Letters to the Editor

Could Susceptibility to Low Hematocrit Interference Have Compromised the Results of the NICE-SUGAR Trial?

To the Editor:

The recently published findings of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR)[1] trial have dramatically changed clinician attitudes toward the achievement of euglycemia in intensive care unit (ICU) patients *(1)*. In defending the proof-of-concept studies that validated the efficacy of normalizing blood glucose in the ICU, Van den Berghe et al. pointed out numerous variances between their original studies and those of the NICE-SUGAR trial *(2)*. They included differences in blood glucose targets, insulin administration, blood sampling, nutritional strategies, clinician expertise, and the relative accuracy of the glucose measurement devices. Recently, *Clinical Chemistry* presented a very interesting Q&A on the use of blood glucose meters to achieve tight glucose control in patients in the ICU *(3)*. Because one of our ICUs participated in the NICE-SUGAR trial, we report here some interesting and relevant data that shed more light on the NICE-SUGAR trial, data that yield more questions than answers.

In our 30-bed general systems ICU at the University of Alberta Hospital, point-of-care glucose concentrations can be measured in 2 different ways: respiratory therapists measure arterial blood gases, hemoglobin, electrolytes, and glucose values with the Radiometer 800 blood gas system (BGA) and nurses measure arterial blood and capillary blood glucose with the LifeScan SureStep Flexx blood glucose meter (BGM). Both the BGA and BGM glucose results are stored in a central laboratory data repository, and we retrieved Radiometer BGA and Lifescan BGM glucose results that were run within 15 min of each other for individual patients. The numeric differences between these paired values graphed against the date of collection (represented by the point data) are shown in Fig. 1. The BGM results were usually higher than the BGA results for the first 3 strip lots, with the difference averaging 0.83 mmol/L or 13.6%. For the next 3 strip lots, this BGM/BGA glucose bias was almost zero (0.03 mmol/L; 1.4%). Neither of the manufacturers, Radiometer or Lifescan, could offer any reason for these difference trends.

Because many BGM systems provide artifactually high glucose concentrations in patients with low hematocrits *(4)*, we graphed the BGM/BGA differences against hemoglobin that was proportional to hematocrit and measured by using the Radiometer analyzer. [The mean hemoglobin concentrations were very similar over the 2 periods, 92.7 (s = 16.9) vs 92.8 (s = 18.1) g/L]. The first 3 glucose reagent-strip lots were more sensitive to the effects of hemoglobin compared to the next 3 lots [glucose difference = $-0.0195 \times$ hemoglobin (mg/L) + 2.41; $r^2 = 0.108$; $P = 0.0001$ (first 3 strip lots); glucose difference = $-0.0103 \times$ hemoglobin (mg/L) +1.09; $r^2 = 0.0926$; $P = 0.0021$ (last 3 strip lots)]. It appears that many of the samples measured with the first 3 lots of strips would have artifactually increased glucose concentrations. Our hospital general systems ICU participated in the NICE-SUGAR study, and the time of the data collection for NICE-SUGAR coincided with the period during which we were using lots 1, 2, and 3. Of the glucose values reported by our ICU for the NICE-SUGAR patients, the LifeScan BGMs were the source of the most of the glucose values. In accordance with the NICE-SUGAR protocol, high glucose values would be treated. During the NICE-SUGAR study, our LifeScan BGMs were providing increased glucose concentration results on most of our ICU patients, because the majority had low hemoglobin concentrations. Treatment of artifactual hyperglycemia can cause hypoglycemia *(5)*, which should be verified by the main laboratory or a point-of-care blood gas glucose measurement. BGM manufacturers produce multiple strip lots that should exhibit minimum variation. It is possible that other NICE-SUGAR study sites that used LifeScan meters would be treating such artifactual hyperglycemia and thus provoking hypoglycemia. It is important to know what proportion of participating institutions used LifeScan meters. It is also important to know the relative frequency of blood glucose measurements that were obtained by using the LifeScan BGM system in NICE-SUGAR study patients compared to more accurate methods such as BGA glucoses. Finally, we should also know the frequency of occasions in which there was subsequent corroboration of hyperglycemia by the main laboratory or by BGA glucose analysis. If a large proportion of study participants used LifeScan systems and relatively few of the hyperglycemic episodes were verified by alternate methods, then perhaps the NICE-SUGAR study should be repeated with more attention paid to the accuracy of the glucose-measuring device *(6)*.

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[1] Nonstandard abbreviations: NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation; ICU, intensive care unit; BGA, blood gas system; BGM, blood glucose meter.
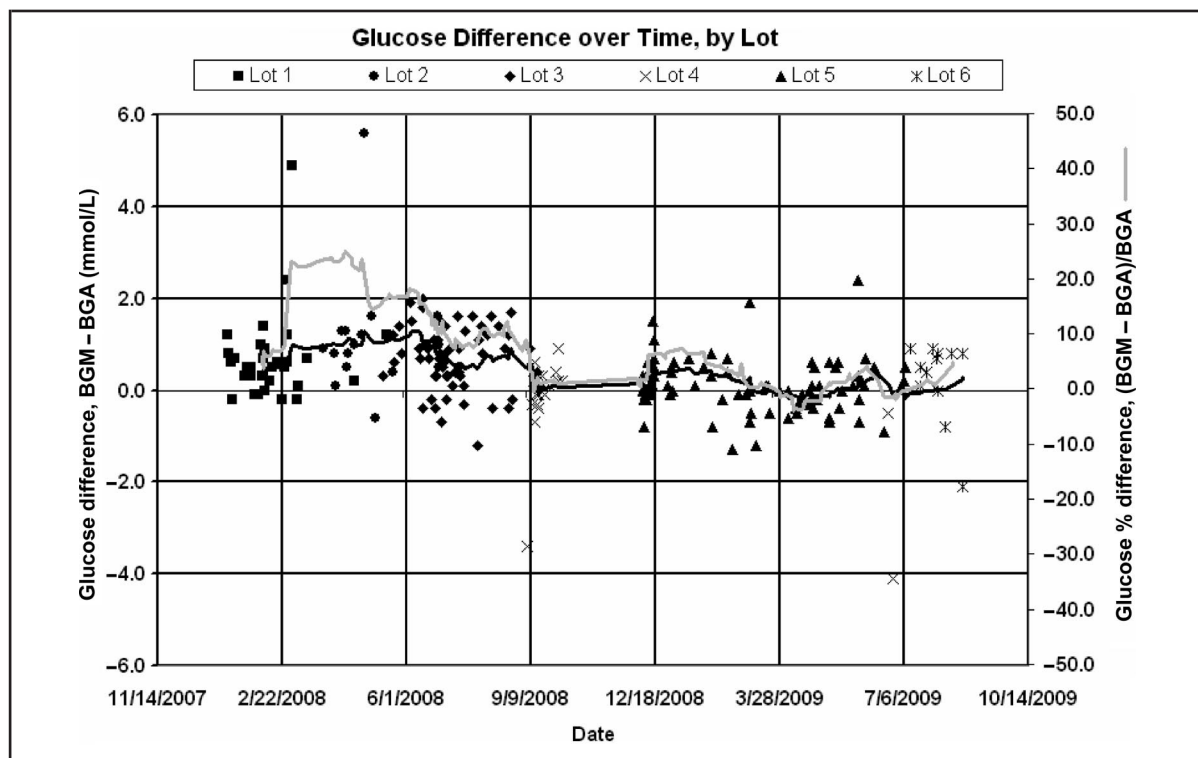
Fig. 1. Glucose differences (BGM − BGA) vs time in any patient who had arterial blood glucose measured on the Radiometer BGA and arterial or capillary blood measured on the LifeScan BGM within 15 minutes.

Six different strip lots were primarily used. The 15-point moving mean of these numeric differences and the moving mean of the relative differences are shown (relative difference data not presented). The numeric differences are represented by 6 different symbols, with each representing a different reagent strip lot. The lines represent lot-specific moving means of the 237 differences (the dark line represents the moving mean of the numeric differences; light line, the moving mean of the relative [%] differences).

References

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