Glycemic Control: How Tight in the Intensive Care Unit?

Aaron J. Weiss, MD, and Jeffrey I. Mechanick, MD†*

Determining the optimal level of glycemic control in critical illness has proven difficult since the original Leuven study conclusions were published in 2001. Conflicting evidence, scientific methodologies, hospital cultures, and a-priori biases have challenged many clinical practice patterns. Specifically, the prioritization of patient safety has resulted in many practitioners changing from a glycemic control target of 80-110 mg/dL to a more liberal target of 140-180 mg/dL. However, a detailed examination of the evidence can provide a more population-specific glycemic control strategy. This position paper presents an approach for cardiac surgery patients in the intensive care unit (ICU) consistent with extant evidence and real-life variables. We argue that in the cardiac surgery ICU, glycemic targets may be as low as 80-110 mg/dL when formal intensive insulin therapy and nutrition support protocols are used with low rates of hypoglycemia, patient safety mechanisms, properly trained staff, and a supportive hospital administration all in force. Cardiac surgery ICUs that already follow this model may continue with 80-110 mg/dL blood glucose targets, whereas others may advance their blood glucose targets in a stepwise fashion: from 140 to 180 mg/dL to 110-140 mg/dL to 80-110 mg/dL, on the basis of their performance.

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In acutely critically ill patients with and without diabetes, "stress hyperglycemia" commonly occurs.[1] The traditional school of thought was that hyperglycemia provided the much-needed metabolic fuel for organ function during the stress response. However, with an increasing body of literature demonstrating a relationship between hyperglycemia and adverse clinical outcomes,[2-9] there is consensus that hyperglycemia is detrimental. A substantial amount of clinical research has sought to determine the optimal level of glucose for critically ill patients. At first, our knowledge base marched forward but then seemed to stumble, and now, the answer has proven somewhat elusive. In this position paper, we hope to clarify an important and timely issue: glycemic targets with intensive insulin therapy (IIT). We will argue for the use of strict glycemic control, which in select cardiac surgery intensive care unit (ICU) settings, can target a blood glucose (BG) level of 80-110 mg/dL.

THE EVIDENCE BASE

The first randomized controlled trial (RCT) testing whether IIT benefitted patients in the ICU was the Leuven study. This proof-of-concept study, conducted in a highly controlled surgical ICU (with predominantly cardiac surgery patients), demonstrated decreased morbidity and mortality in the IIT group.[10] A similar study published from the same institution on patients in a medical ICU setting found in-hospital mortality to be statistically insignificant between the control and intention-to-treat groups but did show a decrease in morbidities in patients in the IIT group who stayed in the ICU for longer than 3 days.[11] It was later shown in a pooled post hoc analysis of the 2 trials that IIT (target: 80-110 mg/dL) significantly reduced overall mortality in patients who stayed in the ICU for >3 days.

Not surprisingly, predicting length of stay in this cohort proved difficult.[12] Multiple RCTs were performed to validate these results, but for the most part, the investigators were unable to replicate the Leuven findings (Table 1). The authors of the Normoglycemia in Intensive Care Evaluation and Sur-

*Department of Cardiothoracic Surgery, Mount Sinai School of Medicine, New York, New York.
†Division of Endocrinology, Diabetes, and Bone Disease, Mount Sinai School of Medicine, New York, New York.
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Address reprint requests to Jeffrey I. Mechanick, MD, 1192 Park Avenue, New York, NY 10128. E-mail: jmechanick@aol.com.

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Table 1. List of Relevant Randomized Controlled Trials and Meta-Analyses That Focus on IIT in Various ICU Settings

Study	Year	Glycemic Target (T) vs Control (C)	Description and Results
Van den Berghe et al[10] (Leuven 1 trial)	2001	T: 80-110 mg/dL C: insulin infusion only if >215 mg/dL with maintenance between 180 and 200 mg/dL	Single institution RCT (n = 1548) in surgical ICU (63% cardiac surgery patients), parenteral nutrition supplemented early in ICU stay, IIT group had reduced ICU mortality, hospital mortality, bloodstream infections, acute renal failure, polyneuropathy, and mechanical ventilation time.
Van den Berghe et al[11] (Leuven 2 trial)	2006	T: 80-110 mg/dL C: insulin infusion only if >215 mg/dL with maintenance between 180 and 200 mg/dL	Single institution RCT (n = 1200) in medical ICU, IIT group had no benefit in mortality but had reduced acute renal failure, mechanical ventilation time, and time spent in the ICU and hospital, morbidity benefit was seen in patients with ICU stays greater than three d.
Arabi et al[34]	2008	T: 80-110 mg/dL C: 180-200 mg/dL	Single institution RCT (n = 523) in mixed ICU setting, IIT group had increased rates of hypoglycemia otherwise no difference in morbidity or mortality.
Brunkhorst et al[35] (VISEP trial)	2008	T: 80-110 mg/dL C: insulin infusion if >200-mg/dl maintenance between 180 and 200 mg/dL	Eighteen institution 2 × 2 factorial trial evaluating septic ICU patients (n = 537), trial was underpowered because of early termination from increased rates of hypoglycemia and adverse events in the IIT group.
Del Carmen De La Rosa et al[36]	2008	T: 80-110 mg/dL C: 180-200 mg/dL	Single institution RCT (n = 504) in mixed ICU setting, IIT group had increased rates of hypoglycemia otherwise no difference in morbidity or mortality.
Preiser et al[37] (GLUCONTROL trial)	2009	T: 80-110 mg/dL C: 140-180 mg/dL	Twenty-one institution RCT (n = 1101) in mixed ICU setting, IIT group did not have a benefit in mortality and had increased hypoglycemic episodes; trial was underpowered because of early termination for unintended protocol violations.
Finfer et al[13] (NICE-SUGAR trial)	2009	T: 80-110 mg/dL C: <180 mg/dL	Forty-two institution RCT (n = 6104) in mixed ICU setting, much later initiation of parenteral nutrition, IIT group had increased mortality mostly because of cardiovascular events, no difference in morbidity, and a higher rate of hypoglycemia.
Griesdale et al[28]	2009	T: both <110 mg/dL and <150 mg/dL C: >150 mg/dL	Meta-analysis examining 26 trials (n = 13,567) in mixed ICU setting, IIT had increased rates of hypoglycemia and no overall mortality benefit but a reduced mortality rate in surgical ICUs.
Marik et al[32]	2010	T: 80-110 mg/dL C: less strict glycemic control	Meta-analysis examining 7 trials (n = 11,425) in mixed ICU setting, IIT group had no overall benefit in mortality and increased rates of hypoglycemia, however, the IIT group supplemented with parenteral nutrition had reduced mortality.
Kansangara et al[38]	2011	T: 80-150 mg/dL but varied between studies C: <200 mg/dL but varied between studies	Meta-analysis examining 21 trials, IIT group showed no consistent evidence of benefit compared with less strict glycemic control, IIT group had an increased risk for hypoglycemia

ICU, intensive care unit; IIT, intensive insulin therapy; NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation; RCT, randomized controlled trial.