Editorial

Association between glycemic variability and mortality: How robust is the evidence?

John Victor Peter, Raj Kumar Mani[1]

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Hyperglycemia is not uncommon in the intensive care unit (ICU) setting.[1] Hyperglycemia may occur in the background of previously diagnosed or undiagnosed diabetes mellitus or as part of a stress response termed stress-induced hyperglycemia.[2-5] Patients with hyperglycemia fare worse compared with those who do not manifest hyperglycemia.[1] Among patients with hyperglycemia, "new hyperglycemic patients" or those with "stress-induced hyperglycemia" appear to have a higher mortality when compared with those with prior diabetes.[3,5] These observations led to the conduct of several studies that focused on glycemic control in ICU patients. Although the initial landmark study on blood glucose control[6] demonstrated a reduction in mortality with tight glycemic control, subsequent trials[7,8] failed to show an association between "tight" glycemic control and mortality. It also became evident from these trials that hypoglycemia was more frequent in those in whom a lower blood sugar was targeted[7,8] and this was associated with a worse outcome.[9,10] More recent observational studies have suggested that the metrics of glucose should not only include mean blood sugar and lowest blood sugar, but a third factor, namely glycemic variability.[10] Glycemic variability has been recently shown to influence the outcome in critically ill-patients.[11-14] These observations led to the concept that three dimensions of glycemic control need to be addressed in ICU patients viz. hyperglycemia, hypoglycemia, and glycemic variability.[15]

In this context, it is therefore appropriate that in this issue of the Indian Journal of Critical Care Medicine Todi *et al*. explored the relationship between glycemic variability and outcome in Indian patients.[16] The authors, in this retrospective study included a heterogeneous population of 2208 ICU patients admitted to a tertiary care hospital. Glycemic variability was assessed as "the standard deviation of the mean blood glucose" as well as the "glycemic liability index."[17] Both these parameters were significantly associated with ICU mortality.[16] The relationship between glycemic variability and ICU mortality was maintained after excluding patients with hypoglycemia. The authors further went on to suggest that patients in the euglycemic range with greater glycemic variability had a higher mortality than patients above the euglycemic range.

In the light of the recent publications on this subject enrolling large number of patients and demonstrating a similar relationship between glycemic variability and outcome, the current study[16] does not add to the existing knowledge on this subject. Although this study provides locally relevant data, several aspects need to be looked at in order to have the right perspective on this topic and set directions for future work.

Like most published literature on glycemic variability, this Indian study[16] was a retrospective review of prospectively collected data. However unlike the other studies, the number of patients included (n = 2208) in the Indian study was much smaller than the three cohorts that enrolled 7049 patients,[13] 66,184 patients[11] and 44,964 patients[12] respectively. Given the retrospective nature of the studies,

From:
Department of Critical Care, Medical Intensive Care Unit, Christian Medical College, Vellore,
Tamil Nadu, [1]Department of Critical Care and Pulmonology, Saket City Hospital, Mandir Marg, Saket, New Delhi, India

Correspondence:
Dr. John Victor Peter, Medical Intensive Care Unit, Christian Medical College Hospital, Vellore - 632 004, Tamil Nadu, India.
E-mail: peterjohnvictor@yahoo.com.au

prospective validation of the relationship between glycemic variability and mortality is important.

Another matter of concern in the published studies is the average number of blood sugar estimations in each patient used for assessing glycemic variability. In the largest study,[11] a total of 132,368 estimations were performed on 66,184 patients having a median length of ICU stay of 2 days. This equates to an average of one blood sugar estimation per patient per day. In the other large study[12] of 44,964 patients, 10 (interquartile range [IQR] 5-21) blood sugar estimations were done over 2.8 days (IQR 1.6-5 days) of ICU stay, equating to 3.6 estimations per patient per day. In the Indian study,[16] an average of 5.1 blood sugar estimations were done per patient during the average ICU stay of 4.9 days resulting in 1.1 blood sugar estimations per patient per day. These suggest that the frequency of blood sugar monitoring was grossly inadequate to detect every episode of dysglycemia and thereby accurately assess the "true" glycemic variability. Increasing the frequency of blood sugar estimations or using continuous glucose monitoring techniques in prospective studies should help overcome this issue.

The tool used for blood sugar estimation in the recent publication[16] also merit discussion. The authors used capillary point-of-care blood glucose measurements without prior standardization against venous glucose. The reliability and accuracy of capillary glucose estimation in the critically ill has been questioned in several publications that demonstrated significant differences between point-of-care blood glucose and laboratory glucose estimations.[18-20] The magnitude of difference prompted authors to caution that use of point-of-care blood glucose estimations to guide therapy may lead to faulty treatment decisions.[18] Against this background, the use of capillary blood glucose with point-of-care testing and the division of these glucose values into very narrow deciles[16] further weakens the study.

In the light of the above concerns, the assertion that glucose variability is associated with increased mortality particularly among euglycemic patients is premature. While in the overall ICU population, a relationship between glycemic variability and morality is likely, the evidence needs to be more robust in the form of carefully planned prospective trials. Unless blood glucose is monitored accurately and more frequently or continuously, in prospectively conducted studies, the relationship between glycemic variability and the outcome would remain as hypothesis generating and needing validation.

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