Journal of Diabetes Science and Technology
2015, Vol. 9(3) 663–667

DOI: 10.1177/1932296814564993
dst.sagepub.com
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Accuracy of Intra-arterial and Subcutaneous Continuous Glucose Monitoring in Postoperative Cardiac Surgery Patients in the ICU

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Abstract

Background: The GluCath® intra-arterial continuous glucose monitoring (IA-CGM) system uses a novel quenched chemical fluorescence sensing mechanism to optically measure blood glucose when deployed in the radial artery. The aim of this study was to compare the accuracy of the IA-CGM and the FreeStyle Navigator® subcutaneous continuous glucose monitoring (SC-CGM) system with standard care. **Methods:** After admission to the intensive care unit (ICU), the IA-CGM was inserted via a 20 gauge radial arterial study catheter and the SC-CGM was placed at the abdominal wall of postoperative cardiac surgery patients with an expected ICU length of stay > 24 hours. Each device was calibrated according to manufacturer instructions. Glucose values of both CGM systems were blinded for the clinical staff. Reference blood glucose samples were collected from the study catheter every 1-2 hours for at least 24 hours and analyzed on a Radiometer ABL blood gas analyzer. **Results:** The IA-CGM and SC-CGM sensors were successfully inserted in 8 subjects. Accuracy assessment was performed with 183 paired points: 85.8% of the IA-CGM measurements and 84.2% of the SC-CGM measurements met ISO 15197:2003 glucometer criteria (within 20%) across a 79-248 mg/dl (4.4-13.8 mmol/L) glucose range. Overall ± SD mean absolute relative difference was 12.3 ± 11.3% for IA-CGM and 11.1 ± 8.3% for SC-CGM (difference –1.2%, 95% CI –3.3 to 0.8; $P = .24$). **Conclusions:** The IA-CGM system directly measured arterial blood glucose and did not interfere with clinical care. However, accuracy was similar to that of the less invasive SC-CGM device.

Keywords

glucose, continuous monitoring, subcutaneous, intra-arterial, accuracy, vascular

Glucose regulation is a key patient management goal in intensive care medicine and glycemic control using intravenous insulin is thus widely practiced in intensive care units (ICUs).[1] Currently, blood glucose concentration is almost universally measured intermittently using either point-of-care glucose meters or blood gas analyzers.[2] However, intermittent glucose measurement has several limitations. It does not provide data very frequently, which could result in missed episodes of hyper- and hypoglycemia. Moreover, it is time-consuming for the ICU nursing staff.[3] Real-time continuous glucose monitoring (CGM) devices in the ICU have the potential to address these limitations.

Several commercially available subcutaneous CGM systems have been tested in critically ill patients.[3-6] Most studies have shown an acceptable correlation between arterial and interstitial glucose using a subcutaneous CGM device, whereas some studies have reported suboptimal accuracy results.[7,8] The unpredictable subcutaneous conditions of intensive care patients is often regarded as a factor that may influence the measurement of glucose concentrations in the interstitial fluid. However, recent data indicate that impairment in microcirculation in cardiac surgery patients was not related to sensor accuracy.[9]

Theoretically, intra-arterial positioning of CGM devices could yield frequent, immediate, and accurate glucose readings. Arterial access is frequently obtained in ICU patients and would be convenient to also use for CGM. Here we report accuracy results of 2 CGM devices, the GluCath® intra-arterial continuous glucose monitoring (IA-CGM)

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system and the FreeStyle Navigator® subcutaneous continuous glucose monitoring (SC-CGM) system, in post-cardiac-surgery patients admitted to the ICU.

Methods

Design and Setting

This investigator-initiated substudy with a head-to-head comparison to a SC-CGM was part of a larger open-label product development study to assess the safety and performance of the GluCath IA-CGM in an intended number of 20 ICU patients (including a cohort of 5 run-in patients). Subjects above the age of 18, scheduled for elective cardiothoracic surgery, and admitted after surgery to the 24-bed medical/surgical ICU in the Onze Lieve Vrouwe Gasthuis (OLVG, Amsterdam, Netherlands) were enrolled. Exclusion criteria were an expected ICU stay of < 24 hours, known pregnancy, known contraindication to heparin (present on the coating of the IA-CGM), and known contraindication for adequate placement of the subcutaneous glucose device. The patients were studied during ICU admission for at least 24 hours and up to a maximum of 48 hours. This study was approved by the ethics committees of the Academic Medical Center and Onze Lieve Vrouwe Gasthuis in Amsterdam in conformation with Dutch and European legislation. All patients or their legal representative provided written informed consent.

Glucose Sensing of CGM Devices

The GluCath IA-CGM (GluMetrics Inc, Irvine, CA, USA) consists of a heparin-bonded sensor, which is deployed intravascularly approximately 2 cm beyond an arterial catheter. The novel quenched chemical fluorescence sensing mechanism of the GluCath IA-CGM has previously been described.[10,11] In brief, blue light travels down an optical fiber to the sensing chemistry at the distal tip of the sensor, which fluoresces green in proportion to the glucose concentration of the blood. It also measures and corrects for pH and blood temperature. Optical signals are processed in the monitor where the fluorescence intensity is converted to a prospectively calibrated glucose value, which is recorded every 10 seconds. The FreeStyle Navigator SC-CGM (Abbott Diabetes Care, Alameda, CA, USA) consists of an electrochemical sensor placed in the subcutaneous adipose tissue and measures glucose using a glucose oxidase method. Glucose readings of the FreeStyle Navigator SC-CGM are displayed every minute.

Intervention

After admission to the ICU, 2 different sensors were inserted in each patient. The GluCath IA-CGM device was inserted through a newly placed Arrow RA-4020 radial arterial catheter (Teleflex, Limerick, PA, USA) and attached directly to the hub of the arterial access of the catheter. Calibration of the IA-CGM was performed 1 and 2 hours after insertion and each subsequent study day at noon. The FreeStyle Navigator SC-CGM device was inserted in the abdominal wall by a positioning system and continuously measured blood glucose after a 1-hour warm-up period and calibration was performed according to manufacturers' instructions (at 1, 2, 10, and 24 hours after insertion, using a FreeStyle test strip and arterial blood specimen). The outputs of both sensors were masked to the investigators and clinical staff, and no clinical decisions were made based on the output of the CGM systems. Ultrasound images were taken of the radial artery prior to IA-CGM insertion, after sensor insertion, and prior to removal. Both sensors were removed after a maximum of 48 hours of CGM or earlier if deemed clinically necessary or when the patient was discharged from the ICU. Glycemic control to a blood glucose target of 90 to 162 mg/dl (5.0 to 9.0 mmol/L) was performed according to a sliding scale algorithm integrated into the patient data management system (PDMS; MetaVision; *i*MD*soft*, Tel Aviv, Israel).[12]

Data Collection

Arterial reference blood glucose samples were obtained every hour during the day and every other hour during the night and were measured on a blood gas analyzer (Radiometer ABL 800 series, Radiometer Medical ApS, Brønshøj, Denmark). The IA-CGM measured glucose every 10 seconds and recorded optical signals, temperature, and prospectively calibrated glucose values, whereas the SC-CGM displayed glucose readings every minute and stored the glucose value every 10th minute. Reference blood draw times were recorded on both the IA-CGM device and in the patient data management system. The IA-CGM value immediately prior to blood draw and a linear interpolation of the stored SC-CGM glucose values were paired with each reference value. In addition, since optimal accuracy of the FreeStyle SC-CGM is reached 5-10 minutes after the reference glucose,[6] sensor values of the SC-CGM 5-10 minutes after the reference glucose were also used to assess accuracy.

Statistical Analysis

Accuracy outcome measures included mean absolute relative deviation (MARD) (the average % difference between sensor glucose values and reference values), median absolute relative difference (ARD), and Bland–Altman analysis. We also assessed accuracy criteria according to the ISO certification criteria for point-of-care glucometers (ISO 15197:2003) and accuracy criteria of Clinical Laboratory Standard Institute standard POCT12-A3. All analyses were performed using Excel (Microsoft, Redmond, WA, USA) and SPSS 20.0 (IBM, Armonk, NY, USA).

Table 1. Accuracy Data of the GluCath Intra-arterial CGM System and the FreeStyle Subcutaneous CGM System.

	GluCath IA-CGM	FreeStyle SC-CGM	*P* value
Number of CGM-reference pairs (n)	183	183	
Number of reference values between "in target range" (90-162 mg/dl) (n)	106	106	
Number of CGM-reference pairs "below target range" (<90 mg/dl) (n)[a]	5	5	
Number of CGM-reference pairs "above target" (>162 mg/dl) (n)	72	72	
Overall MARD ± SD (%)	12.3 ± 11.3	11.1 ± 8.3	.24
MARD 90-162 mg/dl ± SD (%)	12.4 ± 11.8	10.1 ± 7.6	.10
MARD > 162 mg/dl ± SD (%)	11.8 ± 10.9	12.9 ± 9.1	.50
Overall median ARD (IQR) (%)	9.9 (4-16)	9.4 (5-15)	.81
Median ARD 90-162 mg/dl (IQR) (%)	9.0 (4-16)	8.4 (5-13)	.40
Median ARD > 162 mg/dl (IQR) (%)	9.3 (4-16)	12.3 (5-20)	.19

ARD, absolute relative difference; CGM, continuous glucose monitoring; IQR, interquartile range; MARD, mean absolute relative difference; SD, standard deviation.

[a]Number of hypoglycemic measurements is too low to calculate accuracy data of the hypoglycemic range.

Results

Both IA-CGM and SC-CGM were successfully inserted in 8 patients (3 females and 5 male, median age 70 years, range 54 to 84). All patients underwent cardiothoracic surgery: coronary artery bypass graft (CABG) (n = 2), valve replacement (n = 4), CABG and valve replacement (n = 1), or CABG and Bentall surgery (n = 1). Two patients were previously diagnosed with diabetes mellitus, median (IQR) APACHE IV and EUROSCORE predicted mortality were 2.4% (0.6-6.2) and 5.3% (3.3-6.9). Mean glucose (SD) during the intervention was 159 (27) mg/dl (or 8.8 [1.5] mmol/L).

All IA-CGM sensors functioned after the initial in vivo calibration. The devices continuously monitored blood glucose levels for a mean (SD) of 33 (9) hours. No sensors were removed or replaced as a result of device malfunctions. Two sensors were removed due to loss of arterial catheter patency (after 44 and 37 hours of monitoring); the remaining sensors were removed prior to discharge from the ICU or impending non-study-related death (1 patient). There were no device-related serious adverse events. No sensor interfered with clinical care, hemodynamic monitoring, or blood sampling. The loss of arterial catheter patency was due to failure to maintain flush solution in 1 subject and due to nonocclusive, subclinical thrombus that formed around the catheter after the other subject underwent an emergency thoracotomy. No treatment was required.

The SC-CGM device continuously monitored blood glucose levels during a mean (SD) of 29 (10) hours. In 3 patients a new SC-CGM device was placed due to failure of calibration (in 2 patients) or accidental removal during rethoracotomy (1 patient).

A total of 183 paired points were available for performance analysis of the 2 CGM devices. Paired reference glucose values ranged from 79 to 248 mg/dl (4.4-13.8 mmol/L). The MARD ± SD was 12.3 ± 11.3% for the IA-CGM and 11.1 ± 8.3% for the SC-CGM (difference –1.2%, 95% CI –3.3 to 0.8; $P = .24$). Individual IA-CGM sensors exhibited MARD from 8.4% to 17.5%. Individual SC-CGM sensors exhibited MARD from 5.3% to 16.0%.

Detailed accuracy data of the 2 sensors are shown in Table 1. Accuracy of the SC-CGM slightly improved when using sensor values 5-10 minutes after the reference glucose value (ie, taking into account the time delay of subcutaneous measuring of glucose): overall MARD 10.8 ± 8.7%, overall median ARD: 8.8 (4-15)%. *P* values for overall MARD and median ARD between the 2 devices (IA-CGM and delayed SC-CGM measurements) changed in 0.15 and 0.44, respectively. Furthermore, the SC-CGM performed slightly better "in target" compared to "above target" (MARD in target 10.1% and MARD above target 12.9%; $P = .04$), whereas the IA-CGM performed equal across the 2 ranges.

Figure 1 shows Bland–Altman analysis and resulted in a similar mean bias (or systematic error) of –8.0 to –8.6 mg/dl for both sensors. The upper and lower limit of agreement was 39.4 and –56.5 mg/dl for the GluCath IA-CGM and 33.8 and –49.7 mg/dl for the FreeStyle Navigator SC-CGM. There was no consistency in direction of error and no visual trend was observed for more inaccuracy approaching the hypo- or hyperglycemic ranges. The figure also shows paired points meeting the accuracy criteria of the International Organization for Standardization (ISO) standard 15197:2003. The ISO 15197:2003 criteria (within 20% of reference when ≥ 75 mg/dl) were met in 157/183 (85.8 %) of the IA-CGM measurements and in 154/183 (84.2%) of the SC-CGM measurements ($P = .77$). Accuracy criteria of Clinical Laboratory Standard Institute standard POCT12-A3 (within 12.5% of reference when ≥ 101 mg/dl) were met in 113 of 183 (55.4%) of the IA-CGM measurements and in 120 of 183 (64.2%) of the SC-CGM measurements. Fourteen percent (26/183) of the paired points of the GluCath IA-CGM and 16% (29/183) of the paired points of the FreeStyle SC-CGM differed > 20% of the reference analyzer glucose values.

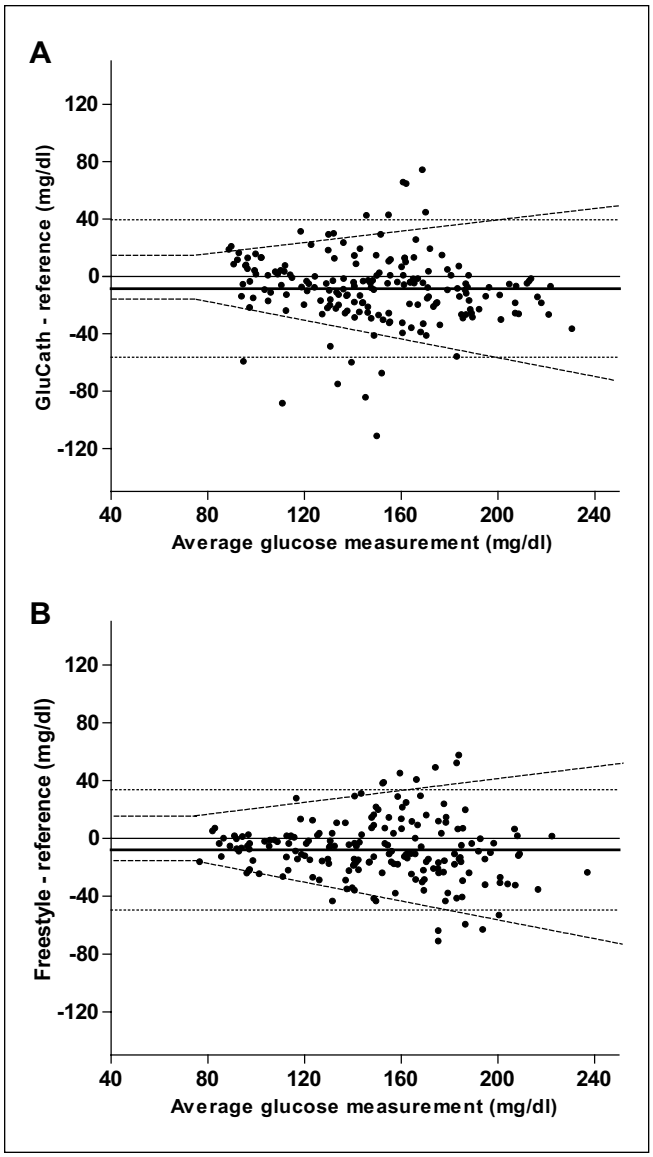

Figure 1. ISO-modified Bland–Altman plots for the (A) GluCath IA-CGM system and (B) FreeStyle SC CGM system. The x-axis represents the average of sensor and reference glucose measurements in mg/dl. The y-axis represents the absolute difference between sensor and reference glucose measurements in mg/dl. The solid line represents the mean difference (GluCath –8.6 and FreeStyle –8.0 mg/dl); dotted lines are drawn at the mean difference ± 1.96 times the standard deviation of the mean difference. The long dashed lines represent the ISO-15197:2003 criteria.

Discussion

This is the first report in literature in which accuracy results are shown of 2 CGM devices in the same ICU patient that differed in positioning and type of glucose measuring. We show similar accuracy with an MARD of 11-12% for both the GluCath IA-CGM and the FreeStyle Navigator SC-CGM compared to arterial reference blood glucose samples in post-cardiac-surgery patients admitted to the ICU.

Our accuracy results for the FreeStyle Navigator are in line with our previous validation studies of this device in a small number of critically ill patients.[6,13] We recently investigated the use of the FreeStyle Navigator CGM system to guide blood glucose regulation in a larger group of critically ill patients (N = 178).[3] Accuracy of the FreeStyle Navigator in this study was lower with an MARD of 17.1%. Improvements in accuracy of the FreeStyle Navigator device may be obtained by performing calibrations more frequently.[14]

Another open-label study investigated the use of the GluCath IA-CGM device in cardiac surgery patients admitted to the ICU and reported similar accuracy with an aggregate MARD of 13.0% (individual sensors ranging from 4.7% to 33.5%).[15] As in all studies in this field, the extent of acceptable deviation between sensor and arterial reference glucose measurements can be debated. Recently, Finfer et al[2] stated in a consensus paper on the measurement of blood glucose in critically ill adults that a desirable point accuracy of CGM systems in critically ill patients is that 98% of glucose readings are within 12.5% of a reference standard and that the remaining 2% of readings should be within 20% of a reference standard. Unfortunately, the current data have not met these performance standards. For most CGM systems assessed in an intensive care setting, larger studies are needed to demonstrate sufficient accuracy in a broad range of critical care settings.

Our study has several limitations. This study was performed in a small number of subjects in a single population, elective post-cardiac-surgery subjects, who are relatively healthy compared to other ICU subjects that may benefit from CGM. In addition, we only measured glucose up to 48 hours and cannot comment on the performance of the devices beyond that point. Finally, we did only obtain glucose levels between 79 and 248 mg/dl and not in the hypoglycemic range.

The GluCath IA-CGM system used in this study was an investigational device used as part of a manufacturer-sponsored product development study. While the system did not interfere with routine care by clinical staff once inserted, the IA-CGM device required a lengthy setup and on-patient securement by study staff. Poor IA-CGM system performance (>11% MARD) in 3 subjects was attributed by the manufacturer to optical signal variability associated with routine patient care activities (eg, receiving personal care, transitions from bed to chair, transport to OR), suboptimal securement, and the administration of 3 interfering medications (mannitol, citrate, glubionate). They did not correspond to clinical conditions of the patient. The company did not obtain funding to further develop their device and has since closed shop.

Reasons for poor SC-CGM system performance were not studied extensively in the current study. One subject was in a cardiogenic shock, which was a complication of an aortic and mitral valve replacement surgery. The subject underwent an emergency thoracotomy. Interestingly, accuracy of the SC-CGM system in this specific subject was good, with an individual MARD of 5.3%. Furthermore, prior research

showed that not microcirculation but peripheral temperature, age, and APACHE IV predictive mortality scores were related to the FreeStyle Navigator sensor accuracy.[9] In addition, an improved next generation FreeStyle Navigator II has recently been introduced and showed good utility and sensor performance in critically ill patients.[16]

In the current study and in the study of Flower et al,[15] no interference with clinical care, hemodynamic monitoring, or blood sampling was found. This suggests a clinically acceptable level of invasiveness when using an intra-arterial CGM device, especially because critically ill patients are already subjected to invasive treatment and monitoring.

Conclusions

This small observational study has shown that the sensor accuracy of both intra-arterial and subcutaneous sensors was similar in cardiac surgery patients with an MARD of 11-12%. The IA-CGM system directly measured arterial blood glucose and did not interfere with clinical care. The SC-CGM system provided a less invasive alternative with similar performance.

Abbreviations

CABG, coronary artery bypass graft; CGM, continuous glucose monitoring; IA-CGM, intra-arterial continuous glucose monitoring; ICU, intensive care unit; IQR, interquartile range; ISO, International Organization for Standardization; MARD, mean absolute relative deviation; OLVG, Onze Lieve Vrouwe Gasthuis; PDMS, patient data management system; SC-CGM, subcutaneous continuous glucose monitoring; SD, standard deviation.

Acknowledgments

We express our gratitude to the medical, nursing, and ICT staff from the Onze Lieve Vrouwe Gasthuis intensive care unit.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: JHD is an advisor for Roche Diagnostics and received research support from Dexcom Inc, Glumetrics Inc, Medtronic, and Abbott Diabetes Care. PS was an employee of GluMetrics. The other authors do not have a financial or nonfinancial conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by GluMetrics Inc, Irvine, CA, USA.

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