EDITORIAL

Glucose in the ICU — Evidence, Guidelines, and Outcomes

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Just over a decade ago, a single-center Belgian study showed that normalization of blood glucose in critically ill patients lowered hospital mortality by more than 30%.[1] Although subsequent studies were unable to reproduce these findings, the appeal of such a straightforward intervention was too great to resist: guidelines from professional organizations[2,3] were published, and editorial commentary[4] highlighted initiatives by the Institute for Healthcare Improvement, the Joint Commission on Accreditation of Healthcare Organizations, and the Volunteer Hospital Association that incorporated tight glucose control as a standard. Indeed, the prestigious Codman Award of the Joint Commission was presented in 2004 for a program of glycemic control in critical care that "saved" patients' lives.[5] Tight glucose control for critically ill patients was in vogue.

The publication in 2009 of a large international trial (the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation [NICE-SUGAR] study[6]) followed that of several negative trials. The NICE-SUGAR study, which involved more than 6100 patients, showed that tight glycemic control didn't decrease mortality — it increased it. Most guidelines were hastily revised. However, in the same year a separate study by Vlasselaers et al.[7] in pediatric intensive care unit (ICU) patients, most of whom had undergone cardiac surgery, showed that normalizing glucose decreased mortality from 6% to 3%, keeping open the question — at least in critically ill children.

The study by Agus et al.[8] now reported in the *Journal* provides new key data. A total of 980 children (up to 36 months of age) admitted to an ICU after cardiac surgery were randomly assigned to usual care or tight glucose control. The results are clear — there was no significant difference in the incidence of health care–associated infections (the primary outcome) or in any of the secondary outcomes, including survival. Moreover, the rate of hypoglycemia (blood glucose level <40 mg per deciliter [2.2 mmol per liter]) in the intervention group (3%) was far less than that previously reported (25%).[7] These findings contrast sharply with those of Vlasselaers et al.,[7] who found that secondary infections, length of stay, and mortality were reduced. Faced with contradictory results from two large clinical trials, how does the clinician know which results are correct?

First, biologic plausibility is important in attributing a survival benefit to a specific intervention. In the first pediatric ICU study, the additional deaths in the control group did not appear to be due to causes related to hyperglycemia,[7] a finding that suggests that the benefit was unlikely to be reproducible. The current authors, exclusively studying children after cardiac surgery, recognized that mortality in this population is usually due to prohibitive anatomy or surgical challenge; these are circumstances not amenable to correction by metabolic control.

Second, might differences in the target plasma glucose explain the discrepant findings? Agus et al. aimed for a higher target range of plasma glucose in the intervention group (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) than was targeted in the first pediatric study (infants, 50 to 80 mg per deciliter [2.8 to 4.4 mmol per liter]; children, 70 to 100 mg per deciliter [3.9 to 5.6 mmol per liter]).[7] Perhaps the lower glucose target is preferable? The weight of evidence is against

this, and if this target were used, the incidence and severity of hypoglycemia would have been greater, as previously reported.[7] Hypoglycemia is never to a patient's benefit, and its negative impact on neurocognitive development in children is of particular concern.

It seems that — as in adults — claims for survival benefit in critically ill children are incorrect. Furthermore, there is no reason why the effects of glucose control in children would be opposite to those in adults. In aggregate, the data do not support a basis for embarking on a pediatric megatrial.

Assuming the results of the NICE-SUGAR study[6] are generalizable, we must be grateful for the future lives saved by avoiding the practice of normalizing glucose in the ICU. At the same time, we should reflect on why a large study with mortality as an end point was needed in the first place.

Perhaps the most important question from a decade of studying glucose control in the ICU is how influential practice guidelines advocating tight glucose control were developed[2,3] yet turned out to be harmful — an issue noted in the lay press.[9] Guideline writers, reflecting on the experience, must accept that there are multiple sources of clinical knowledge[10] and must pay careful attention to trial characteristics — especially study reproducibility — in order to provide advice that genuinely helps clinicians. Clinicians in turn should use guidelines wisely, recognizing that no single source of knowledge is sufficient to guide clinical decisions.[10]

Is the door closed on studying glucose homeostasis in the critically ill? No, but it should be closed on the routine normalization of plasma glucose in critically ill adults and children.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article was published on September 7, 2012, at NEJM.org.

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DOI: 10.1056/NEJMe1209429