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CLINICAL TRIAL REPORT

Understanding the Clinical Issues Involved with Glycemic Control in the Intensive Care Unit

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Paper 1 Van Den Berghe G, Wouters P, et al.; Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med. 2001; 345:1359–1367*

Rating: •Of importance.

Keywords Glycemic control · Intensive insulin · Intensive Care Unit (ICU) · Hyperglycemia · NICE-SUGAR · Glycemic variability · Advanced Glycolytic End-Products (AGES)

Introduction: Critically ill patients, even those without a history of diabetes, commonly have issues with insulin resistance and hyperglycemia, which can lead to a wide variety of complications. Van den Berghe et al. [1] hypothesized that this hyperglycemia, or relative insulin deficiency, may lead to increased death or other complications, and it is unknown whether normalization of blood glucose with insulin affects these patients' outcomes.

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Aims: In this study, the authors performed a prospective, randomized, controlled trial at one center to determine whether normalization of blood-glucose levels with intensive-insulin therapy (IIT) reduces mortality and morbidity among critically ill patients.

Methods: This prospective, randomized, controlled study evaluated a population of adult patients on mechanical ventilation admitted to a surgical intensive care unit (ICU) at a single medical center. Upon admission, patients were randomly assigned to either an (IIT), or conventional-insulin therapy (CIT). They were stratified based on type of critical illness. On admission to the ICU prior to surgery, all patients were given continuous intravenous glucose (200–300 gm over 24 h). The CIT group received a continuous infusion of insulin that was started only if the blood-glucose levels exceeded 215 mg/dL, and adjusted to maintain glucose levels between 180 and 200 mg/dL. In the IIT group, the same insulin infusion was started if blood-glucose levels exceeded 110 mg/dL, and adjusted to maintain glucose in the normal range (80–110 mg/dL). At discharge from the ICU, all patients were treated conventionally and were nutritionally supported in the same fashion. The primary outcome was death from any cause during the ICU stay. Secondary outcomes included hospital death; ICU length of stay; prolonged ICU stay (greater than 14 days); need for ventilatory, vasopressor/inotropic, or renal support; neuropathy of critical illness; markers of inflammation; bloodstream infections; antibiotic use for more than 10 days; transfusion requirements,; and hyperbilirubinemia.

Results: A total of 1548 patients were enrolled in the study. The treatment and control groups were similar with respect to type of cardiac surgery; renal failure; pre-existing

diabetes; incidence of hyperglycemia; and delays in admission to the ICU. The mean intake of protein and nonprotein calories between the two groups was similar. For the IIT group, almost every patient required insulin, with morning-glucose levels maintained at 103 +/−19. For the CIT group, only 39% of the patients were treated with insulin, and the morning-glucose levels were maintained at 153 +/−33. For those patients treated with insulin in the CIT group, morning glucose was 173+/−33, while the nontreated CIT patients had a mean-glucose level (MGL) of 140+/−25. Hypoglycemia occurred in 39 patients in the IIT group, and was defined as a glucose level less than 40 mg/dL. Six patients in the CIT group met this definition. In the IIT study group, 35 patients (4.6%) died in the ICU, while 63 patients (8.0%) died in the CIT control group, with apparent risk reduction of 42%. In-hospital mortality was also reduced in the IIT group, with the greatest reduction in deaths due to multiple-organ dysfunction with a septic focus. The observed reduction in mortality occurred only in the long-stay cohort. A history of diabetes or hyperglycemia at the time of admission did not affect outcome measures. ICU length of stay was reduced in the IIT group compared to CIT controls, but not overall hospital length of stay. Significantly fewer patients in the IIT group required prolonged-mechanical ventilation or renal-replacement therapy. Inotropic and vasopressor support was not different between the groups. Hyperbilirubinemia was significantly lower in the IIT group. The IIT group had a 46% decrease of septic episodes, and their markers of inflammation were less abnormal than the CIT group. Too few patients in the IIT group were in the ICU long enough to be screened for polyneuropathy. Among those screened, patients in the IIT group were less likely to have polyneuropathy of critical illness. There was a positive, linear correlation in both groups between the mean-blood glucose level and risk for polyneuropathy.

Discussion: The authors concluded that IIT to maintain blood glucose at or below 110 mg/dL reduced morbidity and mortality among critically ill patients in the surgical ICU.

Paper 2 Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive Versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med.* 2009; 360:1283–1297.

Rating: •Of Importance.

Introduction: Over the past decade, there has been debate regarding the optimum target range for blood glucose in patients treated in the ICU. While the findings from the 2001 Van den Berghe [1] study suggested that strict-glucose control in the ICU setting could reduce morbidity and mortality, these results could not be uniformly reproduced by other investigators. In fact, a meta-analysis of 29 randomized trials found that intensive therapy did not lower mortality rates in the hospital when compared to conventional control [2]. However, most of the studies in the meta-analysis were small, singlecenter trials, with little uniformity on hyperglycemic control.

Aims: The authors designed the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial as a pragmatic randomized "effectiveness" trial to evaluate the impact of strict-glucose control on morbidity and mortality in a large, heterogeneous cohort of critically ill patients [3].

Methods: This multinational, multicenter, randomized controlled trial, involved 42 hospitals across Canada, the United States, Australia, and New Zealand. Patients were recruited if they were anticipated to stay 3 or more days in the ICU, with randomization occurring within the first 24 h of admission. IIT and CIT were compared in an unblinded fashion in 6104 patients in a mixed ICU setting. Intravenous insulin was used to keep blood-glucose levels between 81 and 108 mg/dL (4.5–6.0 mmol/L) in the IIT group, versus a range of 144–180 mg/dL (<10.0 mmol/L) in the CIT group. The insulin protocol was discontinued when patients were either discharged from the ICU, or advanced to oral diet. The primary end point was defined as death from any cause within 90 days after randomization. Secondary outcomes included survival time during the first 90 days; cause of death; length of stay in the ICU and in the hospital; duration of mechanical ventilation; and need for renal replacement therapy.

Results: A total of 3054 study patients were randomized to undergo IIT, and 3050 controls were assigned to undergo CIT. The two groups had similar characteristics at baseline. The treatment effect was similar when comparing operative patients and nonoperative patients (OR for death in the IIT versus CIT group, 1.31 and 1.07, respectively; $P=0.10$). In regard to the primary outcome, a total of 829 patients (27.5%) in the IIT group and 751 (24.9%) in the CIT group died (OR for IIT, 1.14; 95% CI, 1.02 to 1.28; $P=0.02$). The mean-absolute difference of blood-glucose levels for the two treatment groups was 29 mg/dL. Severe hypoglycemia occurred more frequently in the IIT group (6.8%) when compared to the CIT group (0.5%, $P<0.0001$). There were no significant differences in morbidity between the two groups in terms of need for corticosteroid therapy; ICU length of stay; hospital length of stay; duration of mechanical ventilation; or need for renal replacement therapy.

Discussion: Based on their results, the authors concluded that intensive-glucose control increased mortality among adults in the ICU. A blood-glucose target of ≤180 mg / dL resulted in lower mortality compared to a target of 81–108 mg/dL.

Paper 3 Krinsley, JS: Glycemic Variability: A Strong Independent Predictor of Mortality in Critically Ill Patients. *Crit Care Med*. 2008 Nov;36(11):3008–13.

Rating: •Of importance

Introduction: Several studies have shown hyperglycemia in the critically ill is associated with an increase in mortality [4–6]. However, recent trials have had conflicting results when IIT has been instituted [7–9]. The incidence of severe hypoglycemic episodes (<40 mg/dL) and variability of blood-glucose levels have been identified as confounding factors when interpreting results from these studies. Data from the Diabetes Control and Complication Trial showed that increased glycemic variability (GV) in type-1 diabetic patients was associated with increased rates of retinopathy, despite similar hemoglobin A1c levels [10]. Some studies suggest that GV may be more toxic and/or may cause greater oxidative stress than sustained hyperglycemia [11, 12].

Aims: The purpose of this study was to investigate whether GV had an independent effect on mortality in a heterogeneous population of critically ill patients.

Methods: This retrospective-cohort study identified patients at a single-medical center admitted to an ICU between 1999 and 2007, who had at least three venous glucose samples analyzed at the hospital's central laboratory. The ICU patients were included in the study from a variety of medical, surgical, and trauma services (but not from a cardiovascular surgical service). From February 2003 to January 2005, the ICU instituted tight-glycemic control with a range for blood glucose of 80–140 mg/dL. After January 2005, the goal range was changed to 80–125 mg/dL. The cohort group, which consisted of 3252 patients, was divided into 5 separate mean-glycemic ranges: 70–99, 100–119, 120–139, 140–179, 180+mg/dL. Within each glycemic range, standard deviations were calculated for each patient's MGL and divided into 4 quartiles as a reflection of a patient's GV. Modified APACHE II scores were also calculated for each patient.

Results: The study found age, modified APACHE II score, and MGL contributed independently to the risk of mortality. They also demonstrated a decrease in the risk of mortality during the period of tight glycemic control (OR 0.67–0.96). In each subgroup based on MGL, there was a significant increase in mortality as the standard deviation (SD) increased from the lowest (least variability) to the highest (greatest variability) quartile. The difference was more dramatic in the MGL subset range 70–99 mg/dL, where a fivefold increase in mortality was seen from the 1st to the 4th quartile (5.9% versus 30.1%). Diabetes, modified APACHE II score, and need for mechanical ventilation each had an independent positive correlation to SD. Tight glycemic control correlated inversely to SD and wide GV. ICU length of stay increased significantly in the lowest quartile, compared to the 3 higher quartiles in the entire cohort (4.1 versus 6.3,6.5, and 6.4 days, respectively). Severe hypoglycemia did occur at least once in 93 patients, which conferred an independent increased risk of mortality. The increase in mortality associated with high GV was not related to incidence or severity of hypoglycemia.

Discussion: The major conclusion of this study was that increasing GV was strongly related to increasing mortality in this heterogeneous population of critically ill patients. The authors concluded that this effect was particularly strong among patients in the euglycemic range, with a fivefold increase in mortality among patients with MGLs of 70 mg/dL– 99 mg/dL when comparing the 1st and 4th quartiles of GV.

Comments

Van den Berghe's [1] first paper represented not only an innovative landmark study, but was considered by many to be a "tipping point" that dramatically changed practice around the globe. This study seemed to clarify for the first time that tight-glucose control would provide a mortality benefit. The patient population was critical in this study, and primarily consisted of patients in a surgical ICU undergoing cardiovascular surgery. Previous studies with the glucose insulin potassium (GIK) therapy with glucose, insulin, and potassium for patients undergoing cardiac surgery suggest that this is one patient population that particularly benefits from insulin therapy [13]. Also, the nutritional therapy in this study reflected the European practice of providing a large parenteral glucose load prior to surgery [14]. A criticism of the study would suggest that it is the rescue from the glucose load by insulin that resulted in the mortality benefits. The incidence of hypoglycemia in the IIT group was significantly greater than that seen in the conventional group, which resulted in a sharp criticism of the study. Van den Berghe [15] defended hypoglycemia as being brief or short in duration, suggesting that an overzealous response to hypoglycemia resulting in hyperglycemia might be a

bigger factor for increasing risk to the ICU patient. Advanced glycolytic end-products (AGES) increase with any episode of hyperglycemia [16]. However, if a period of hypoglycemia precedes a period of hyperglycemia, the level of AGES may be even greater. AGES acts like endotoxin on the Toll–like receptor-4 to stimulate inflammation [15]. When the study was repeated 5 years later in a medical ICU in patients predominantly on enteral feeding, the mortality benefit seen previously could not be reproduced [17].

The NICE-SUGAR trial was developed in direct response to the Van den Berghe studies [1, 3, 17]. Although it was clear that glucose control in an ICU setting was important, concern over periods of hypoglycemia necessitated the design of this study comparing IIT (keeping the glucose levels between 80 and 110 mg/dL) versus conventional or moderate-insulin therapy (keeping the serum glucose between 140 and 180 mg/dL). The NICE-SUGAR trial could not reproduce the mortality benefit seen in the first Van den Berghe study [1, 3]. The difference in results initially was attributed simply to study design (the difference between a single-center versus a multicenter trial), with the results of a multicenter trial clearly trumping the results of the earlier single-center study. The patient mix in the NICE-SUGAR trial more closely resembled the second Van den Berghe [3, 17] study of a mixed ICU with patients receiving both enteral and parenteral therapy. Mortality rate was actually higher with IIT in the NICE-SUGAR trial compared to conventional therapy, a difference attributed to the higher incidence of hypoglycemia [3]. The comparison of these studies was interpreted by the community of critical care physicians to indicate that moderate CIT is indicated in the ICU setting, keeping the blood-glucose level between 140 and 180 mg/dL (which was safer than IIT where blood-glucose levels were kept lower between 80 and 10 mg/dL). A counterargument suggests that there are two issues present in this situation: adequacy of nutritional therapy, and degree of intensity of insulin therapy [15]. The delivery of early enteral nutrition in the ICU is difficult, often resulting in hypocaloric feeding that is inadequate in meeting a patient's caloric requirements. If a patient receives "sufficient" nutrition, predominantly because early supplemental parenteral nutrition has been added to the hypocaloric enteral feeding to minimize the cumulative caloric balance, then better outcome may be achieved by IIT. In those patients receiving "insufficient" nutritional therapy, predominantly by hypocaloric enteral feeding alone, without supplemental parenteral nutrition (or for whom parenteral nutrition is added later), then moderate-glucose control may result in a better outcome [15].

The Krinsley [18] paper added an additional element to the controversy of glucose control in the ICU setting. This is one of the first papers to confirm that glucose variability is a risk factor for mortality independent of the absolute level of glucose. In other words, mortality is increased with hyperglycemia by itself [15]. However, within a given range of blood-glucose levels, wider variability is associated with greater mortality than less variability [18]. The explanation for these findings or the mechanisms proposed for this mortality effect is not clear, but may represent one of three phenomena. First, the glucose variability may simply reflect disease severity. Second, greater glucose variability may represent poor compliance by nursing service with a particular protocol for insulin therapy. Or third, variability of glucose levels in hyperglycemia may have a direct toxic effect contributing to greater risk of mortality [18]. The discussion is somewhat academic, as the treatment for glucose variability is the same as that for basic-glucose control. In other words, having a protocol in place for glucose control with good compliance by nursing service will reduce risk for mortality from both hyperglycemia and glucose variability.

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