Research Article

Accuracy of a real-time continuous glucose monitoring system in children with septic shock: A pilot study

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Abstract

Aims: The aim of this prospective, observational study was to determine the accuracy of a real-time continuous glucose monitoring system (CGMS) in children with septic shock. **Subjects and Methods:** Children aged 30 days to 18 years admitted to the Pediatric Intensive Care Unit with septic shock were included. A real-time CGMS sensor was used to obtain interstitial glucose readings. CGMS readings were compared statistically with simultaneous laboratory blood glucose (BG). **Results:** Nineteen children were included, and 235 pairs of BG-CGMS readings were obtained. BG and CGMS had a correlation coefficient of 0.61 ($P < 0.001$) and a median relative absolute difference of 17.29%. On Clarke's error grid analysis, 222 (94.5%) readings were in the clinically acceptable zones (A and B). When BG was < 70, 70–180, and > 180 mg/dL, 44%, 100%, and 76.9% readings were in zones A and B, respectively ($P < 0.001$). The accuracy of CGMS was not affected by the presence of edema, acidosis, vasopressors, steroids, or renal replacement therapy. On receiver operating characteristics curve analysis, a CGMS reading <97 mg/dL predicted hypoglycemia (sensitivity 85.2%, specificity 75%, area under the curve [AUC] =0.85). A reading > 141 mg/dL predicted hyperglycemia (sensitivity 84.6%, specificity 89.6%, AUC = 0.87). **Conclusion:** CGMS provides a fairly, accurate estimate of BG in children with septic shock. It is unaffected by a variety of clinical variables. The accuracy over extremes of blood sugar may be a concern. We recommend larger studies to evaluate its use for the early detection of hypoglycemia and hyperglycemia.

Keywords: Children, continuous glucose monitoring system, septic shock

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Introduction

In patients admitted to the Pediatric Intensive Care Unit (PICU), hypoglycemia and hyperglycemia are both common. While hypoglycemia is clearly associated with poorer outcomes, hyperglycemia is known to be associated with increased morbidity in critically ill children with septic shock.[1-6] It is unclear whether hyperglycemia is an etiological factor contributing to worse outcomes or merely a marker of critical illness. Nonetheless, intensive glycemic control has been utilized in critically ill adults and has been shown to be associated with improved outcomes in certain populations.[7-9] The close monitoring of blood glucose (BG) is thus an essential element in the management of critically ill patients. There is a paucity of similar data in children.

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BG is monitored in the PICU either by laboratory estimation on a venous sample (gold standard) or at the point of care by a bedside glucometer. The former is time-consuming and may result in an unacceptable delay in a critical care setting. Both methods provide only intermittent results due to which significant variations in-between measurements may be missed.

Real-time continuous glucose monitoring systems (CGMS) are now available which use a percutaneously inserted sensor that provides interstitial fluid glucose measurements every 5 min. This has been validated and found to be accurate in critically ill adults.[10] There are so far, very few studies in children with septic shock.[11]

Recent severe sepsis and septic shock guidelines in children recommend close glucose monitoring. As poor peripheral perfusion and interstitial edema are common in children with septic shock, there are concerns that an interstitial sensor may not accurately reflect BG. We, therefore, conducted this prospective study to determine whether a real-time CGMS can accurately reflect BG and detect hypoglycemia and hyperglycemia in critically ill children with septic shock.

Subjects and Methods

Approval was obtained from the Hospital Ethics Committee for conducting this study. All children aged 30 days to 18 years admitted to the PICU who fulfilled the following criteria were included:

- Have septic shock as defined by the International Pediatric Sepsis Consensus Conference definition for sepsis and organ dysfunction in pediatrics[12]
- Have an arterial catheter inserted as part of routine therapy
- Require frequent glucose monitoring as part of routine management.

We excluded children known to have diabetes mellitus. Informed consent was obtained from the parents/guardians before patients were enrolled.

Data were collected prospectively. A disposable real-time CGMS sensor (Enlite sensor and Guardian real-time CGMS, Medtronic, Northridge, CA) was inserted percutaneously in study patients into the anterior abdominal wall to the right of the umbilicus. The sensor was calibrated using bedside BG estimation with a glucometer (Optium Xceed, Abbott, IL) on an arterial sample, initially at the time of insertion and then every 6 h. The CGMS device measures interstitial glucose by glucose oxidase method and is designed to provide readings every 5 min (possible total of 288 readings over 24 h, for up to 7 days) which are displayed in real time on a pager-sized monitor. The data can be retrieved electronically. It has a measuring range of 40–400 mg/dL (2.2–22.2 mmol/L) and can give an alarm whenever readings are outside a set range or approaching the limits of the range. The alarm limits were set at 70 mg/dL and 180 mg/dL to signal hypoglycemia or hyperglycemia, respectively.

Arterial blood samples were taken for laboratory glucose (BG) estimation by glucose oxidase-peroxidase method (Autoanalyzer, Biosystems, Spain) every 6 h, and additionally when the CGMS detected readings outside the set range (as defined previously) which were acted on as clinically appropriate. BG readings and coinciding CGMS readings were noted for analysis. When BG readings detected hypoglycemia or hyperglycemia, CGMS trends for the next 30 min were also analyzed to study possible time lags between BG and CGMS. CGMS calibration and laboratory glucose sampling were both performed every 6 h but spaced out so that they did not coincide. There was no formal protocol for glucose control, which was managed as per physician's discretion. The CGMS sensor was used until the resolution of shock and discontinued thereafter.

Patient demographics, admission diagnosis, duration of shock, duration of CGMS use, and the PICU length of stay were recorded. At the time of each BG sampling, the use of therapeutic modalities (mechanical ventilation, vasoactive drugs, steroids, insulin, and renal replacement therapy), and the presence of edema were noted. The patient outcome was noted. The Pediatric Index of Mortality III (PRISM III) score was used to define the severity of illness. The severity of shock was measured using the vasoactive-inotrope score. The data from the CGMS sensor was transferred to a database after its use on an individual patient. Microsoft Excel (MS Office 2007 for Windows, Microsoft Inc.,) was used to manage the collected data.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation while categorical variables were expressed as a percentage. As per accuracy criteria accepted for CGMS statistics by the US Food and Drug Administration,[13] paired CGMS and BG readings were compared for numerical accuracy using Pearson's correlation coefficient (r) and median relative absolute difference (RAD) and for clinical accuracy by Clarke's error grid analysis (EGA). RAD was calculated as follows:[13]

$$RAD = \frac{BG - CGMS}{BG} \times 100$$

In the EGA, readings were graphically plotted on the grid depending on the zone they would fall in. The significance of Zone A to E is as follows: Zone A: CGMS and BG values are both below 70 mg/dL or CGMS deviates from BG by < 20%; points in this zone are considered clinically accurate. Zone B: CGMS readings deviate from BG by > 20% but results in benign or no treatment; values in zone B lead to clinically appropriate action. Readings in these zones are considered clinically acceptable. Zone C: CGMS reading leads to overcorrection of an acceptable BG reading. Such interventions may lead to hyperglycemia or hypoglycemia. Zone D: This represents dangerous failure to detect or treat abnormal values. CGMS readings may lie in an acceptable range while the BG is outside the target range. Zone E: CGMS readings are opposite to BG readings and interventions performed are opposite to what may be required. Readings in zones C, D, and E represent erroneous BG estimation resulting in inappropriate interventions.[13,14] The Bland–Altman analysis was used to measure the agreement between both methods.

The measures of numerical and clinical accuracy were tested across various subgroups. Fisher's exact test was used to compare categorical variables while Mann–Whitney U-test was used for nonparametric, unpaired data.

When hypoglycemia or hyperglycemia was detected by BG, the pre- and post-event CGMS trends over 30 min were studied to note whether the trends predicted or detected the event. The incidence of hypoglycemia or hyperglycemia was expressed as episodes per 1000 patient-hours of sensor use. The effect of hypoglycemia detected through CGMS on the outcome was studied using multiple logistic regression. We used receiver operating characteristics (ROC) curves to determine the sensitivity and specificity of CGMS in predicting hypoglycemia (BG < 70 mg/dL) and hyperglycemia (BG > 180 mg/dL).

We used Medcalc Statistical Software version 14.10.2 (Medcalc Software bvba, Ostend, Belgium) for statistical analysis. A two-tailed $P < 0.05$ was considered significant.

Results

Nineteen patients were included in the study. The patient characteristics are described in Table 1. The sensors were tolerated well, and none of the patients had any adverse reactions due to the sensor. There was no sensor malfunction. In one patient, the sensor was removed prematurely as the patient had to be taken for an MRI.

Table 1: Baseline patient characteristics

Characteristic	Median/n
Age (months)	36 (14-84)
Sex (male)	13 (68.4)
Diagnosis (*n*)	
Pneumonia	2 (10.5)
Nonlocalized infection	4 (21.05)
Neurological	4 (21.05)
Renal	1 (5.2)
Metabolic	2 (10.5)
Malignancy	3 (15.78)
Hepatic	2 (10.5)
PRISM III score	14 (9.5-17.5)
Duration of shock (h)	75 (47.5-109.5)
Duration of CGMS (h)	71 (50-84.5)
PICU LOS (h)	168 (83.5-264)
Mechanical ventilation (*n*)	19 (100)
Renal replacement therapy (*n*)	1 (5.2)
Steroids	6 (31.5)
Outcome (died)	7 (36.8)

Data are expressed as median (IQR) or as *n* (%). PRISM: Pediatric risk of mortality score; CGMS: Continuous glucose monitoring system; LOS: Length of stay; IQR: Interquartile range; PICU: Pediatric Intensive Care Unit

A total of 235 pairs of CGMS and BG readings were obtained. The median BG was 105 (87–123) mg/dL, and median CGMS was 110 (92–128) mg/dL. The Pearson correlation coefficient (r) was 0.61 [$P < 0.001$, Figure 1]. The median RAD was 17.29% (6.2–31.9). The Clarke's error grid distribution is described in Figure 2. Two hundred twenty-two (94.5%) observations were in the clinically acceptable zones A and B (A 155 [65.96%], B 67 [28.51%], C 0 [0%], D 17 [7.23%], and E 0 [0%]). On Bland–Altman analysis, the mean difference (bias) was −5.08 ± 36.6 mg/dL with 93.6% of the readings lying within the limits of agreement (−76.8–66.6) [Figure 3].

There were 25 BG readings in the hypoglycemia range, detected across 10 patients (17.05/1000 patient-hours). In 6 (24%) of these hypoglycemic events, CGMS readings showed hypoglycemia simultaneously. On pre- and post-event analysis of CGMS trends, hypoglycemia was detected on 4 of these occasions and predicted in 2 in the pre-event 30-min period. In the other 19 hypoglycemic events, none was detected by CGMS simultaneously or predicted in the pre- or post-event CGMS trends.

There were 13 episodes of hyperglycemia detected across 8 patients (8.87/1000 patient-hours). Six (46.2%) of these events were reflected in the simultaneous CGMS readings. On all 6 occasions, hyperglycemia

was predicted as well as detected in the pre-event CGMS trend. In 1 additional instance, hyperglycemia was predicted pre-event but detected only in the postevent trend while on one occasion, it was predicted pre-event but not detected at all. Using multiple logistic regression, hypoglycemia detected through CGMS was not an independent predictor of outcome.

Subgroup analysis is described in Tables 2 and 3. Median RAD and the percentage of readings in zones (A + B) on EGA distribution were better when BG was in the normoglycemic range but were significantly worse when BG readings were < 70 mg/dL ($P < 0.001$).

On ROC curve analysis, a CGMS reading of 97 mg/dL predicted hypoglycemia with a sensitivity of 85.2% and specificity of 75% (area under the curve [AUC] = 0.85, 95% confidence interval [CI]: 0.78–0.92, $P < 0.0001$, Figure 4). A CGMS reading of 141 mg/dL predicted hyperglycemia with a sensitivity of 84.6% and specificity of 89.6% (AUC = 0.87, 95% CI: 0.82–0.99, $P < 0.0001$, Figure 5).

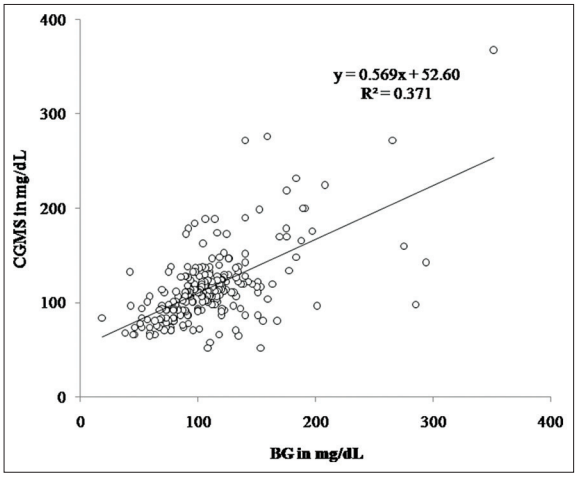

Figure 1: Scatter plot showing correlation between blood glucose (BG) and continuous glucose monitoring system (CGMS)

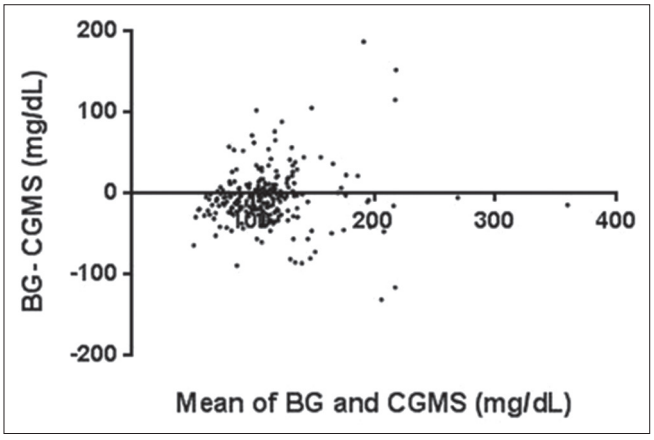

Figure 3: Bland–Altman plot of continuous glucose monitoring system (CGMS) versus blood glucose (BG). Mean difference − 5.08 ± 36.6 mg/dL (limits of agreement − 76.6–66.6)

Discussion

We found that the numerical and clinical accuracy of CGMS appeared to be reasonably good over the majority of our observations, and this was largely unaffected by several clinical variables even up to 7 days of sensor use. However, we found that its performance was not satisfactory in extremes of BG. As the aim of using CG monitoring would be to detect or predict hypoglycemia

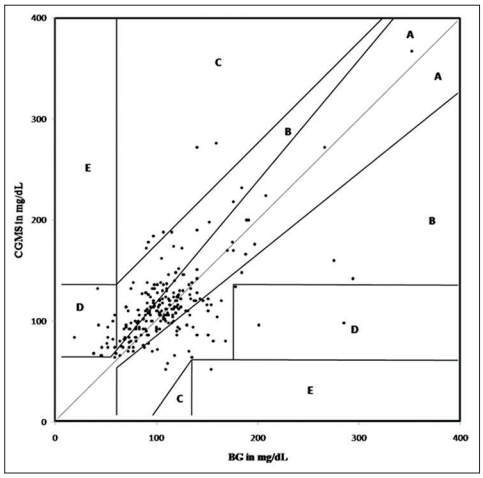

Figure 2: Clarke error grid: Blood glucose (BG) versus continuous glucose monitoring system (CGMS) readings. Zone A: 398 (63.1%); Zone B: 210 (33.2%); Zone C: 4 (0.36%); Zone D: 17 (2.7%); Zone E: 1 (0.15%)

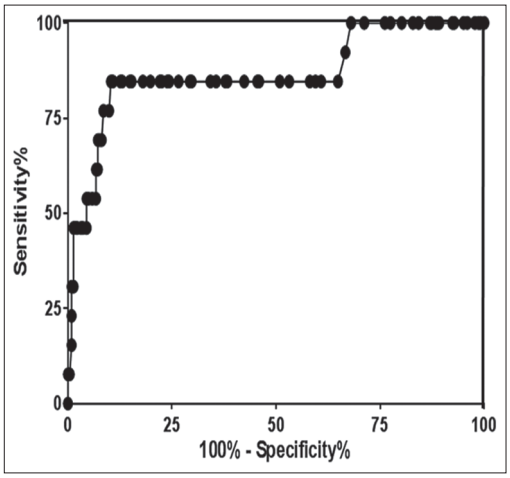

Figure 4: Receiver operating characteristics curve for accuracy of continuous glucose monitoring system (CGMS) in predicting hypoglycemia. Continuous glucose monitoring system <84 mg/dL predicts hypoglycemia with a sensitivity of 75% and specificity 83.3% (area under the curve = 0.81)

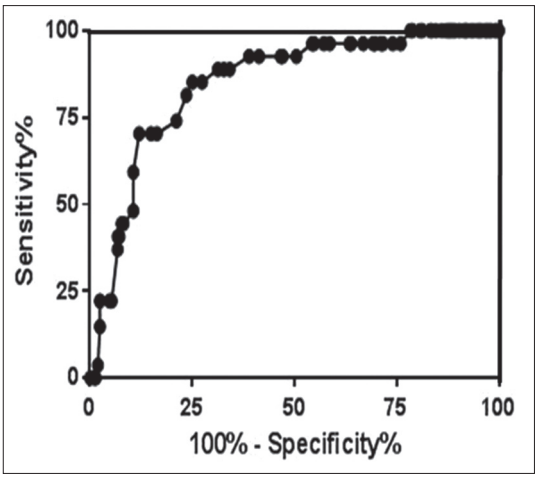

Figure 5: Receiver operating characteristics curve for accuracy of continuous glucose monitoring system in predicting hyperglycemia. Continuous glucose monitoring system >140 mg/dL predicts hyperglycemia with a sensitivity of 84.6% and specificity 89.6% (area under the curve = 0.87)

Table 2: Correlation and median RADs across subgroups

Subgroup	Person's correlation coefficient (r)	Median RAD	
		RAD	*P*
Hypoglycemia	−0.11	43.5	0.0001[a]
Normal BG	0.39	15.2	
Hyperglycemia	0.36	11.7	
Edema	0.527	16.7	0.4[b]
No edema	0.702	17.4	
Acidosis	0.544	15.08	0.26[b]
No acidosis	0.67	17.52	
VIS			
<16	0.435	16.1	0.47[b]
>16	0.673	17.5	
Steroids	0.66	16.9	0.69[b]
No steroids	0.598	17.24	
Sensor use			
<72 h	0.6	25.6	0.73
>72 h	0.69	15.21	
Survived	0.532	16.45	0.10[b]
Died	0.66	17.5	

[a]Kruskal-Wallis test; [b]Mann-Whitney U-test. RADs: Relative absolute differences; VIS: Vasoactive-inotrope score; RRT: Renal replacement therapy; BG: Blood glucose

Table 3: Clarke's error grid analysis across subgroups

Subgroup	Error grid analysis zones						
	A (%)	B (%)	C (%)	D (%)	E (%)	A + B (%)	*P**
BG							
<70	11 (44)	0 (0)	0 (0)	14 (56)	0 (0)	11 (44)	<0.001
70-180	131 (66.5)	66 (33.5)	0 (0)	0 (0)	0 (0)	197 (100)	
>180	7 (53.8)	3 (23.1)	0 (0)	3 (23.1)	0 (0)	10 (76.9)	
Edema	85 (62.5)	41 (30.15)	0 (0)	10 (7.35)	0 (0)	126 (92.65)	1.000
No edema	66 (66.67)	26 (26.27)	0 (0)	7 (7.07)	0 (0)	92 (92.93)	
Acidosis	73 (62.9)	34 (29.3)	0 (0)	9 (7.7)	0 (0)	107 (92.2)	0.82
No acidosis	75 (63)	33 (27.7)	0 (0)	11 (9.2)	0 (0)	108 (90.7)	
VIS							
<16	76 (64.4)	32 (27.1)	0 (0)	10 (8.47)	0 (0)	108 (91.5)	0.662
>16	70 (59.8)	35 (29.9)	0 (0)	12 (10.2)	0 (0)	105 (89.7)	
Steroids	42 (61.7)	20 (29.4)	0 (0)	6 (8.8)	0 (0)	62 (91.1)	1.000
No steroids	104 (62.3)	47 (28.1)	0 (0)	16 (9.5)	0 (0)	151 (90.4)	
Sensor use							
≤72 h	104 (54.5)	71 (37.2)	0 (0)	16 (8.4)	0 (0)	175 (91.6)	0.0001
>72 h	27 (62.8)	12 (27.9)	0 (0)	4 (9.3)	0 (0)	39 (90.7)	
Survived	88 (67.1)	34 (25.9)	0 (0)	9 (6.8)	0 (0)	122 (93.1)	0.18
Died	58 (55.7)	33 (31.7)	0 (0)	13 (12.5)	0 (0)	91 (87.5)	

Data are expressed as *n* (%). *Fisher's exact test. VIS: Vasoactive-inotrope score; RRT: Renal replacement therapy; BG: Blood glucose

and hyperglycemia, the accuracy of CGMS at these extremes becomes crucial. However, the accuracy of CGMS was poor when BG was below 70 mg/dL, and despite a reasonably good sensitivity for detecting hypoglycemia, it is worthwhile to note that CGMS failed to detect 76% of the hypoglycemic events.

While several previous studies in critically ill adults, children, and neonates have also shown CGMS to be reasonably accurate,[10,11,15-18] these studies did not analyze its accuracy over different BG ranges. As in our study, Branco *et al*. found that the difference between CGMS and laboratory glucose was wider in the range below 74 mg/dL.[19]

With regards to detecting hyperglycemia, CGMS appeared more promising as its clinical accuracy in this range was superior and the number of undetected events fewer when compared to hypoglycemic events.

It may be fair to assume that the glucose levels in interstitial fluid could vary depending on the degree of tissue perfusion and on the BG level itself. Factors such as interstitial edema, shock, acidosis, and the use of vasopressors can likely affect tissue perfusion and, therefore, create a difference between blood and interstitial glucose levels, thus resulting in a disparity between BG and CGMS readings. However, our results suggested otherwise. The effects of edema, vasopressors, acidosis, and steroids have been investigated by other researchers as well, and their findings seem similar to ours.[10,11,19,20] Piper *et al*. and Branco *et al*. investigated the effect of hypothermia on CGMS. While the former reported no effect, the latter found that active cooling may limit its accuracy.[19,20]

One of our major limitations was the small sample size due to which our observations on CGMS accuracy in hypoglycemia or hyperglycemia need to be interpreted with caution. Second, as our BG sampling frequency was spaced out too widely, we could not use the CG-EGA[13] which helps to detect glucose trends and identify hypoglycemia or hypoglycemia early, as it compares the

rate of change of glucose in BG and CGMS on a scatter plot rather than point values alone. Studies which have used the CG-EGA performed BG testing as frequently as every 30 min to 4 h.[10]

In view of these shortcomings, we feel that further investigation is required to evaluate the use of CGMS in pediatric septic shock. Given that BG could be monitored continuously, this would result in better control of BG in critically ill children, particularly in detecting and preventing hypoglycemia. A reduction in nursing workload in a busy intensive care setup would be another advantage of such systems.

Conclusion

Real-time CG monitoring may be a good screening tool for bedside glucose monitoring as it is feasible, safe, fairly accurate and unaffected by a large range of physiological states such as severity of shock, acidosis, and tissue edema. Accuracy over extremes of blood sugar may be a concern, especially with hypoglycemia. We recommend larger studies to evaluate its use for the early detection of hypoglycemia and hyperglycemia.

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Conflicts of interest

There are no conflicts of interest.

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