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CONTROVERSIES in
Continuous Glucose Monitoring

The Need for Continuous Blood Glucose Monitoring in the Intensive Care Unit

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Abstract

Insulin-based regimens decrease morbidity and mortality among critically ill patients by way of keeping glucose at tight control. Utilizing these regimens involves multiple measurements of glucose by way of finger pricking or through indwelling vascular catheters in order to adjust insulin doses. The limitations and risks of these methods of glucose monitoring are related to potential erroneous measurements, increased risk of infection, and a significant excess workload. An automated blood glucose monitoring device for glucose monitoring of critically ill patients is needed to improve patient care while avoiding the disadvantages of currently used glucose monitoring methodologies.

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Elevated glucose levels in critically ill patients have been shown to be related to increased mortality and length of hospital stay in adults and children.[1,2] The impact of tight glycemic control on clinical outcomes of patients in the intensive care setting has recently gained recognition. Landmark studies by Van den Berghe *et al*.[3,4] and others demonstrated reduced mortality in patients who reached target glucose values in the range of 80–110 mg/dl and whose stay in the medical intensive care unit (ICU) was longer than 72 hours and reduced morbidity in all patients who reached these strict target glucose values. In a pooled data set analysis,[5] the same group showed that intensive insulin therapy with target blood glucose <110 mg/dl was beneficial for all medical or surgical ICU patients except those with a prior diagnosis of diabetes, yet also carried a greater risk for hypoglycemia.

Thus, it is now accepted that insulin-based treatment regimens decrease morbidity and mortality in critically ill patients,[6] yet strict glycemic control should be performed in a manner that minimizes the risk of hypoglycemia. Importantly, as the majority of ICU patients are at decreased levels of consciousness and increased stress, the detection of hypoglycemia in these patients depends solely on glucose monitoring. The American Diabetes Association and the American Association of Clinical Endocrinologists have published guidelines that recommend a glucose target as close to

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Abbreviation: (ICU) intensive care unit

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110 mg/dl for all critically ill patients.[7,8] A cost analysis study of intensive glycemic control in critically ill adult patients revealed that strict glucose control saved an average of $1580 per patient.[9] This substantial saving was the result of shorter ICU and overall hospital length of stay, decreased ventilator-dependent days, and reduced total laboratory costs. Similarly, in mechanically ventilated patients admitted to a surgical intensive care unit, the excess cost of hospitalization in patients treated conventionally compared to those treated according to the intensive insulin regimen was 2638 Euro per patient.[10] These observations suggest that the cost of intensive glucose management is outweighed by the improved clinical outcomes and is worth pursuing also from an economical standpoint.

The foundation of strict glycemic control by intensive insulin therapy protocols demands frequent and accurate glucose monitoring. The majority of suggested protocols[11] demand a minimum of hourly glucose monitoring for successful glycemic target achievement while reducing the risk of hypoglycemia. Currently there are two common procedures used to measure point of care blood glucose: via a venous/arterial blood by way of an indwelling vascular catheter and via capillary (also called finger prick) blood. Venous/arterial vascular blood sampling is time-consuming, carries a risk of infections and complications, and involves a relatively large amount of blood drawn. Performing hourly or semihourly finger pricking using standard point of care glucometers is still the most commonly used method. This method is time-consuming, labor intensive, and prone to measurement errors. There is a substantial difference in the performance of glucometers when comparing operators with different level of expertise, as the precision of the meters handled by experienced operators (expressed as the coefficient of variation) is in the range of 6.7–11%, whereas the precision of values obtained by less experienced ones may range from 13.7 to 45.7%! As many as 62% of values obtained in intensive care units deviate from reference laboratory values by >20%.[12] It is clear that such discrepancies in glucose levels would surely have an impact on dosing of insulin regimens. The large coefficient of variation of finger-prick bedside glucometer results in comparison to glucose measured from arterial or venous blood in a reference laboratory is not only due to operator's performance. Local perfusion of the site of measurement may have a major impact on the glucose levels. Low perfusion states, commonly encountered in ICU patients, together with increased regional glucose utilization, may result in a biased capillary glucose measurement. Atkin and colleagues[13] demonstrated that in patients in shock, capillary glucose was on average 67.5% of the reference laboratory blood glucose. Only 36% of patients had finger stick-derived capillary glucose levels within 20% of the measured reference. However, venous-derived glucometer measurement accurately reflected laboratory-derived reference glucose levels. Another source of bias in finger stick-derived capillary glucose measurement may be skin temperature. Lower core temperatures, as seen in induced hypothermia for specific surgical interventions, can cause a significant underestimation of blood glucose due to peripheral hypoperfusion.[14]

Continuous glucose monitoring by way of subcutaneous glucose sensors is a new and promising modality for promoting better glucose control in patients with diabetes. Some have suggested that such devices may be a solution for the need of strict glycemic monitoring in the intensive care setting. The performance of such devices in the out-of-hospital setting is very promising for improvement of day-to-day glucose control of patients with diabetes, yet reported deviations of the sensor-derived glucose measurement (median absolute relative error of 17.3% in comparison to glucometers),[15] specifically in the low-to-normal glucose range, suggest that its use for the adjustment of intensive insulin protocols for the achievement of strict glycemic control in a narrow glucose range may still be premature. When tested in the ICU setting, the MiniMed continuous glucose monitoring system was compared to standard capillary glucose measurements and demonstrated a mean glucometer-sensor difference of 19.7 ± 18.3 mg/dl, yet a comparison to reference venous/arterial blood glucose was not performed.[16] All the subcutaneous continuous glucose monitoring devices on the market (Guardian RT, Navigator, and DexCom) utilize comparable glucose-oxidase methodology of glucose measurement and derive their results from interstitial fluid glucose, converted by a specific algorithm to reflect blood glucose. The utilization of interstitial fluid measurements in critically ill patients introduces additional sources of bias into the glucose measurement. The insertion site used most commonly for continuous glucose monitors is the subcutaneous tissue of the abdominal wall. Glucose levels in the abdominal subcutaneous interstitial fluid may be affected by local blood flow and temperature, the dynamics of systemic blood glucose changes, and the distance between the sensor and the blood vessel supplying the area of interest.[17] Local perfusion and temperature of the abdominal subcutaneous tissue may be substantially affected by manifestations of critical illness, such as shock, sepsis, or external cooling, thus creating a major bias in glucose assessments. Another important subset of patients who would benefit from strict glycemic control

are those in surgical and trauma intensive care units, specifically patients with burns, with abdominal trauma, and/or with surgical interventions that may limit the utilization of interstitial glucose monitoring.[18] The fact that interstitial glucose may have a certain lag behind blood glucose in cases of rapid dynamic changes of systemic glucose levels introduces an additional source of error and overall further limits the use of sensor-derived glucose levels as a sole means of decision making regarding the adjustment of intensive insulin protocols.

For the implementation of intensive insulin protocols for strict glycemic control in the ICU setting, there is an urgent need for an automated continuous vascular blood glucose monitor. The assessment of vascular-derived samples should minimize the sources of bias of capillary and interstitial fluid glucose typically encountered in critically ill patients. Such a system must be automated, as the excessive labor and risk of contamination involved in repetitive sampling from indwelling vascular catheters are unacceptable. The system should provide customizable options for sampling intervals, minimize caregiver manipulation, reduce patient's risk, and, most importantly, provide glucose measurements that reflect the cerebral glucose supply. This system should supply results in real time and be reliable enough to allow safe adjustments of the insulin protocols while avoiding hypoglycemia.

Such a glucose monitoring device will enable state-of-the-art patient care alongside an improved safety profile, as well as a reduced medical personnel workload.

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