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Impact of Glucose Meter Error on Glycemic Variability and Time in Target Range During Glycemic Control After Cardiovascular Surgery

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Abstract

Background: We retrospectively studied the impact of glucose meter error on the efficacy of glycemic control after cardiovascular surgery.

Method: Adult patients undergoing intravenous insulin glycemic control therapy after cardiovascular surgery, with 12-24 consecutive glucose meter measurements used to make insulin dosing decisions, had glucose values analyzed to determine glycemic variability by both standard deviation (SD) and continuous overall net glycemic action (CONGA), and percentage glucose values in target glucose range (110-150 mg/dL). Information was recorded for 70 patients during each of 2 periods, with different glucose meters used to measure glucose and dose insulin during each period but no other changes to the glycemic control protocol. Accuracy and precision of each meter were also compared using whole blood specimens from ICU patients.

Results: Glucose meter 1 (GM1) had median bias of 11 mg/dL compared to a laboratory reference method, while glucose meter 2 (GM2) had a median bias of 1 mg/dL. GM1 and GM2 differed little in precision (CV = 2.0% and 2.7%, respectively). Compared to the period when GM1 was used to make insulin dosing decisions, patients whose insulin dose was managed by GM2 demonstrated reduced glycemic variability as measured by both SD (13.7 vs 21.6 mg/dL, $P < .0001$) and CONGA (13.5 vs 19.4 mg/dL, $P < .0001$) and increased percentage glucose values in target range (74.5 vs 66.7%, $P = .002$).

Conclusions: Decreasing glucose meter error (bias) was associated with decreased glycemic variability and increased percentage of values in target glucose range for patients placed on intravenous insulin therapy following cardiovascular surgery.

Keywords
glucose meter, glycemic control, glycemic variability, insulin therapy

Glycemic control may decrease morbidity and mortality in critically ill patients, though the optimal glucose concentration remains controversial.[1-3] Use of handheld glucose meters allows rapid treatment decisions to be made for patients on intravenous insulin. However, patients in the intensive care unit (ICU) are on multiple medications, and often have abnormal hematocrit, which may affect the performance of glucose meters.[4,5]

The degree to which glucose meters correlate with laboratory glucose measurement varies between glucose meter technologies,[4] and correlation in the hypoglycemic and hyperglycemic ranges is poor for some meters.[6,7] Though newer meter technologies may provide more accurate glucose measurement,[8-10] there is still substantial concern about the use of glucose meters for management of glycemic control in the ICU.[11,12]

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Error simulation models have been used to estimate the impact of glucose meter error on the rate and magnitude of insulin dosing errors in the context of glycemic control.[13-15] A few investigators have used simulation models to estimate the impact of glucose monitor error on short-term outcomes (efficacy) of glycemic control, as measured by glycemic variability, time in target range, and rates of hypoglycemia or hyperglycemia.[16-18] However simulation models have reached differing conclusions about the impact of glucose monitor error on glycemic control efficacy. We performed a retrospective study of the impact of glucose meter error on the efficacy of glycemic control, as measured by glycemic variability, time in target range, and incidences of hypoglycemia and hyperglycemia.

Methods

Bias and Precision of Glucose Meters in the ICU

In an experiment previously described,[8] we retrospectively analyzed 1602 paired (collected within 5 minutes of each other from the same patient) whole blood glucose meter and serum glucose values obtained from ICU patients over the time period August-October 2012. During this period GM1, the Roche AccuChek Inform (Roche Diagnostics, Indianapolis IN), was used for all whole blood glucose measurements. After implementation of GM2, the Nova StatStrip (Nova Biomedical, Waltham, MA) glucose meter, we retrospectively analyzed 1093 paired glucose meter and serum glucose obtained values from ICU patients over the time period June-August 2013.

To determine the precision of glucose meters in the ICU, we performed 5 whole blood GM1 glucose measurements, using 5 different glucose meters, on arterial whole blood samples from 20 different ICU patients. For each set of 5 glucose meter results, we calculated the mean glucose value and standard deviation of the 5 replicates. Coefficient of variation (CV) was calculated by dividing the mean standard deviation by the mean glucose. The same experiment was repeated with 5 GM2 devices using samples from 20 (separate) ICU patients, allowing a direct comparison of precision between devices when used with fresh arterial whole blood tested at the bedside.

Measures of Glycemic Variability

While there are many measures of glycemic variability, we focused on standard deviation (SD) and continuous overall net glycemic action (CONGA) for this study as these measures are among the most sensitive to acute excursions or hourly variability in glucose concentration:[19]

$$\text{SD} = \text{square root}\left[\sum \left(\text{BG}_n - \text{BG}_{mean}\right)^2 / \text{n-1}\right]$$

$$\text{CONGA} = \text{square root}\left[\sum \left(\text{Dt} - \text{Dt}_{mean}\right)^2 / \text{n}-1\right]$$

$$\text{Where Dt} = \text{BG}_n - \text{BG}_{n-1}$$

Power Study for Glycemic Variability After Cardiovascular Surgery

To estimate the number of patient glucose records needed to detect a change in glycemic variability after cardiovascular surgery, we collected GM1 glucose values from 40 patients who had 12-24 consecutive (within 120 minutes) glucose values obtained while on the institutional glycemic control protocol in the 24-48 hours after cardiovascular surgery. Twenty patients without a diagnosis of diabetes mellitus (ND) and 20 patients with a diagnosis of type 2 diabetes mellitus (T2DM) were selected. Based on the observed mean CONGA for this data set with an SD of 8.18, a 2-sided Wilcoxon rank sum test was used to determine that 72 patients would be needed to detect a 20% or greater reduction in glycemic variability as measured by CONGA, with a 5% level of significance (α error) and power of 90% (β of .90).

Glycemic Variability, Time in Target Range, and Incidences of Hypoglycemia and Hyperglycemia

During period 1 (June-November 2012), clinical databases were used to identify patients who had cardiovascular surgery and 30 or more glucose measurements over a hospital admission. Clinical records were then reviewed (in order of ascending medical record number) to identify 35 ND and 35 T2DM patients who had cardiovascular surgery at Mayo Clinic Hospital, St Marys Campus (Rochester, MN) and were placed on glycemic control (intravenous insulin protocol) in the cardiovascular surgery ICU. Insulin dosing decisions during period 1 were made exclusively based on whole blood glucose results obtained with GM1. Patients were eligible if they received intravenous insulin and had 12 or more consecutive (within 120 minutes of previous measurement) glucose values while on glycemic control. The first 12-24 consecutive glucose values obtained in the cardiovascular surgery ICU while on intravenous insulin were used for measurement of SD, CONGA, and percentage values in target glucose range (110-150 mg/dL). All incidences of hypoglycemia (glucose concentration < 70 mg/dL) and hyperglycemia (glucose concentration > 200 mg/dL) were also recorded.

The same process was used to identify 70 similar patients (35 ND, 35 T2DM) patients during period 2 (August 2013-February 2014), when all insulin dosing decisions were based on whole blood glucose obtained with GM2. During each period the glycemic control protocol called for hourly

Table 1. Demographic Information and Patient Characteristics for 70 Patients With 12-24 Consecutive Glucose Values Recorded After Cardiovascular Surgery During Each Study Period.

	Period 1 (June-November 2012)	Period 2 (August 2013-February 2014)	*P* value
Age (years), median (IQR) [overall range]	70 (61, 76) [28-92]	67 (57, 75) [29-86]	.16
Gender	39 male, 31 female	42 male, 28 female	.61
Diabetes status	35 ND, 35 T2DM	35 ND, 35 T2DM	N/A
Number of glucose measurements, median (IQR)	22 (18, 24)	21 (18, 24)	.19

IQR, interquartile range; N/A, not applicable; ND, no diagnosis of diabetes mellitus; T2DM, type 2 diabetes mellitus.

adjustment of insulin dose based on the whole blood glucose meter value. The target glucose range during each period was 110-150 mg/dL. The glycemic control protocol (insulin dosing categories) and personnel performing glucose meter measurements did not change between periods. The study design was approved by the Mayo Clinic Institutional Review Board.

Statistics

Statistical significance of differences in median glucose was assessed by generalized estimating equations to account for multiple measurements per patient. Differences in median SD, CONGA, percentage values in target range, and patient age were assessed by Wilcoxon rank sum test. Differences in gender were assessed by chi-square test. $P < .05$ was considered statistically significant for all comparisons.

Results

Precision and Accuracy of Glucose Meters in ICU Patients

To measure precision of GM1 when fresh (no anticoagulant) arterial whole blood samples from ICU patients are analyzed at the bedside, we performed 5 glucose meter measurements using 5 different glucose meters from each of 20 ICU patients. The mean glucose value among the 100 measurements was 142 mg/dL. The mean SD from the 20 sets of replicates was 2.9 mg/dL, with mean CV of 2.0% (2.9/142). We repeated the same experiment using GM2 on 20 separate ICU patients. Mean glucose for the 100 measurements was 140 mg/dL. The mean SD from the 20 sets of replicates was 3.8 mg/dL, for a mean CV 2.7% (3.8/140).

The accuracy of GM1 and GM2 in the ICU was evaluated by retrospectively analyzing 1602 (GM1) and 1093 (GM2) paired glucose meter whole blood and laboratory serum glucose values from ICU patients. Median (interquartile range) bias for GM1 whole blood glucose was 11 (6 to 18) mg/dL, compared to 1 (–5 to 5) mg/dL for GM2.[8] The range of laboratory serum glucose values in the GM1 data set was 32-411 mg/dL, with 32 serum values in the hypoglycemic range (glucose < 70 mg/dL) and 94 serum glucose values in the hyperglycemic range (glucose > 200 mg/dL). The range of laboratory serum glucose values in the GM2 data set was 40-497 mg/dL, with 17 hypoglycemic and 132 hyperglycemic lab serum values. Accuracy criteria as defined in Clinical and Laboratory Standards Institute guideline POCT12-A3 (± 12 mg/dL of serum glucose value for serum glucose values < 100 mg/dL and ± 12.5% for serum glucose ≥ 100 mg/dL)[20] were met for 1105/1602 (69%) of GM1 and 1043/1093 (95%) of GM2 whole blood glucose values. Using accuracy criteria of ± 15 mg/dL for reference glucose < 100 mg/dL and ± 15% for reference values ≥ 100 mg/dL, 1288/1602 (80%) of GM1 and 1065/1093 (97%) of GM2 values met accuracy criteria. When used on ICU patients GM2 exhibited decreased error compared to GM1, due to decreased bias.

Patient Demographics and Characteristics

The age and gender of the 70 patients enrolled during each period did not differ (Table 1). During each period we intentionally enrolled equal numbers of patients who did not have a diagnosis of diabetes mellitus (ND) and who had a diagnosis type 2 diabetes mellitus (T2DM) at the time of surgery. The median number of glucose measurements per patient did not differ between periods (Table 1).

Glycemic Variability and Time in Target Range

Median glucose concentration, median glycemic variability as measured by SD, and median glycemic variability as measured by CONGA decreased significantly during period 2 (GM2 used to dose insulin) compared to period 1 (GM1 used to dose insulin) (Table 2). The median number (percent) of glucose values in the target range (110-150 mg/dL) increased in period 2 compared to period 1 (Table 2).

Comparison of ND and T2DM Patient Populations

For ND patients, neither median glucose nor median percentage glucose values within target range differed between period 1 (GM1 insulin dosing) and period 2 (GM2 insulin dosing). However glycemic variability decreased significantly as measured by both SD (~18%) and CONGA (~26%) when using GM2 to manage insulin (Table 3).

Table 2. Median Glucose Concentration, Glycemic Variability, and Time in Target Glucose Range for Patients With Glucose Monitoring and Insulin Dosing by GM1 (Period 1) and GM2 (Period 2).

	Period 1 (June-November 2012)	Period 2 (August 2013-February 2014)	*P* value
Glucose concentration (mg/dL), median (IQR)	141 (126, 156)	136 (125, 148)	.005
Glucose SD (mg/dL), median (IQR)	21.6 (16.9, 26.3)	13.7 (12.4, 19.1)	<.0001
Glucose CONGA (mg/dL), median (IQR)	19.4 (16.0, 24.2)	13.5 (10.9, 17.3)	<.0001
Percentage glucose values in target range, median (IQR)	66.7 (50.0, 74.2)	74.5 (58.5, 86.7)	.002

CONGA, continuous overall net glycemic action; IQR, interquartile range; SD, standard deviation. To convert mg/dL to mmol/L, multiply by 0.0555.

Table 3. Median Glucose Concentration, Glycemic Variability, and Time in Target Range in Patients Without a Diagnosis of Diabetes Mellitus (ND) and Patients With Type 2 Diabetes Mellitus (T2DM) During Period 1 (GM1) Compared to Period 2 (GM2).

	ND			T2DM		
	Period 1	Period 2	*P* value	Period 1	Period 2	*P* value
Number of patients	35	35	N/A	35	35	N/A
Glucose concentration (mg/dL), median (IQR)	134 (122, 149)	133 (121, 145)	.06	146 (132, 162)	139 (128, 153)	.02
Glucose SD (mg/dL), median (IQR)	18.7 (16.3, 25.6)	15.4 (12.4, 19.9)	.004	22.4 (17.7, 28.0)	13.6 (12.3, 18.3)	<.0001
Glucose CONGA (mg/dL), median (IQR)	18.3 (13.3, 21.6)	13.5 (10.2, 19.0)	.04	21.4 (18.3, 27.5)	13.5 (11.7, 15.2)	<.0001
Percentage glucose values in target range (%), median (IQR)	68.8 (61.9, 79.2)	73.7 (62.5, 87.5)	.10	61.9 (46.7, 72.7)	78.3 (54.2, 85.7)	.006

CONGA, continuous overall net glycemic action; IQR, interquartile range; N/A, not applicable; SD, standard deviation. To convert mg/dL to mmol/L, multiply by 0.0555.

Among T2DM patients, median glucose value decreased significantly from 146 to 139 mg/dL between periods 1 and 2 (Table 3). Compared to patients without diabetes, patients with T2DM exhibited a more substantial decrease in glycemic variability, by ~39% (SD) and ~37% (CONGA), during period 2. There was also a statistically significant increase in percentage of glucose values in target range observed for T2DM patients (Table 3). Thus the impact of decreased glucose meter error (bias) on glycemic variability appears to be more substantial for patients with a diagnosis of T2DM than for those without a diagnosis of diabetes. Because glycemic variability strongly correlates with mean glucose concentration,[21] the larger glycemic variability effect observed for T2DM patients may be in part attributed to the decreased median glucose for this patient population during period 2.

Hypoglycemia and Hyperglycemia

During period 1 a single patient experienced an episode of hypoglycemia (<70 mg/dL), and 26 patients (7 ND and 19 T2DM) experienced at least 1 episode of hyperglycemia (>200 mg/dL). During period 2 there were no patients who experienced hypoglycemia and 6 patients (one ND and 5 T2DM) who experienced 1 or more episodes of hyperglycemia.

Discussion

One previous study directly measured the impact of glucose meter error on the efficacy of glycemic control. In this study 12 severe burn patients were randomized to have glucose monitoring and insulin dosing using 1 of 2 glucose meters. Patients monitored with the more accurate glucose meter had decreased glycemic variability as measured by CONGA, mean amplitude of glycemic excursions and mean of daily differences. Patients randomized to the more accurate device also experienced fewer hypoglycemic events.[22] The increased severity of illness and length of time on glycemic control (often weeks) among burn patients may have allowed these investigators to detect effects of meter error on glycemic control efficacy that would be difficult to measure in other patient populations.

In one of the first simulation studies to address impact of glucose meter error on glycemic control efficacy, investigators developed a robust in silico simulation model to predict the impact of self-monitoring glucose device error on glycemic variability, rates of hypoglycemia, risk of hypoglycemia, and long-term glucose control for patients with type 1 diabetes. These authors predicted that glycemic variability, risk of hypoglycemia, and observed incidence of hypoglycemia would all increase as the allowable error of the meters increased between 5% and 20%, with a threshold effect for risk of hypoglycemia between 10% and 15% meter error.[17] While this model remains one of the most sophisticated models to predict glucose values in response to carbohydrate intake and insulin dose, it is based on insulin dosing and carbohydrate intake observed during self-monitoring of blood glucose in the home, rather than intravenous insulin dosing in the ICU environment.

In a study designed to probe the impact of glucose monitor bias, precision, and measurement frequency on glycemic control efficacy in the ICU, another group developed a simulation model to relate insulin dose to glucose response using variable insulin sensitivity, starting glucose concentration, rates of gluconeogenesis, and rates of intravenous glucose infusion.[16] When hourly glucose measurements (glucose meter model) were used to monitor glucose and dose insulin, the authors predicted a threshold effect such that with decreasing precision (CV between 10% and 20%) rates of hypoglycemia, glycemic variability, and time in target range were all adversely impacted. More frequent glucose measurement (every 5 minutes to model continuous glucose sensors) mitigated these effects, such that greater imprecision could be tolerated without adversely impacting glycemic control efficacy. While increasing bias was also predicted to impact rates of hypoglycemia and hyperglycemia, bias alone (without varying precision) was not predicted to impact glycemic variability.[16]

Another group of investigators created a simulation model to assess the impact of glucose monitor error on glycemic control efficacy in the ICU by creating 56 virtual patients based on the observed relationship between insulin dose and glucose response in 56 adult medical and surgical ICU patients (12 with diabetes).[18] Rather than simulate hourly glucose measurements, the authors simulated glucose measurement and insulin dose adjustment according to 3 commonly used glycemic control protocols. The authors predicted that varying total error (expressed as mean absolute relative deviation in the article) from ~15% to ~7% would have minimal impact on mean glucose, glycemic variability (SD), or time in target range using any of 3 commonly used glycemic protocols (Yale protocol, NICE-SUGAR protocol, University of Washington protocol).[18] The authors did predict that decreasing glucose meter error would reduce the rates of hypoglycemia (glucose < 70 mg/dL) and severe hypoglycemia (glucose < 40 mg/dL) for 2 of the 3 protocols (Yale and University of Washington), but effects of glucose meter error were less significant than differences predicted between protocols. One of the primary conclusions was that protocol used, not glucose monitor error, was the primary determinant of glycemic control efficacy.[18] While one simulation model predicted that glucose monitor error and measurement frequency were major determinants of glycemic control efficacy,[16] the other predicted that effects of monitor error were minor compared to inherent differences between protocols.[18]

Among those modeled, our glycemic control protocol most closely resembles the University of Washington protocol, with both specifying that insulin dose change under most circumstances with every 20-30 mg/dL increment in glucose value (narrow dosing window) and each glucose value used alone (without considering rate of change) to make insulin dose decision.[14,23] The University of Washington protocol was predicted to result in the greatest percentage of patients experiencing hypoglycemia (36-41% of patients) and severe hypoglycemia (3.2-5.0% of patients),[18] rates that do not differ markedly from those observed empirically for this protocol.[24] In contrast we observed few incidences of hypoglycemia among the 140 patients in the study. This is consistent with our previous observation that using GM1 to manage ICU patients with our protocol, only 4 of 1513 (0.26%) of patients experienced severe hypoglycemia, and only 33 of 1513 (2.2%) had any glucose value < 60 mg/dL.[14]

One key difference in our protocol (compared to the University of Washington protocol modeled) is that in our practice glucose monitoring and insulin dose adjustment is fixed at hourly for all patients receiving intravenous insulin. In contrast the protocols modeled call for reduced glucose monitoring and insulin adjustment frequency as glucose levels stabilize.[18] The much lower rate of hypoglycemia we observed, compared to both simulation predictions and empiric observations from the University of Washington protocol, suggests that increasing glucose measurement frequency may improve the efficacy of glycemic control. This was in fact predicted by the simulation model of Boyd and Bruns.[16] Future simulation models might explore whether differences in glycemic control efficacy between protocols are predicted when glucose measurement and insulin dose adjustment is performed hourly.

We previously conducted 2 simulation model studies to relate glucose meter error to insulin dosing errors during glycemic control.[13,14] The error simulation models suggested that for glycemic control protocols that use individual glucose values to titrate insulin and where most glucose values fall into narrow insulin dosing categories, decreasing glucose meter error will significantly reduce the rate of insulin dosing errors. We also observed empirically that insulin dosing errors were significantly reduced by switching from GM1 to GM2.[8,14] In this study we found that patients monitored with the meter exhibiting reduced bias had decreased glycemic variability (as measured by both CONGA and SD), fewer incidences of hyperglycemia, and increased percentage values in target range compared to a similar cohort of patients monitored with a less accurate device. Together the results demonstrate that reducing glucose meter error (bias) during glycemic control reduces insulin dosing errors, which in turn improves the efficacy of glycemic control. Our results support simulation model predictions[16] that imply that glucose monitor error is a major determinant of glycemic control efficacy.

Our study and others[4,25] demonstrate that there is little difference in the precision of commonly used hospital-use glucose meters, with CV < 5% such that imprecision is unlikely to be a factor in glycemic control efficacy. Because constant bias is not predicted to impact glycemic variability,[16] our results may not appear consistent with simulation model predictions. However when used to measure whole blood glucose in critically ill patients, GM1 exhibits a proportional positive bias, such that significantly increased positive bias

is observed at glucose concentrations > 150 mg/dL.[6,26] Because simulation models are limited in the ability to model the effects of changing bias or precision,[16] the inability to adequately model the effects of proportional positive bias observed with GM1 may have caused previous investigators to significantly underestimate the impact of reduced glucose meter bias on the efficacy of glycemic control in the ICU.

Limitations

We compared glycemic control efficacy between 2 cohorts of patients placed on the same glycemic control protocol after cardiovascular surgery. While the patient demographics and characteristics did not differ between cohorts, and the glycemic control protocol (including target range, insulin dosing categories, personnel performing testing, testing frequency) did not change, we cannot eliminate the possibility that other practice changes or attitudes toward hyperglycemia between study periods impacted the results. Specifically, protocol compliance was not measured during either time period. Another limitation is that incidences of hypoglycemia and hyperglycemia were based only on glucose meter values and were not confirmed by laboratory glucose measurement.

Conclusions

Implementation of a glucose meter with reduced bias was associated with decreased glycemic variability and hyperglycemic episodes, and increased percentage values in target glucose range. The results suggest that improved glucose meter analytic performance will result in improved glycemic control efficacy for patients placed on similar glycemic control protocols following cardiovascular surgery.

Abbreviations

CONGA, continuous overall net glycemic action; CV, coefficient of variation; GM1, glucose meter 1; GM2, glucose meter 2; ICU, intensive care unit; ND, no diagnosis of diabetes mellitus; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Declaration of Conflicting Interests

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