Commentary

Liberal glucose targets for critically ill diabetic patients: is it time for large clinical trials with more personalized endpoints?

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The field of glycemic control for critical care patients has evolved progressively since the publication of the guidelines for the use of insulin infusions in critically ill patients (1). At that time, the data were inadequate to define an optimal target for insulin therapy, and the committee endorsed the goal to keep glucose less than 10 mmol/L for ICU patients to reduce mortality. This same trigger has been promoted by the ADA (2). While select populations may benefit from tighter levels of glucose control, the need for safety is paramount—avoiding hypoglycemia (<4 mmol/L) and minimization of glucose variability are important for optimal patient outcome. However, a contrary perspective is that hyperglycemia is a marker for stress response and severity of illness, and control of glucose may be detrimental—particularly when attempting to achieve low targets such as 4.4–6.1 mmol/L (3).

The impact of several other issues remains unresolved. Co-morbidities such as preexisting diabetes which will be discussed in detail in this paper, the safety and effectiveness of the treatment protocol, the choice of monitoring device and site of blood sampling, and the influence of nutritional support all warrant attention to optimize patient safety.

While equipment and protocols are modifiable, patient co-morbidity is not. A series of papers from Australia have provided a compelling perspective that sets the stage for future trials. Patients with diabetes are known to have a lower mortality than non-diabetics for any level of hyperglycemia (4). In particular, patients with poor glycemic control, evidenced by elevated glycated hemoglobin (HbA_{1c}) may respond differently to stress. A protective effect of chronic hyperglycemia has been suggested contributing to a blunted response to oxidative stress, and injuries. Patients with a background of poor glycemic control did not display an increase in morality with the degree of hyperglycemia that was seen in non-diabetics, suggesting that treatment endpoints should not be the same for all patients (5). Further elucidation of a difference in the risk of hyperglycemia by diabetics versus non-diabetics was illustrated by Egi and colleagues who showed an association between poor glycemic control (HbA_{1c} >7%) and lower mortality despite acute hyperglycemia compared with a comparable population with HbA_{1c} <7% in a retrospective database assessment (6). Krinsley and colleagues affirmed this association in a combined database of 44,964 patients admitted to 23 ICU's showing an association between tight glucose control (4.4–6.1 mmol/L) and higher mortality compared with more liberal treatment endpoints (> 6.1 mmol/L) (7).

HbA_{1c} is a potential tool to identify patients who may have greater tolerance of acute hyperglycemia in the ICU as a result of prior poor glucose control. However, refinement of the predictive accuracy for the development of critical illness has been proposed using the Stress Hyperglycemia Ratio (SHR) (8). The SHR is calculated as the admission glucose divided by the estimated average background glucose (eAG)—from the HbA_{1c}. The authors suggest that SHR may be a better biomarker to assess the impact of stress-induce hyperglycemia on patient outcome by controlling for the influence of background hyperglycemia. A prospective trial would need to validate if SHR can predict the risk for critical illness and if so, whether its use to trigger therapy for hyperglycemia at higher glucose levels can improve patient outcome.

A different, but similar approach was suggested for patients with a history of diabetes, using eAG as a benchmark value for degree of glucose change. Glycemic

distance from that benchmark was measured for conventional (6–10 mmol/L) and liberal (10–14 mmol/L) glucose targets (9). In this cohort study of 80 patients during 2 treatment periods, the authors showed that the liberal treatment group had fewer episodes where glucose fell below the eAG (relative hypoglycemia) and a reduced dose of insulin was administered. Whether a relative glucose measure proves to be a better measure of treatment safety or effectiveness than absolute hyper or hypoglycemia will need to be demonstrated in a larger population with clinically important outcome measures.

A more recent paper by Kar and colleagues has explored the impact of liberal glycemic targets on patient outcome, and is the focus of this commentary. They similarly used a prospective, sequential cohort study design to evaluate whether a more liberal treatment trigger of glucose greater than 14 mmol/L is safer than the standard trigger of 10 mmol/L (10). These authors treated a select number of patients with type 2 diabetes and chronic hyperglycemia (HbA_{1c} ≥7%) during 6 month periods (N=52 standard over 4,047 hours *vs*. N=31 liberal over 3,244 hours) after excluding patients who were discharged before the HbA_{1c} was reported, or HbA_{1c} >7% but without blood glucose >10 mmol/L. The specifics of the treatment protocol were not publicly available at the time of this commentary, but the standard group received human insulin for glucose >10 mmol/L with a target of 6–10 mmol/L. The liberal group treatment trigger was >14 mmol/L with a target 10–14 mmol/L. Effectiveness of glycemic control was estimated with time-weighted mean glucose, hypoglycemia, clinical outcomes, inflammatory biomarkers, and glycemic variability. Glucometers were used for bedside measurement, but the source of blood was not defined (capillary *vs*. venous/arterial).

Despite the small numbers, the patients were similar between cohorts, although there was a trend toward greater use of mechanical ventilation in the liberal group (P=0.07). Mean glucose values were different between groups. The standard group had a lower nadir glucose and had more patients with a low relative glucose (4.1–6 mmol/L) than the liberal group, 8% *vs*. 65%, P=0.01. The liberal treatment group had a trend toward a lower relative risk of moderate-severe hypoglycemia [0.47 (95% CI, 0.19–1.13), P=0.09], but no significant difference was shown between groups in time-weighted glucose or amount of insulin administered per day. There was lower glycemic variability with the liberal goal target. A larger trial would be needed to examine important clinical outcomes with liberal versus standard glucose control strategies.

There are limitations to this single center study, which was underpowered to show any significant differences in most parameters, and important outcomes such as infection rates were not reported. The authors acknowledge other limitations such as lack of blinding, the potential for temporal changes, and the possibility that liberal therapy may not be as safe as standard targets.

Moving forward, it appears that numerous questions remain about the optimal glycemic target, but optimally, treatment protocols will be designed with patient-specific criteria in mind, such as presence of diabetes or other chronic conditions. While not addressed in these studies, there remains a need to further define if different approaches should be taken for medical versus surgical patients, as suggested in the subsets of the NICE-SUGAR study (11). Future clinical trials will need to be large, multicenter trials, using protocols that are shown to be safe, but still relatively straightforward to implement.

Translation of clinical trials of glycemic control into practice remains a challenge for clinicians and there is a tendency to implement a protocol and not evaluate or revise them in response to new data. Although NICE-SUGAR demonstrated the risk of an intensive glucose control target in 2009, de-adoption of these low targets has been slow (11,12). While the notion of using different glucose targets for different patient populations is daunting, future protocols may need that type of personalization to achieve desired outcomes. Computerized protocols with increasing sophistication have been developed and can be used to manage the many variables that influence glycemic control for future clinical trials (13).

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Footnote

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