

Tight Glucose Control in the Intensive Care Unit: Are Glucose Meters up to the Task?

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Many institutions use tight glycemic control (TGC)⁴ protocols in their intensive care units (ICUs). TGC protocols became standard of care after the initial, very promising, studies demonstrating that it improved patient outcomes (1). For instance, Van den Berghe et al. (1) demonstrated that TGC reduced mortality by one-third in surgical intensive care patients. Other early studies of TGC also demonstrated marked and significant benefits in infection rates and mortality. Typical TGC protocols consist of placing postoperative and critically ill patients on a continuous intravenous insulin infusion, checking their blood glucose concentrations on an hourly basis (or other schedule), and giving a bolus of insulin and/or changing the infusion rate of insulin based on the glucose concentration, with a goal of maintaining glucose between 4.4 and 6.7 mmol/L (80 and 120 mg/dL). Of the numerous variations in protocols regarding timing and frequency of glucose measurements, insulin infusion rates, and target glucose values, all have a goal of maintaining tight glycemic control in critically ill patients.

A new metaanalysis has suggested that TGC protocols offer limited if any benefits in critically ill adults and revealed that these protocols resulted in a 3- to 5-fold increased risk of hypoglycemia (2). The metaanalysis examined 29 randomized controlled trials that met predefined inclusion criteria. Of the 27 trials that examined mortality as an endpoint, 16 favored TGC and 11 favored usual care, but the reductions in relative risk were statistically significant (95% confidence) in only 2 of the 16 favoring TGC and in none of the 11 favoring usual care. The only outcome for which TGC demonstrated a significantly reduced risk was the development of septicemia; this was seen in surgical in-

tensive care patients but not in medical ICU patients. The metaanalysis concluded that TGC may not be as beneficial as predicted from some of the original studies and may cause harm. We would like to raise the question of whether error introduced by measuring glucose with point-of-care (POC) glucose meters in some, but not all, of the studies may have contributed to the findings of this metaanalysis.

The use of glucose meters in hospitals became common in the late 1980s, and their use became standard of care in virtually all inpatient settings by the mid-1990s without evidence that it improved patient outcomes or decreased costs. It just happened. Nevertheless, the encouraging results of TGC studies in the early part of this decade appeared to provide the first evidence-based support for POC glucose testing in hospitalized patients. Whereas POC testing is clearly needed if TGC protocols are to be implemented (central laboratory testing would be too slow), the choice of device to use for POC glucose testing in TGC protocols may not be as clear, nor is the sample type for testing. The original TGC study by Van den Berghe et al. (1) used a precise arterial blood gas instrument for glucose measurement and obtained arterial blood samples for testing. In other studies, some showing benefit for TGC and others not, blood glucose meters and capillary blood samples have been used to measure glucose. Similarly, glucose meters and capillary blood samples are widely used in hospitals for TGC. We believe that one possibility for the mixed results of the TGC studies examined by Wiener et al. (2) may be the methods and samples used to measure glucose.

Glucose meters are less precise than central laboratory or blood gas analyzer methods and can display large mean differences from laboratory methods. The most recent College of American Pathologists proficiency testing data (Surveys C-B 2008 and WBG-B 2008) shows CVs for all 29 central laboratory methods (5664 laboratories) to be 2.5% to 4.3%, and the bias between any 2 methods to be no more than 11%. In contrast, CVs between 17 glucose meter methods (19 597 sites) were 12% to 14%, and bias between any 2 methods was as much as 41%. It should be noted that some of the bias between methods could be due to matrix effects. Nevertheless, one study from the CDC of 5

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⁴ Nonstandard abbreviations: TGC, tight glycemic control; ICU, intensive care unit; POC, point of care.

common glucose meters showed mean differences from a central laboratory method to be as high as 32% and CVs in the hands of a single trained medical technologist to range from 6% to 11% (3). At our institutions, total imprecision for glucose meters shows a CV of approximately 5% to 6%, whereas it is approximately 1% for our central laboratory methods. One of us (M.G. Scott) also identifies in the laboratory information systems glucose meter values that are repeated within 15 min of each other for billing and compliance purposes. Interestingly, about 1.3% of meter values are repeated within 15 min. One week of data from August 2007 showed 84 repeat measurements with a mean difference between repeat values of 106 mg/dL (range of differences 5–361 mg/dL). Clearly, repeat testing often is performed because users believe the results to be incorrect. However, we have no idea how many erroneous values are being obtained and not repeated! In addition to imprecision and bias as sources of error, some glucose meters are affected by pO_2 ; thus meter-reported glucose concentrations will be (artificially) lower in capillary samples than in venous or arterial samples from patients with poor perfusion. Critically ill patients in intensive care units frequently have vast marked and sustained decreases in pO_2 and in capillary perfusion. Taken together, the evidence leads us to believe that inaccurate glucose meter values lead to insulin dosing errors in some of the studies reviewed in the metaanalysis by Wiener et al. (2), and it is likely that those errors will lead to an increased risk of hypoglycemia in patients under TGC protocols.

Unfortunately, the methods used to measure glucose are frequently not described in studies of TGC. In examining the original articles included in the metaanalysis, we found that the glucose method was described in only 10 of the 27 studies. Interestingly, the original Van den Berghe et al. study (1) that showed a 34% decrease in hospital mortality used arterial blood samples and a precise arterial blood gas instrument for glucose measurement (1). Many of the studies that failed to show improved mortality for medical ICU patients used POC glucose meters and, in some cases, capillary blood samples (2).

The design and specifications for glucose meters were not established for the purpose of monitoring and making insulin dosage decisions in TGC protocols. This is obvious from the different regulatory requirements in the US for “acceptable performance” of glucose meters and central laboratory methods. Allowable error for the central laboratory is 10%; for glucose meters, it is 20%. The FDA allows 20% error for package insert claims of glucose meters. Similarly, the National Academy of Clinical Biochemistry and the American Diabetes Association recommend that central laboratory methods, not glucose meters, be used

for the diagnosis of diabetes. If a device is not to be used for diagnosis, which is dependent on a single cutoff value, how can it be expected to have adequate performance characteristics where precise cutoff values are used to make insulin dosage decisions?

Boyd and Bruns (4) carried out simulation modeling studies to simulate the effects of meter imprecision and inaccuracy on the administered dose of insulin for 2 insulin administration algorithms. Their simulations demonstrated a direct and continuous relationship between increases in the total error of meters and the rate of incorrect insulin dosages by either algorithm. A simulated total analytical error of 5% led to incorrect insulin doses in 8% to 23% of cases, whereas total analytical error of 10% led to incorrect insulin doses in 16% to 45% of cases. These dosage error rates seemed to be affected only slightly by choice of algorithm or range of blood glucose considered. To provide 95% correct insulin dosing required both the bias and imprecision of the meter to be $<2\%$. Although this study considered only simple “sliding scale” dosing algorithms in routine daily monitoring of insulin, it has obvious implications for the use of meters in TGC.

Because of the total dependence of treatment decisions in these protocols (and most likely of outcomes) on patient glucose values, we believe it to be important that future glucose meters used in these protocols have decreased total error and be subject to the same regulatory requirements as central laboratory methods. Alternatively, studies of the value of TGC should use more accurate methods for glucose. Anything less may continue to lead to mixed outcomes in studies investigating the value of TGC and possible harm to patients being treated under these protocols.

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