Commentary

How to compare adequacy of algorithms to control blood glucose in the intensive care unit?

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Related to *Research* by Vogelzang *et al*., see page 201

Abstract

Vogelzang *et al*. retrospectively assessed a derivative marker of blood glucose control over time in the intensive care unit (ICU), "the hyperglycemic index" (HGI), in relation to outcome. The HGI predicted mortality better than other indices of blood glucose control that do not take the duration of hyperglycemia into account. This provided further support to the concept of maintaining normoglycemia with insulin throughout intensive care in order to improve outcome. The HGI was also proposed as a tool to assess performance of glucose control algorithms. This, however, implies similar sampling frequency for the compared algorithms. Just as we prefer continuous, online display of blood pressure and/or cardiac output for optimal titration of inotropes and vasopressors, a continuous display of blood glucose levels is mandatory for optimal titration of insulin therapy in ICU. We anxiously await the development and validation of such devices.

Keywords algorithm, glucose, insulin, intensive care, mortality

In this issue of *Critical Care*, Vogelzang and coworkers [1] present the results of a retrospective study in which they assessed the relationship between a derivative marker of blood glucose control, which they label 'the hyperglycaemic index' (HGI), and patient outcome in a 12-bed surgical intensive care unit (ICU). They define the HGI as the area under the curve (AUC) of blood glucose above the cutoff of 6.0 mmol/l, divided by the length of ICU stay. They report that the HGI predicts 30-day mortality better than do other indices of blood glucose control, such as blood glucose on admission, mean blood glucose, mean morning blood glucose and maximal blood glucose level. Those investigators thus conclude that the HGI is a useful tool with which to assess glucose control in the ICU patient.

The study aimed to address two questions at once. First, Vogelzang and coworkers investigated the value of the HGI – a marker of duration as well as severity of hyperglycaemia during intensive care – as a predictor of ICU mortality, and compared it with other indices of blood glucose control that do not take time into account. Second, the authors planned to assess this HGI as a tool for comparing adequacy of titration algorithms in reaching a preset level of glucose control in the ICU. Unfortunately, however, the study was not in my view designed to answer this more relevant second question.

The HGI was calculated retrospectively from charts of 1779 patients who had been admitted to the authors' ICU over the preceding 12 years. This retrospective analysis inevitably did not have a predefined sampling interval for blood glucose measurement or a preset insulin titration algorithm. The statistical association between the HGI and mortality at 30 days was studied in univariate analyses, and its predictive potential was compared with those of other measures of blood glucose control (blood glucose on admission, mean blood glucose, mean morning blood glucose and maximal blood glucose level) in multivariate analyses. The authors confirmed the findings of previous studies [2,3] that persistence of hyperglycaemia during intensive care performed better than measures of blood glucose control that do not take time into account, but which have previously been shown to predict ICU mortality [4,5]. However, the receiver operating characteristic (ROC) curve of the HGI revealed an AUC of only 0.64, indicating that capacity to predict mortality

AUC = area under the curve; HGI = the hyperglycaemic index; ICU = intensive care unit; ROC = receiver operating characteristic.

was relatively poor although perhaps statistically a little better than for the other markers of blood glucose control. Whatever the cutoff level for 'normality' in intensive care patients was chosen, the AUC of the ROC remained below 0.65 and thus remained a poor predictor as compared with other paramaters. For example, Acute Physiology and Chronic Health Evaluation II score or serum insulin-like growth factor binding protein 1 concentration both have AUCs of the ROC of about 0.8 (the latter being an indicator of hepatic insulin resistance or lack of insulin effect on the liver) [6].

The statistical association between the HGI – an index of glycaemic control over time – and mortality provided further support to the concept of controlling blood glucose to normal with insulin titration throughout the ICU stay in order to improve outcome [2,7]. It is precisely this which was proven by our large, prospective, randomized and controlled study [7], in which we titrated intensive insulin therapy to maintain a blood glucose below 6.1 mmol/l throughout intensive care. The observation by Vogelzang and coworkers [1] of a slightly better AUC of the ROC when the HGI used a cutoff of 6–8 mmol/l as compared with 4–6 mmol/l does not provide evidence supporting use of a higher target of blood glucose control in the ICU. Indeed, such a differentiation between targets can only be evaluated in a randomized controlled interventional study. The Leuven study [7,8] clearly showed that infusing insulin targeted at an average morning blood glucose of 5.7 mmol/l reduced mortality and morbidity as compared with the control group (average morning blood glucose 8.5 mmol/l). An intermediate level of blood glucose was found to be inferior to a target of below 6.1 mmol/l in terms of the effect on morbidity as well as mortality [8].

In order to achieve normoglycaemia during intensive care, most ICUs require a titration algorithm, particularly during the start-up phase when it is introduced to the nursing staff. If the performance of such algorithms is to be assessed, then a tool for objectively evaluating the adequacy of blood glucose control is indeed mandatory. Vogelzang and coworkers [1] propose that the HGI is such a tool. They claim that the HGI takes into account the unequal distribution of glucose sampling and is not falsely lowered by low glucose values. There are, however, some conditions to be satisfied before the HGI can be considered as a suitable tool to compare adequacy of glucose control algorithms. A first condition is that the blood glucose profile, on which the HGI is calculated, is one with a relatively high number of blood glucose measurements, ideally a continuous or close to continuous blood glucose reading over time. Secondly, in order to compare blood glucose control in two patient groups using the HGI, the sampling interval in the two groups should be comparable. Indeed, when the number of measurements is reduced, this can dramatically alter the HGI, depending on the variability in the blood glucose profile. Let us take a theoretical example of a blood glucose profile following a sinusoid curve crossing the target line of 6.0 mmol/l four times over a certain time period, with dramatically raised levels for half of the time. On multiple sampling, this pattern would be evident, and an elevated HGI would be calculated. However, if the blood samples were taken infrequently, for example only four times and by chance only at the time points when the blood glucose level crossed the target line, then calculation of HGI would yield a falsely normal value.

Just as we prefer a continuous, online display of blood pressure and/or cardiac output for optimal titration of inotropes and vasopressors, a continuous blood glucose measurement and display of blood glucose levels would be of tremendous value in the titration of insulin therapy. Unfortunately, no such devices are yet available to measure glucose in the blood, and currently available devices designed to measure glucose in the subcutaneous adipose tissue still require validation in the ICU setting. Availability and validation of such devices will render intensive insulin therapy easier and safer. Closed loop systems, with computer-assisted titration of insulin dose, will go a step further, and this will also reduce nursing workload and further lower the risk for hypoglycaemia. We anxiously await the arrival of such devices and their ability to optimize life-saving intensive insulin therapy in the ICU. Until this becomes a reality, insulin titration algorithms should include frequent measurement of blood glucose, which implies adequate training of the nursing team. After all, it is the members of the nursing team who have proven to be the most proficient in executing this task.

Competing interests

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