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Analysis: Continuous Glucose Monitoring during Intensive Insulin Therapy

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Abstract

Results of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, intensive insulin therapy (IIT), and use of a continuous glucose sensor in intensive care units (ICU) were analyzed. The NICE-SUGAR trial was unable to determine if optimal intensive insulin therapy decreases mortality. Continuous glucose monitoring (CGM) technology has the potential to improve glycemic control with low glucose variability and low incidence of hypoglycemia. Interstitial fluid CGM may not be useful in perioperative and ICU settings. Studies evaluating the accuracy and reliability of CGM devices, based on a whole blood sample in perioperative and ICU settings, are needed. Once a reliable CGM sensor for ICU use is identified, a large, prospective, controlled, multicenter study could determine if optimal IIT with a low or zero incidence of hypoglycemic events improves mortality.

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Intensive insulin therapy (IIT) in critically ill patients gained popularity after the first van den Berghe's study in 2001.[1] However, subsequent studies questioned the clinical benefit of IIT. Two recent meta-analyses found that IIT did not influence mortality and were associated with an increased risk of hypoglycemia.[2,3] A resolution of the controversy was expected following publication of the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial results, the first large, multicenter, multinational study evaluating IIT.[4] In this trial, 6104 patients were randomized into an intensive glucose control group with a target blood glucose range of 81 to 108 mg/dl or into a conventional glucose control group with a target of <180 mg/dl. Mortality was higher in the intensive control group (27.5%) than in the conventional control group (24.9%) with an odds ratio of 1.14 (95% confidence interval, 1.02 to 1.28; $P = 0.02$). Although the study was adequately powered to show a mortality difference between the groups, the difference in the mean time-weighted glucose level (TWGL) was only 29 mg/dl; 115 ± 18 and 144 ± 23 mg/dl in the intensive control group and conventional group, respectively. A large portion of the patients placed in the control group had relatively good glycemic control (as assessed by their TWGL), and any additional benefit of intensive glucose control may be offset by the higher risk of hypoglycemia. This small difference between the intensive insulin group and the

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Abbreviations: (CGM) continuous glucose monitoring, (EGA) error grid analysis, (ICU) intensive care unit, (IIT) intensive insulin therapy, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, (POC) point of care, (SD) standard deviation, (TWGL) time-weighted glucose level

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control group of patients clouds the interpretation of data, as a large number of the patients overlap. Approximately 30% of the control group patients had their TWGL value within 1 standard deviation (SD) of the mean TWGL of the intensive insulin group. Approximately 37% of the intensive insulin patients had their TWGL value within 1 SD of the mean TWGL of the control group. It has been suggested that an overlap of glucose levels in controls and intervention groups should not exceed 20%.[5]

Moreover, the NICE-SUGAR clinical methods used for blood sampling, handling, and glucose measurement were not standardized, optimized, or categorized. Use of multiple point-of-care (POC) devices in different institutions with different sites for blood draws could give erroneous glucose level readings. Intensive care unit (ICU) studies showed that 15% of capillary glucose values differed from the whole blood laboratory reference values by more than 20%.[6] Measurement error may be more pronounced in the hypoglycemia range and in sicker patients with hand edema and low peripheral blood flow. POC capillary blood glucose measurements can differ from peripheral venous measurements by up to 70 mg/dl.[7] The glucose difference between different POC devices could be as great as 32 mg/dl even using arterial blood only.[8] The analytical difference is more than the difference between intensive control and conventional groups in the NICE-SUGAR trial.

Finfer and Delaney[9] suggested that even a negative finding of the NICE-SUGAR study would not provide evidence for abandoning glucose control. They suggested finding affordable frequent and highly accurate measurements of blood glucose in the ICU and called for a similar study to determine if IIT can reduce mortality under optimal conditions. This could be accomplished by using a standardized method of blood sampling and continuous glucose monitoring (CGM) technology. CGM systems give real-time glucose levels, trends, direction and rate of changes, and alarms for hypo- and hyperglycemia. All of these features are useful for achieving optimal glucose control with low variability and no hypoglycemic events. In a previous review of CGM technology, Klonoff[10] suggested that CGM should be used in situations when tighter glucose control without hypoglycemia is sought.

Studies examining the use of CGM in hospitalized patients are sparse. It has been emphasized that CGM may help optimize IIT in the ICU, but the accuracy of CGM needs to be improved.[11] Rabiee and colleagues[12] assessed the reliability and accuracy of a subcutaneous sensor (DexCom™ STS; San Diego, CA) in general surgical ICU and burn ICU patients, as well as in a clamp study in morbidly obese volunteer subjects before bariatric surgery. In this observational study, the target range for IIT in ICU patients was 90–120 mg/dl. The DexCom STS sensor, when compared with the Accu-Chek in ICU patients [Clarke error grid analysis (EGA) showed an A region of 68.26%, a B region of 31.83%, and a C region of 0.75%, matching pairs, $r = 0.718$, $P < 0.001$] and the Hitachi glucose analyzer (75% of pairs fell in the A region and 25% in the B region of Clark EGA, $r = 0.796$, $P = <0.001$), did not perform well. In the clamp part of the study, the plasma glucose was clamped at 95 mg/dl for 2 hours and, after a 1-hour recovery, was raised to about 190 mg/dl for 2 hours. The CGM was even less accurate in morbidly obese subjects when compared with the Beckman analyzer (42.29% pairs were in the A Clark EGA region, 55.90% were in the B region, and 4.08% were in the C region, $r = 0.638$, $P < 0.001$). By comparing two different populations, the authors have attempted to separate the effects of the patient (i.e., obesity) from the situation (i.e., ICU setting), as ICU patients may have abnormal interstitial fluid composition and poor tissue perfusion, leading to hypoxia, acidosis, and edema. This study suggests that interstitial fluid CGM systems may have decreased accuracy in morbidly obese patients. Further CGM research is required for this population.

Rabiee and associates[12] reported high CGM failure rate in ICU patients. In a large majority of ICU patients, the CGM signal was lost for several hours. Furthermore, the DexCom device had a 50% false negative rate in 30 hypoglycemic events (<70 mg/dl) as measured by the Accu-Chek POC meter. Moreover, hypoglycemia detected by the DexCom CGM was false 92% of the time. Only 14 of 167 events were confirmed by an Accu-Chek measurement to be true hypoglycemia. Although Accu-Chek glucose was measured by clinical nurses using different blood sources (venous, arterial, and capillary), which could bias the results, the study suggests that subcutaneous CGM may not be suitable in the ICU setting, especially for detecting hypoglycemia.

Interstitial fluid glucose sensor performance in critically ill and postsurgery patients is highly variable, secondary to a low perfusion state and high oxygen consumption. An intravascular or blood sensor could have an advantage in this setting. Blood sensors can be categorized into two groups: (1) an external flow-through blood sensor type attached to an intra-arterial or intravenous catheter with an external enzyme/electrochemical or optical sensor that measures blood or plasma glucose and (2) an intravascular blood sensor type inserted into the lumen of an artery

or central/peripheral vein with an enzyme/electrochemical/optical/fluorescence sensor that measures blood or plasma glucose. The GlucoScout (International Biomedical, Austin, TX) is the only currently approved CGM for in-hospital glucose monitoring. This in-hospital CGM utilizes enzyme glucose oxidase and electrochemical methods to measure glucose in whole blood. The device automatically delivers a sample of patient blood from a vascular catheter to an external sterile flow-through glucose sensor. The GlucoScout is limited by mechanical issues related to delivering a blood sample from a peripheral venous catheter to the external flow-through glucose sensor. The device may alarm frequently when unable to acquire a blood sample. Flush volume may be excessive in some patients. Several other CGM devices are in development:

- The Edwards/DexCom intravenous blood glucose system (DexCom Corporation, San Diego, CA, and Edwards Lifesciences, Irvine, CA) has a miniature enzyme-based electrochemical glucose sensor located within the lumen of an intravenous catheter.
- The OptiScan continuous glucose monitor (OptiScan Biomedical Inc., Hayward, CA) transports a blood sample to an external device, processes the sample to plasma, and performs a glucose measurement using mid-infrared optics.
- The GluCath (GluMetrics, Inc., Irvine, CA) is a small-diameter fiber optic platform with sensing fluorescent chemistry on the distal tip that is inserted into the lumen of a peripheral vein or artery. Clinical studies have shown high accuracy in the hypoglycemic range compared to other CGM systems.

Rabiee and colleagues[12] found DexCom CGM's detection of hypoglycemia and hypoglycemic alarms not clinically useful. Accuracy in the hypoglycemic range is important for implementing optimal IIT with zero severe hypoglycemic events. This could make CGM more clinically acceptable by nurses, avoiding false positive and false negative hypoglycemic alarms.

Studies evaluating the accuracy and reliability of a CGM device based on whole blood samples in perioperative and ICU settings are needed. Once small studies identify the most suitable CGM device for the ICU setting, a large, prospective, controlled, multicenter study similar to the NICE-SUGAR trial should determine if optimal IIT with near normal glycemic control and low or zero hypoglycemic events improves patients outcome. Until the results of this study become available, glucose control should be targeted in the 140- to 150-mg/dl range, starting IIT when the glucose level is above 180 mg/dl, as suggested in a new American Association of Clinical Endocrinologists/American Diabetes Association statement.[13]

In conclusion, the NICE-SUGAR trial did not determine if optimal IIT with a near normal blood glucose target and low incidence of hypoglycemia decreases mortality. CGM technology providing real-time glucose levels, trends, direction and rate of changes, and alarms for hypo- and hyperglycemia has the potential to improve glycemic control with low glucose variability and zero incidence of hypoglycemia, making it an optimal device for research and clinical use. Interstitial fluid CGM may not be useful in perioperative and ICU settings. Studies evaluating the accuracy and reliability of CGM devices, based on a whole blood sample in perioperative and ICU settings, are needed. Once a reliable CGM sensor for ICU use is identified, a large, prospective, controlled, multicenter study is needed to determine if IIT with a near normal glycemic target and a low or zero incidence of hypoglycemic events improves mortality.

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