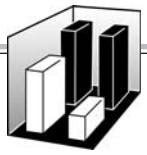

Jean-Louis Vincent, MD, PhD

Tight Glucose Control: Sweet or Sour?

The NICE-SUGAR study investigators; Finfer S, Chittock DR, Su SY, et al.: **Intensive versus conventional glucose control in critically ill patients.** *N Engl J Med* 2009, **360:**1283–1297.

Rating: •Of importance.

Introduction: The debate about the potential benefits of tight glucose control in intensive care patients has been ongoing since the exciting initial single-center study by Van den Berghe et al. [1], which demonstrated reduced mortality in patients managed according to a protocol aimed at maintaining blood glucose between 80 and 110 mg/dL compared with the then-standard goal of less than 215 mg/dL. However, later multicenter studies failed to reproduce these findings [2,3].

Aims: To determine whether intensive control of blood glucose levels in critically ill patients could reduce mortality rates.

Methods: In this multicenter, randomized, controlled trial, 6104 critically ill patients expected to require treatment on the intensive care unit (ICU) for at least 3 days were randomly assigned to intensive glucose control (target blood glucose 81–108 mg/dL) or conventional glucose control (target < 180 mg/dL). Glucose control was achieved using an intravenous infusion of insulin in saline, guided by treatment algorithms accessed through a secure website. The primary end point was death from any cause within 90 days after randomization. Secondary outcomes were survival time during the first 90 days, cause-specific death, and durations of mechanical ventilation, renal replacement therapy, and ICU and hospital stays.

Results: Baseline characteristics of the two groups were similar. No significant differences existed in 28-day mortality between the intensive and conventional glucose groups, but at 90 days the mortality rate was increased in the intensive treatment group with an OR of 1.14 (95% CI, 1.02–1.28, $P = 0.02$) for death with intensive control. This increased risk remained significant after adjustment for predefined baseline risk factors (adjusted OR 1.14, 95% CI, 1.01–1.29, $P = 0.04$). Deaths from cardiovascular causes were more common in the intensive group. Subgroup analyses suggested no significant difference between groups in surgical versus nonsurgical patients, patients with versus without diabetes, patients with versus without severe sepsis, or patients with an Acute Physiology and Chronic Health Evaluation score ≥ 25 versus < 25. There was a trend toward treatment benefit in patients with trauma versus no trauma and in patients receiving corticosteroids at baseline versus those not receiving corticosteroids. Interestingly, no differences existed between groups in the length of ICU or hospital stay or in duration of mechanical ventilation. Severe hypoglycemia was reported in 6.8% of the intensive group compared with 0.5% of the conventional group ($P < 0.001$).

Discussion: In this large, multicenter study, intensive glucose control, compared with conventional control, increased the absolute risk of death at 90 days by 2.6 percentage points; this corresponds to a number needed to harm of 38. In assessing differences between their results and other studies, the authors mention that their patients received predominantly enteral nutrition, compared with other studies where patients were predominantly fed parenterally. The authors highlight the strengths of the study, including the large number of patients and hence good statistical power, the standardized management of blood glucose levels among centers, the nearly complete follow-up (data on vital status at 90 days were available for 98.6% of patients), and the predefined statistical analysis plan. Limitations mentioned include the use of a subjective criterion, expected length of ICU stay, for study inclusion, lack of biologic data to assess mechanisms, inability to conceal treatment assignments after randomization, and failure to achieve the precise glucose target in a substantial proportion of the intensive treatment group. The authors conclude that that they cannot recommend use of the lower glucose target (81–108 mg/dL) in critically ill adults.

Comments

The role of tight glucose control in critically ill patients has been hotly debated in recent years. An initial study by Van den Berghe et al. [1] in surgical ICU patients suggested that managing patients according to a strict protocol to keep glucose levels between 80 and 110 mg/dL reduced mortality rates. The benefit of the intensive insulin therapy was attributable to its effect on mortality among patients who remained in the ICU for more than 5 days, and the greatest reduction in mortality involved deaths resulting from multiple organ failure with a proven

septic focus [1]. As a result of this study, several national medical organizations encouraged a tighter approach to glucose control, and it was included in guidelines for management of the patient with severe sepsis [4]. Intensivists began to pay more attention to blood glucose levels in their patients, and various protocols were designed and tested in many units. However, initial enthusiasm was dampened after two randomized, controlled trials—one in patients with severe sepsis [2] and one in medical and surgical ICU patients [3]—were stopped prematurely because of a failure to demonstrate any improvement in survival and an increased risk of adverse events, notably hypoglycemia.

The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was the result of a collaboration between the Australian and New Zealand Intensive Care Society Clinical Trials Group, the George Institute for International Health, the Canadian Critical Care Trials Group, and the Vancouver Coastal Health Research Institute. The results of NICE-SUGAR went one step further than earlier, smaller randomized, controlled, multicenter studies [2,3], and actually suggested a mortality hazard with tight glucose control with a 2.6% increased absolute risk of death at 90 days. A recent meta-analysis of 26 studies assessing the effects of a tight glucose protocol compared with a standard approach, which included the NICE-SUGAR data, concluded that intensive insulin therapy significantly increased the risk of hypoglycemia sixfold and conferred no overall mortality benefit among critically ill patients [5]. So, should we all abandon the concept of tight glucose management in our patients? The NICE-SUGAR study was certainly a well-conducted and large (> 6000 patients) randomized, controlled study, and its results add important data to the evidence base on glucose control. However, compared with earlier studies, which used glucose concentrations of less than 215 mg/dL [1] or 180 to 200 mg/dL [2] as their control groups, the NICE-SUGAR study discussed here compared tight control with an already lower glucose level of 144 to 180 mg/dL. The results obtained suggest this midway level may actually be an appropriate target, as indeed suggested by the guidelines for the management of patients with severe sepsis and septic shock, which acknowledged the risks of hypoglycemia with very low glucose targets and recommended that blood glucose levels be maintained at less than 150 mg/dL [6]. Clearly, further analyses of the NICE-SUGAR data will be conducted, including the possible effect of nutrition, the precise causes of death, and possible interactions with concomitant steroid use. Subgroup analyses may also help identify specific groups of patients who would benefit most from a tighter approach to glucose control.

Randomized, controlled trials are notoriously difficult to conduct in critically ill patients largely because of the heterogeneity of the "ICU patient." Once again, it would seem, an intervention that showed promise in a single-center study has not withstood transfer to the broader multicenter arena. But perhaps it is not so surprising that in such a mixed group of patients, some may benefit from the intervention under investigation whereas others may not, and some may experience detrimental effects. The overall result of the study therefore is determined by the overall balance of beneficial and harmful effects. Rather than regard this as a negative trial of tight glucose control, or as a reason to return to the past, somewhat random, approach to glucose control, we could rather see it as encouraging us to target a blood glucose in the range of 144 to 180 mg/dL until further studies clearly identify the groups of patients in whom tighter control may be warranted.

Acknowledgement

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Disclosure

No potential conflict of interest relevant to this article was reported.

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