Editorials

Blood Glucose Monitoring in the Intensive Care Unit: Toward Defining Bias and Imprecision Thresholds for (Near) Continuous Sensors

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Hyperglycemia is a hallmark of critical illness and is firmly associated with adverse outcomes in both adults and children treated in the intensive care unit (ICU).[2] The association between hyperglycemia and adverse outcomes follows a J-shaped curve, with the lowest risk associated with blood glucoses within the reference intervals for fasting [for adults 80–110 mg/dL (4.4–6.1 mmol/L)]. To address causality in such an association, an intervention-based randomized controlled trial (RCT) is required, in which one group is randomly allocated to receive insulin titrated to blood glucose reference intervals and the other group to a strategy that tolerates hyperglycemia as determined by the disease process. In 2001, the results of the first RCT performed in surgical ICU patients were published, showing that titrating insulin to maintain blood glucose within the reference intervals for fasting during critical illness reduced morbidity and mortality (1). Additionally, a subsequent RCT in adults suffering from nonsurgical critical illnesses (2) and another RCT performed in critically ill children, for whom the age-adjusted blood glucose target reference intervals were even lower (3, 4), showed reduced morbidity and mortality. Subsequent, so-called repeat studies, performed in the more "real-life" multicenter setting, did not confirm these promising results, and one study showed an even higher mortality with strict blood glucose control (5). The reasons for these conflicting results remain debated. Even today, more than 10 years after the first RCT was published, the issue of how to best control blood glucose concentrations with insulin infusion in the ICU continues to be one of the most controversial topics in critical care medicine.

A large part of this controversy has been attributed to methodological differences among the studies (6).

The 3 initial RCTs showing that outcome could be improved by lowering the blood glucose concentrations of adult and pediatric ICU patients used a very accurate and precise instrument to measure blood glucose concentrations in undiluted whole blood samples drawn from an arterial line, and only after extensive training allowed nurses to adjust the insulin infusion based on a customized and validated guideline (1, 7). The subsequent studies did not implement such high degrees of standardization. For example, these later studies allowed the use of all sorts of hand-held blood glucose meters, mostly those that use enzyme-impregnated strips that were not designed for this purpose because the total error was too large to allow titration of the treatment to such narrow target ranges for blood glucose (8).

Earlier modeling studies (9) previously revealed that, with higher total errors such as those of point-of-care devices used in the multicenter trials (10), the risk of undetected hypoglycemia inevitably increased dramatically, the effective prevention of hyperglycemia was reduced, and the glucose variability increased into the potentially dangerous range (11). The impact of such high total errors could thus explain why titrating insulin based on readouts generated by such devices may have caused harm that could, in turn, have offset any potential benefit of strict blood glucose control that was achievable with accurate and precise tools (9). These early simulation studies identified a total error of <10% as mandatory for this purpose, a number that was subsequently incorporated into guidelines for point-of-care blood glucose testing in acute settings (12).

In the meantime, the critical care community had come to realize that measuring blood glucose concentrations intermittently at a high enough frequency to allow safe blood glucose control was costly and very time-consuming for the ICU nursing staff and, even then, left large windows of time during which no information about the actual blood glucose concentrations was given to the medical team. This insight created a demand for a more continuous display of blood glucose concentrations in the ICU setting. The medical community assumed that devices that could measure blood glucose in a (near)continuous way, with a dis-

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[2] Nonstandard abbreviations: ICU, intensive care unit; RCT, randomized controlled trial.

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play of trends over time, would provide a much better control of blood glucose and would allow the titration of insulin to become much easier. Several medical device companies set out to develop such tools. This turned out to be much more difficult than anticipated. Also, as more frequent readouts would be available to the clinician, the question arose whether requirements for total error could be somewhat less stringent.

In this issue of *Clinical Chemistry*, Boyd and Bruns have addressed this very important question *(13)*. They investigated the effects of a higher frequency of blood glucose measurement, in this case every 5 min, which reflects what could be obtained with (near)continuous devices being developed, on the quality of blood glucose control with insulin (incidence of undetected hypoglycemia, degree of hyperglycemia, and blood glucose variability) compared with a typical intermittent sampling strategy of 1 readout every hour. The authors addressed this question via complex simulation studies that made use of (*a*) a simplified patient model (distribution volumes, variable starting blood glucose concentrations, insulin sensitivities, rates of gluconeogenesis, and rates of intravenous glucose infusion), (*b*) simulated assay bias varying between −20% and +20% and imprecision varying from 0% to 20% CV, and (*c*) 2 available algorithms for insulin adjustments and therapeutic corrections of hypoglycemia.

The results of this study are important and timely. First, as shown previously, higher assay bias and imprecision were shown to worsen the quality of blood glucose control with the tested algorithms. Second, a higher measuring frequency, which could be achieved with (near)continuous devices, did not decrease the deleterious effect of increasing bias (tested for systematic error ranging from −20% to +20%) but did reduce the negative impact of increasing imprecision from 5% to 20%.

This elegant study is the first to provide sound mathematical evidence that a less stringent requirement for imprecision may suffice for (near)continuous devices compared to the required imprecision for intermittent measurement tools used for blood glucose monitoring in the ICU. If this conclusion is confirmed, it will have a major impact on the process of making such tools available to the clinicians in ICUs worldwide. However, although the authors clearly showed that a higher measurement frequency did reduce the negative impact of imprecision, they have not answered the question of exactly how precise such a tool should be, or in other words, which imprecision and bias thresholds are acceptable for clinical use of such (near)continuous devices. This question should be further addressed in validation studies.

The study also has a few limitations that need to be taken into account before the conclusions can be translated to the clinic for decision-making about the safety of new (near)continuous devices. First, the patient model used in the simulation studies to predict blood glucose values in response to adjusted insulin doses was rather rudimentary. Recently, more advanced patient models have become available, which could affect the results *(14, 15)*. Second, as the authors discussed, defining the threshold for imprecision that may suffice for safe use of (near)continuous blood glucose sensors is also likely to depend on the type of algorithm being used to advise the nurses on the insulin dose adjustments. The 2 algorithms tested by the authors were relatively simple and were developed for use with intermittent blood glucose measurements; thus, they were not specifically designed for use with (near)continuous readouts of blood glucose. Inferentially, when information on blood glucose becomes available at a much higher resolution so that trending over time can be interpreted and integrated in the decision process, the type of controller could also be optimized. More sophisticated algorithms are available and being updated for use with higher-resolution blood glucose signals *(16)*.

This important work by Boyd and Bruns has several major implications *(13)*. First, the work underlines the need for validation studies of all new blood glucose sensors, intermittent or (near)continuous, with accurate analysis of bias and imprecision compared with the state-of-the-art tools, before these sensors are introduced into clinical ICU practice. Second, not only the blood glucose sensors but also the insulin titration algorithms being used should be evaluated critically, preferably via RCTs, against the current state of the art *(15)*. And finally, the combination of both an accurate and precise (near)continuous or intermittent sensor and an effective algorithm should allow us to retest the original hypothesis that strict blood glucose control within the healthy fasting reference intervals during critical illness reduces morbidity and mortality compared with tolerating hyperglycemia. Only with such accurate and precise glucose sensors, and an effective algorithm, will it be possible to correctly test this hypothesis in the real world of multicenter studies.

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