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SYMPOSIUM

An Analysis: Hyperglycemic Intensive Care Patients Need Continuous Glucose Monitoring—Easier Said Than Done

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Abstract

Experts and agencies increasingly advocate tight glycemic control (TGC) using intensive intravenous insulin therapy in critically ill patients. Questions remain about the "best" glucose goal, the universal benefit of TGC in the heterogeneous adult intensive care unit (ICU) population, and concerns about the underrecognized incidence of hypoglycemia and its neuropsychological sequelae. TGC is time-consuming for ICU staff, and pathophysiologic, technical, and personnel factors impact the accuracy of point-of-care glucose monitoring. TGC in the ICU requires safe, accurate, robust, rapid, and continuous glucose measurements (CGM) that lack interference from drugs or other substances. Establishment of reliable CGM may provide the foundation for a closed loop, microprocessed system resulting in an artificial islet cell. This commentary focuses on reports from two respected groups on the potential use of CGM devices in the critically ill. It emphasizes the challenges of applying this technology in the ICU and looks to future refinements to address them.

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As two clinically active adult intensivists, we feel that the need for continuous glucose monitoring in the critically ill adult is clear-cut. Nonetheless, our viewpoint regarding the practicalities and demands in applying this technology in the intensive care unit (ICU) may differ from many of this journal's subscribers. The feasibility or "proof of principle" paper by Ganesh's group in Philadelphia[1] and the overview of a refined continuous intravenous technology by Kunjan and Lloyd[2] in this issue of *Journal of Diabetes Science and Technology* stimulate our comments. We salute these authors and others in their pursuit of reliable monitoring and their concept of a functional, robust, and safe artificial pancreas. However….

The ICU population is a unique one where the introduction of innovative technologies is challenging and may be met with unintended consequences when compared to successful application in ambulatory or ward patients. ICU patients are often limited in their ability to communicate, receiving sedation or analgesics, and are in a dynamic highly stressed state. ICU patients typically receive a host of medications, and many suffer end organ dysfunction(s), including neurologic, cardiopulmonary, renal, hepatic, hematologic, and pancreatic. Patients are often fed in a relatively nonphysiologic or unique manner, either via total parenteral nutrition or via specialized enteral feedings. Most, if not all, of our patients are sedentary.

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Abbreviations: (FDA) Food and Drug Administration, (ICU) intensive care unit, (IIT) intensive insulin therapy, (POC) point of care, (TGC) tight glycemic control

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Further, all ICUs are not created equal; many are general medical–surgical units, whereas others are highly specialized or subspecialized such as coronary care units or neurointensive care units where patient characteristics may be quite broad. Imagine the young previously healthy closed head-injured motorcyclist versus the older, compromised stroke victim who has significant comorbidities, yet both often receive side-by-side care in neurocritical care units. Further, there are significant differences in how ICUs are staffed, community versus academic centers, and whether intensivists are actively involved in day-to-day care and in the development of protocols and practice guidelines.

Depending on the ICU population, approximately 5–20% of critically ill patients are known to have diabetes.[3,4] The highest incidence is in the cardiothoracic surgery unit where upwards of 25–30% of patients have diabetes.[5,6] In contradistinction to the highly controlled type 1 diabetes patients reported in the study by Ganesh and colleagues,[1] the vast majority of diabetic ICU patients are type 2, adult onset, frequently, but not always, overweight and rather inactive. Because a significant number of type 2 diabetes patients do not know they have diabetes,[7] this is likely to be an important underestimation of the true incidence. Further, an unknown number of adult ICU patients who do not have diabetes develop hyperglycemia at the time of their presentation or during their ICU course. Stress hormone-induced hyperglycemia and inflammatory cytokine/chemokine mediated abnormalities in glucose production, utilization, and metabolism further exacerbate dysglycemia in the critically ill. Interestingly, recent reports raise the question as to whether hyperglycemic nondiabetic ICU patients have greater morbidity and mortality than their equally dysglycemic critically ill diabetic counterparts and whether normalization of glucose in hyperglycemic nondiabetic patients improves outcomes.[3,5,7–12]

In 2001, Van den Berghe and her Flemish colleagues[11] reported the results of their tight glycemic control (TGC) using intensive insulin ICU study that James Krinsley[13] stated "launched a 1000 (tight glucose control) protocols." The impressive findings of the study were not necessarily universally applicable to all ICU patient populations nor were the feeding protocols "routine" compared to American ICU standards. Further, cardiac surgical patients dominated the study and their length of ICU stay and morbidity and mortality were felt by some to be excessive.

The critical care world is increasingly inundated with different studies in various critically ill populations[4,12,14,15] espousing the need for TGC, most commonly via protocols or approaches that use continuous intensive insulin therapy (IIT). Blood glucose is measured most commonly on an hourly, two or four hourly basis, most frequently using point-of-care (POC) devices often using capillary blood. Recent reports have emphasized the pitfalls associated with POC glucose monitoring in the critically ill, which led some to advise that arterial or proximal venous samples be used instead of capillary blood or that POC monitoring be replaced by reference laboratory analysis, particularly in anemic, hypotensive, hypoperfused, and/or unstable ICU patients.[16–21]

We can envision no clinical scenario where hyperglycemia (>126 mg/dl or 7 mmol/liter) provides a survival advantage. Increasing concerns, however, over iatrogenic hypoglycemia mediated by overly aggressive IIT protocols or misguided infusion adjustments based on spurious POC glucose results call into question what is reasonable glycemic control in the ICU. The deficiencies in current ICU glucose monitoring technology are likely underrecognized, most importantly by intensive care providers, and continuous outpatient techniques using subcutaneous and percutaneous methods appear unlikely to provide needed solutions.[22]

The challenges to develop a monitor that provides frequent and precise glucose measurements, all the more demanding given the inherent variability in critically ill patients, are the subject of two articles in this issue of the Journal of Diabetes and Science Technology. Both articles evaluate Food and Drug Administration (FDA)-approved devices. The article by Ganesh and colleagues[1] evaluates a continuous blood chemistry monitor, VIA®, whereas the article by Kunjan and Lloyd[2] presents the technology of continuous glucose monitoring using a portable automated blood sampling system.

Although development of a continuous glucose monitor has been touted to have the most significant applicability in the critical care setting,[23] neither study evaluates this patient population. Ganesh and colleagues[1] evaluated healthy volunteers and stable type 1 diabetes patients; this differs significantly from the dysglycemic ICU population where type 2 and stress-induced hyperglycemia predominate. Further, the degree of glucose variability in ICU patients is quite marked and has been reported to be associated with increased mortality.[24] Kunjan and Lloyd[2] tested human samples; additional details of the population are not provided.

Both of these studies attempted to address some of the technical issues likely present with ICU blood glucose sampling. The Cascade Metrix system reported by Kunjan and Lloyd[2] uses a "small" peripheral venous blood sample of an undisclosed amount and is not reinfused. The authors claim that this approach prevents thrombosis without increasing infectious risk, although supporting data are lacking in this article. This may be applicable for a device *in situ* for 72 hours but may not be true when the assembly is required for longer monitoring periods typically due to increased ICU lengths of stays. ICU patients who derived the most benefit from TGC had ICU stay >3 (medical)–5 (surgical) days in some studies.[3,11]

In contrast, the sampling method of Ganesh and colleagues[1] can be used with central venous or peripheral arterial access. All locations present thrombotic risks. Peripheral vein sampling may not be feasible or may prove inaccurate with hypoperfused ICU patients. In the ICU, peripheral vein sampling would require, at a minimum, two dedicated peripheral sites—one for sampling and a second for insulin administration. Additional access will typically be needed for other ICU medications (antibiotics, vasoactive drugs). Dedicated access sites will also be required with central venous or radial artery sampling. Concurrent central venous sampling gives rise to logistical issues that include interference from simultaneously infusing medications through an adjacent port, as well as the unpredictable impact of concurrently infusing glucose containing fluids or insulin. The VIA system requires 60 minutes of static flow time daily for sampling, which may increase thrombotic and infectious risks.

Both studies used FDA-approved devices, which currently require that glucose measurements be within ±20% agreement of laboratory results,[25] likely unsatisfactory for use in unstable ICU patients. The study by Kunjan and Lloyd[2] created a Clarke error grid analysis with reference laboratory measurements, but the range of measurements was limited to less than 100 mg/dl (58–144 mg/dl), a much narrower glucose range than seen with critically ill patients. The study by Ganesh and colleagues[1] compares VIA with a POC device (Hemocue 201) rather than reference laboratory, thus introducing concerns that others have raised[26,27] about the accuracy and the limitations of these devices in the critically ill population. Glucose measurements with VIA were consistently higher than POC in the hypoglycemic range, raising concerns about unrecognized hypoglycemia and its sequelae. Initial analysis revealed a difference that was highly dependent on the average glucose value, and the authors attempted to correct for this difference by using a linear regression analysis. In the ICU patient, glucose measurements need to be timely and accurate to ensure appropriate ITT.

The call for TGC in critically ill patients using IIT frequently continues to grow, yet the optimal level and ranges of glucose still remain questioned. Concerns over underrecognized or underappreciated hypoglycemia remain and are increasingly acknowledged as practitioners become more aware of the limitations of POC measurements and the host of variables involved in providing timely, accurate, and reliable glucose measurements at the bedside. The development and refinement of rapid, reliable, precise, and accurate glucose measurement on a continuous or near continuous basis are increasingly recognized as needed to optimize the metabolic care of critically ill patients. Emerging technologies on the horizon include nanotechnology, microprocessed, and sample separation approaches. The latter may eliminate whole blood sampling issues. The two articles in this issue represent two technologies that may have applicability in the ICU, although currently have limitations in that unique setting.

The ongoing NICE SUGAR trial[28] is scheduled to complete enrollment of 6000 prospective and randomized ICU patients into two groups: euglycemia vs slightly less intense control (<150 mg/dl, I think). These results may help determine the optimal glucose level and advance knowledge of glucose monitoring accuracy while ensuring safety. As evidenced by the techniques represented by the articles in this issue, progress is being made to address glucose monitoring limitations and concerns. The best practice for glucose monitoring, however, has yet to be determined!

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