people (16% of the world's population between the ages of 15 and 49 years) and more than 25 million Americans (17% of the adult U.S. population) are infected with HSV-2. In adults, the infection is seldom fatal, but it is associated with substantial morbidity and is costly, generating almost $1 billion annually in direct medical costs in the United States alone. HSV-2 infection is associated with an increase in the risk of HIV infection by a factor of two to four, and up to 2800 neonatal herpes cases occur in the United States annually, often resulting in severe disability or death.

The data from these trials are consistent with the majority of observational studies of male circumcision and HPV infection. A meta-analysis