Glucose management in the intensive care unit: are we looking for the right sweet spot?

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Abstract: In a recently published issue of *Critical Care Medicine*, Kar and colleagues investigated glucose management of critically ill patients with type 2 diabetes. In this commentary, we discuss the challenges of investigating glucose control in the critically ill, why so many internally valid studies in this field lead to conflicting results, and the obstacles preventing investigators from reaching a conclusive answer.

Keywords: Critical care; diabetes; glucose control; hyperglycemia; hypoglycemia

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Despite multiple studies, the optimal method of glucose management in the intensive care unit (ICU) remains unclear. Recently published in *Critical Care Medicine*, Kar and colleagues investigated glucose management of critically ill patients with type 2 diabetes (1). Kar and colleagues studied two targets, 10 mmol/L (180 mg/dL) and 15 mmol/L (280 mg/dL), to trigger initiation of treatment for hyperglycemia. They compared episodes of hypoglycemia, degree of glycemic variability and mortality outcomes, as well as biomarker levels, finding less glycemic variability in the higher glucose target group. This study is of interest to the clinician because it underscores a theme common to intensive insulin therapy: it is unclear how to generalize these results to other ICUs.

The study by Kar and colleagues, thoughtful though it is, suffers from the same problem that plagues all studies on intensive glucose control: because we lack replicable methods, the study results, while internally valid, are often not generalizable to other ICUs that use different glucose protocols and see different patients. As a result, investigators often report findings that differ significantly from each other (2-5).

Critically ill diabetic patients have a different response to insulin therapy than non-diabetic patients, perhaps due to their relative tolerance to glycemic variability and hyperglycemia (5-7). The literature has demonstrated that a one-size-fits-all approach to glycemic management is flawed, as surgical patients, cardiac patients, and medical patients have different responses to glucose targets (2,3,8). Even the amount time a patient is on protocol results in a different response to glucose (2). A study ICU that has short lengths of stay may have a different experience with glucose management than one that has longer lengths of stay. Many patients are managed with subcutaneous insulin and the impact of excluding this group is often lacking from study data collection (7). In short, the methods of patient selection yield an internally valid positive result in a subset of patients, but often are not generalizable to other patient populations.

It is uncertain whether the glycemic variability observed in critical illness is in of itself harmful, or rather an epiphenomenon of critical illness. Even if we were to assume all glycemic variability was iatrogenic, such variability would be idiosyncratic to a given study protocol, which dictates the target glucose, the frequency of glucose checks and the magnitude of insulin adjustments. It is conceivable that using a different protocol, one might have reduced glycemic variability with lower glucose targets. Studies on insulin therapy also commonly report hypoglycemic episodes as an adverse outcome. Similar to glycemic

variability, hypoglycemia may be an epiphenomenon of critical illness, and iatrogenic hypoglycemia may be idiosyncratic to the study protocol. Multiple studies using different protocols report different rates of glycemic variability and hypoglycemia (2-5). Determining the harms of hypoglycemia or variation is difficult; any study that intentionally induced hypoglycemia or increase variation would be clearly unethical.

Complicating this further is that adherence to study protocols is often poor (9). Most studies of intensive insulin therapy are unblinded, and use protocols that allow considerable unnecessary variation in clinician management. The largest trial of intensive insulin therapy had high rates of clinician error contributing to hypoglycemia (10). Consequently, even studies that implement the same protocol are often limited by the high amount of clinician variation, which again limits generalizability.

A potential solution to this absence of external validity would be to embrace a computerized closed-loop system using continuous glucose monitoring. In such a scenario, continuous feedback would ideally prevent both iatrogenic variation and hypoglycemia (and perhaps minimizing spontaneous variation), allowing investigators to truly ask which glucose target is the best. Other sites could use the exact same algorithm, as it could be exported with high reliability and high compliance. Sadly, this solution is not yet a reality. While there are some open-loop systems that use computerized decision support (11), there are no true closed-loop systems commonly used today. Current continuous blood glucose measurement systems have limited reliability (12). However, both continuous blood glucose monitoring systems and computerized decision support are rapidly advancing and may soon be ready to answer the question of optimal glucose management.

Whether or not achieving euglycemia will really affect mortality is also unclear, or whether hyper- or hypoglycemia are epiphenomena of a disease state for which outcome is unaffected by glucose control (within reasonable levels of 80–180 mg/dL). It may be that the optimal glucose management may be intensive insulin therapy of 95 mg/dL without glucose variation or hypoglycemia, but this is not yet feasible; improved protocols and adherence to study procedures might add clarity.

The overall goal of an intervention in the ICU should be to improve relevant patient outcomes, while at the same time providing efficient care. Yet, study procedures and methods are rarely efficient (13). There is too much variation in study design and outcomes within even a narrow field such as this with easy-to-collect data and measurable endpoints. Calls for collaborative trial design, especially in a field such as this, may be the only way to increase external validity, perhaps answering the question of optimal glucose control as well as many others in critical care (13).

Looking to the future of glucose control, we not only need to know the optimal glucose targets but the optimal way to achieve these targets. Our current state of investigation is hampered by the use of several different protocols, each with their idiosyncrasies. To truly answer this question, we need a milieu where most institutions are using a protocol with excellent replicability, portability, and compliance. In such a world, one can then test the effects of a particular glucose target for a particular population.

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Footnote

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