ORIGINAL RESEARCH

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Feasibility and safety of continuous glucose monitoring systems in acute myocardial infarction subjects undergoing primary percutaneous coronary interventions

Abstract

Purpose: The purpose of this study was to evaluate the feasibility and safety of continuous glucose monitoring systems (CGMS) in ST segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary interventions (p-PCI) in coronary care units (CCU).

Methods: CGMS was performed for 3 days during CCU hospitalization for each of the subjects. The correlation between glucose values, recorded with CGMS, and finger-stick capillary glucose values was examined. The parameters and safety of CGMS were also investigated.

Results: Data from 219 subjects were included in the statistical analysis. Correlation analysis showed a strong positive correlation between interstitial glucose values recorded by CGMS and the corresponding capillary glucose values ($P < 0.001$). The daytime mean blood glucose (MBG), the nighttime MBG and PT7.8 were the highest in the first day of CGMS compared with the second and third day. Furthermore, there were no indications of major hemorrhage or hematoma at the site of sensor insertion. Any adverse events were mild.

Conclusions: CGMS glucose values are relatively accurate and reliable. CGMS were safe and can be used as a tool to detect trends in glucose levels and to predict upcoming glucose excursions in STEMI patients undergoing p-PCI.

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It is commonly accepted that continuous glucose monitoring systems (CGMS) can provide detailed and accurate glucose information. Relaying this detailed glucose information to patients has been shown to have a positive influence on glycemic control, including reductions in glucose variability, time spent in nocturnal hypoglycemia, time spent in hyperglycemia and levels of glycosylated hemoglobin [1–4]. Hyperglycemia commonly occurs during acute myocardial infarction (AMI), and in-hospital hyperglycemia is a strong predictor of mortality in AMI patients both with and without a history of diabetes mellitus [5–6]. The adverse outcomes associated with in-hospital hyperglycemia have prompted professional societies to recommend glucose control in AMI patients [5–7]; however, implementation of glucose control has been hindered by fear of hypoglycemia, as low glucose levels have been associated with adverse outcomes in AMI patients [8–9]. Patients with ST-segment elevation myocardial infarction (STEMI) who are undergoing primary percutaneous coronary interventions (p-PCI) should receive aggressive management and treatment in coronary care units (CCU). As glucose management is a significant component of CCU activity, CGMS are particularly attractive for managing blood glucose (BG) because of their potential to detect hypo- and hyperglycemia as they occur. Many studies have concluded that CGMS face challenges in terms of sensitivity, stability, calibration and the physiological delay between BG and interstitial glucose (IG) concentration [10–12]. Moreover, CGMS are more expensive than finger-stick capillary BG monitoring, which partly restricts their use. Few investigations of the BG profiles of non-diabetic populations have been performed using CGMS [13]; furthermore, no specific data exists that evaluates BG profiles using CGMS for STEMI patients undergoing p-PCI in the CCU. The aim of this study was to investigate the feasibility and safety of using CGMS in STEMI non-diabetic patients undergoing p-PCI.

Materials and Methods

Study Design and Patient Population

This was a prospective observational study. All STEMI subjects who were undergoing p-PCI were recruited in the CCU. Non-diabetic STEMI patients were enrolled from two major hospitals in Beijing, China (Beijing Anzhen Hospital, Beijing Daxing Hospital and Capital Medical University). This study was conducted from January 2013 to November 2013.

The CGMS sensor was inserted into the abdominal subcutaneous tissue and calibrated every 6 hours, according to the manufacturer's indications (using finger-stick blood glucose values). A fully automatic biochemistry analyzer (Hitachi

7600-020, Japan, Enzymatic methods) was employed to determine hepatic and renal function, and levels of triglycerides, high-density lipoprotein cholesterol, total cholesterol and low-density lipoprotein cholesterol. Glucocard X-meter (Arkay Inc., Japan) was used to determine finger-stick capillary BG. During the study period, all of the subjects were provided standard mixed meals. The total calorie intake was 126 kJ/kg per day, and consisted of 50% carbohydrates, 15% proteins and 35% fats. The calorie distribution between breakfast, lunch, and dinner was 20%, 40% and 40%, respectively. The three daily meals had to be eaten from 6:30 to 7:30, 11:30 to 12:30 and 18:00 to 19:00, and each meal had to be consumed within 30 minutes.

The inclusion criteria included the following: 1) ST-segment elevation myocardial infarction undergoing p-PCI; 2) no history of diabetes; and, 3) written informed consent. The exclusion criteria included the following: 1) new onset diabetes; 2) hemodynamic instability; and, 3) lack of informed consent. This study was approved by the institutional medical ethical committee.

Definition of STEMI

STEMI was defined as complaints of chest pain with ECG signs that indicated acute myocardial infarction (ST-segment elevation >2 mm in precordial leads and >1 mm in limb leads) [14]. All of the patients were transported directly to the catheterization laboratory on arrival, and acute coronary angiography was performed with subsequent PCI, when indicated, as part of the routine treatment for all STEMI patients in these institutions. The interventional strategy was determined at the physician's discretion. All of the patients were pretreated with aspirin, heparin and clopidogrel during transportation to the hospital, or were administered at the emergency ward [15].

CGMS

The CGMS consisted of a disposable subcutaneous needle-type sensor and an external monitor. The sensor is an amperometric system that uses glucose oxidase, which generates an electric current proportional to the glucose concentration in the interstitial fluid [16]. The sensor measures interstitial glucose every 10 s and records the mean values at 5-min intervals. The sensor was left in place for 3 days for collection of data. The criteria for optimal accuracy of the CGMS were adopted from previous established criteria [17,18] and included a correlation between the sensor and meter readings of at least 0.79, a mean absolute difference of no more than 28% when the daily range (Min-Max) of meter values was ≥ 5.6 mmol/l, and a mean

absolute difference of no more than 18% when the daily range (Min-Max) of meter values was <5.6 mmol/l.

CGMS parameters

The 24-hour mean BG (24 h MBG) was calculated as the mean BG level of 288 readings measured by the CGMS over 24 hours. Daytime and nighttime mean BG levels were defined as BG levels from 6:00 a.m. to 10:00 p.m. and 10:00 p.m. to 6:00 a.m., respectively. For each subject, the proportions of time spent in the BG ranges of ≤ 3.9 mmol/l, 3.9-7.8 mmol/l and ≥ 7.8 mmol/l were determined from the CGMS data. The percentage of time (PT) that BG levels were ≤ 3.9 mmol/l and ≥ 7.8 mmol/l over a 24 hour period were recorded as PT3.9 and PT7.8, respectively [19,20]. All of the above parameters were based on the mean values obtained on Days 1, 2 and 3. Data from the CGMS devices were downloaded using the CGMS Software 3.0 (Medtronic MiniMed, Inc. Northridge, CA, US).

Definitions of adverse events

All adverse events, while the sensor was being used, which had a possible relationship with the CGMS sensor, were reported. At the end of the study, each participant completed a questionnaire that focused on sleep disturbances, discomfort related to the sensor, discomfort related to the adhesive tape, local hypersensitivity, local itching, local pain, local redness and/or local subcutaneous hemorrhage. The CCU nurses inspected the insertion site twice daily for signs of local adverse events.

Statistical Analyses

CGMS parameters were analyzed using Medtronic MiniMed CGMS Software 3.0. The results are expressed as the mean $\pm$ SD. We used the χ^2 test to compare the categorical variables and the 2-sample t-test for continuous variables. Intergroup differences were tested with one-way analysis of variance (ANOVA). The significance and the correlation between the glucose levels measured by finger-stick and by CGMS were analyzed using linear regression analysis. A P value of <0.05 (two-sided) was considered significant. Data were analyzed with SPSS 21.0 (Chicago, Illinois).

Results

Based on the inclusion criteria and the exclusion criteria, 234 STEMI patients undergoing p-PCI were enrolled in the study. Nine cases were excluded from the final analysis because the CGMS signal was interrupted or did not meet the accuracy

requirements, and six cases were excluded because of new onset diabetes. Data from the remaining 219 subjects (154 men and 65 women) were included in the statistical analyses. Table 1 provides the basic characteristics of the study patients by gender. Compared with women, men had a higher blood pressure (both systolic and diastolic) ($P<0.05$) and smoking rate ($P<0.001$) and lower levels of high-density lipoprotein cholesterol ($P=0.005$).

Correlation analysis of interstitial glucose values by CGMS and corresponding capillary BG

The correlation between the CGMS glucose mean values and the finger-stick capillary glucose mean values for the 219 study subjects were analysed. The average of the 657 CGMS glucose mean values and the corresponding finger-stick glucose mean values were 6.60 ± 1.08 mmol/l and 7.08 ± 1.05 mmol/l, respectively. Figure 1 shows a positive correlation between these two values ($R^2 = 0.676$, $P < 0.001$). In addition, the correlations between CGMS glucose mean values and finger-stick capillary glucose mean values were compared for each day: a strong positive correlation on the first ($R^2 = 0.647$, $P < 0.001$, Figure 2), second ($R^2 = 0.710$, $P < 0.001$, Figure 3) and third days ($R^2 = 0.672$, $P < 0.001$, Figure 4).

Characteristics of the glucose profiles in STEMI patients undergoing p-PCI by CGMS

Glucose profiles using the 3-day mean data from the 219 subjects are shown in Figure 5. The MBGs for the 3 days were 6.88 ± 1.13 mmol/l, 6.54 ± 0.89 mmol/l, and 6.43 ± 0.93 mmol/l, respectively ($P < 0.001$). Table 2 shows the comparison of the glucose values for each of the 3 days as measured by CGMS. There were significant differences in the daytime MBG, the nighttime MBG, PT7.8, PT3.9-7.8, PT3.9, Max BG, and Min BG ($P < 0.05$). The daytime MBG, the nighttime MBG and PT7.8 were the highest in the first day, compared with the second and third days. The daytime MBGs for the first, second, and third day were 6.93 ± 1.35 mmol/l, 6.56 ± 1.14 mmol/l, and 6.46 ± 1.18 mmol/l ($P < 0.001$), respectively. The nighttime MBGs were 6.81 ± 1.41 mmol/l, 6.47 ± 1.32 mmol/l, and 6.31 ± 1.45 mmol/l ($P < 0.001$), and the PT7.8 were $23 \pm 25\%$, $19 \pm 18\%$, and $18 \pm 16\%$ ($P = 0.013$), respectively. PT3.9-7.8 and PT3.9 were $72 \pm 24\%$ and $5 \pm 10.6\%$ in the first day, $80 \pm 19\%$ and $3 \pm 11.8\%$ in the second day, and $78 \pm 21\%$ and $2 \pm 7\%$ in the third day, respectively ($P < 0.05$). The Max BG and Min BG were 10.06 ± 2.49 mmol/l and 4.18 ± 0.95 mmol/l in the first day, 10.22 ± 2.56 mmol/l and 5.35 ± 0.84 mmol/l in the second

day, and 9.37 ± 2.40 mmol/l and 4.71 ± 0.88 mmol/l in the third day ($P < 0.001$).

The safety of CGMS in non-diabetic STEMI patients undergoing p-PCI

Table 3 shows the adverse events that occurred in the 234 subjects on whom the CGMS was used. In our study, all of the adverse events were mild. The most frequent adverse event was discomfort related to the adhesive tape. The rate of local minor hemorrhagic events was 2.1%: two resulted in sensor removal; two influenced the sensor's accuracy; and, one did not influence the sensor's precision. There were no major hemorrhages or hematomas at the site of the sensor insertion. The percentage of participants who did not experience any local adverse

events was 89%, and no other adverse events resulted in sensor removal.

Discussion

The principal finding of our study was that the use of CGMS was found to be feasible and safe in STEMI patients undergoing p-PCI. Uncontrolled hyperglycemia in hospitalized patients, with or without a previous diagnosis of diabetes, has been associated with adverse outcomes and longer lengths of stay [21]. Hyperglycemia is a common phenomenon in critically ill patients, and can be attributed to a variety of different reasons [22-23]. The current literature does not provide a consensus on the accuracy of CGMS glucose values: some studies revealed that CGMS can be accurate and useful [24-29], while

TABLE 1. Characteristics of the subjects at admission by gen

	Men	Women	t/ χ^2	P-value
Number of participants	154	65	NA	NA
Age (years)	54 ± 17	53 ± 19	0.384	0.702
BMI, kg/m ²	24.5 ± 4.1	25.1 ± 4.6	0.954	0.341
Left ventricular EF, %	54.2 ± 7.3	53.1 ± 7.5	1.011	0.313
WBC counts (10 ⁹ /L)	10.06 ± 2.8	10.37 ± 3.1	0.725	0.469
Serum creatinine, mg/dL	0.85 ± 0.21	0.87 ± 0.26	0.599	0.550
Total cholesterol (mg/dl)	195 ± 42	191 ± 45	0.630	0.529
Triglycerides (mg/dl)	95 ± 30	87 ± 28	1.838	0.067
HDL-C (mg/dl)	54 ± 15	60 ± 13	2.809	0.005
LDL-C (mg/dl)	121 ± 32.1	114 ± 27.3	1.538	0.125
Fasting plasma glucose (mg/dl)	89 ± 8.2	87 ± 7.8	1.673	0.096
Systolic blood pressure (mmHg)	125 ± 28	116 ± 23	2.286	0.023
Diastolic blood pressure (mmHg)	72 ± 9	69 ± 8	2.327	0.021
Coronary risk factor (n, %)				
Hyperlipidemia	77 (50)	30(46)	0.271	0.603
Hypertension	86(56)	27(42)	3.746	0.053
Current smoking	88(57)	5(8)	45.750	0.000
Family history	21 (15)	6(13)	0.821	0.365
Obesity	40(26)	16(25)	0.044	0.833

Data are reported as the mean $\pm$ SD or n (%).

BMI, body mass index; EF, ejection fraction; WBC, white blood cell; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol

TABLE 2. Comparison of the CGMS values over 3 days

Factors	First day	Second day	Third day	F	P
MBG (mmol/l)					
24 h	6.88±1.13	6.54±0.89	6.43±0.93	12.081	<0.001
Daytime	6.93±1.35	6.56±1.14	6.46±1.18	8.921	<0.001
Nighttime	6.81±1.41	6.47±1.32	6.31±1.45	7.344	<0.001
Percentage of time at glycemia (%)					
BG ≥ 7.8 mmol/l	23±25	19±18	18±16	4.408	0.013
3.9 < BG < 7.8 mmol/l	72±24	80±19	78±21	8.264	<0.001
BG ≤ 3.9 mmol/l	5±10.6	3±11.8	2±7	5.099	0.006
SD of blood glucose (mmol/l)	1.36±0.74	1.29±0.57	1.28±0.63	0.983	0.375
Max BG (mmol/l)	10.06±2.49	10.22±2.56	9.37±2.40	7.241	<0.001
Min BG (mmol/l)	4.18±0.95	5.35±0.84	4.71±0.88	94.65	<0.001

Data are reported as the mean ± SD or n (%). SD, standard deviation; BG, blood glucose; MBG, mean blood glucose

TABLE 3. Frequency of adverse events in the 234 persons using CGMS

Adverse events	Number of events	Percentage
Sleep disturbances	13	5.6%
Discomfort related to the sensor	6	2.6%
Discomfort related to the adhesive tape	30	12.8%
Local adverse events		
Hypersensitivity	16	6.8%
Itching	20	8.5%
Redness and/or pain and/ or hypersensitivity and/or itching	24	10.3%
Minor hemorrhage	5	2.1%
Major hemorrhage or hematoma	0	0
No local adverse events	208	89%

other studies argued that CGMS glucose values are not sufficiently accurate and reliable to be used for therapeutic decisions [30-32]. Currently, clinical experience with CGMS in CCUs is limited, particularly for STEMI patients undergoing p-PCI. Our results showed an improved correlation between interstitial glucose values measured by CGMS and the corresponding capillary BG. Furthermore, there were strong positive correlations in day-by-day comparisons ($P<0.001$); therefore, we believe that CGMS glucose values are relatively accu-

rate and reliable and can be used in STEMI patients undergoing p-PCI.

Stress hyperglycemia is the result of sympathetic nervous system activation and increased production of catecholamines and cortisol that stimulate the processes of glycogenesis, glycogenolysis and lipolysis [33,34]. Goyal *et al.* demonstrated that admission glucose and changes in glucose levels within the first 24 hours predict the risk of mortality at 30 days in ACS patients without a history of diabetes and that the risk of 30-

FIGURE 1. Correlation between finger-stick capillary glucose mean values and CGMS glucose mean values in 219 STEMI patients undergoing p-PCI

FIGURE 2. Correlation between finger-stick capillary glucose mean values and CGMS glucose mean values on the first day

FIGURE 3. Correlation between finger-stick capillary glucose mean values and CGMS glucose mean values on the second day.

FIGURE 4. Correlation between finger-stick capillary glucose mean values and CGMS glucose mean values on the third day.

FIGURE 5. Continuous glucose profiles representing the mean blood glucose values measured by GCMS over 3 days of monitoring for 219 STEMI patients undergoing p-PCI.

day mortality decreased by 9% per 11 mg/dL reduction in glucose within the first 24 hours after ACS[35]. The present study reported the CGMS glucose values over 3 days and proved that stress hyperglycemia is common among STEMI patients undergoing p-PCI. Furthermore, our study showed that the fluctuation in the 3-day CGMS glucose values, the 24 h MBG, the daytime MBG, the nighttime MBG and PT7.8, were highest on the first day compared with the second and third day ($P < 0.05$). PT3.9 was $5 \pm 10.6\%$ on the first day, $3 \pm 11.8\%$ on the second day, and $2 \pm 7\%$ on the third day ($P < 0.05$). These data indicate that we should focus on the hyperglycemia and hypoglycemia of AMI subjects in order to reduce adverse cardiac events. This is the first study to reveal fluctuations in glucose levels of STEMI patients undergoing p-PCI.

For p-PCI subjects, intensive antiplatelet and anticoagulation therapeutics are necessary to reduce adverse cardiovascular events; therefore, the safety of using CGMS requires further assessment. Jadviscokova *et al.* [36] investigated the adverse events due to CGMS and found that there were only minor local adverse events: hypersensitivity (18%), itching (14%) and subcutaneous hemorrhage (5%). Additionally, discomfort related to the adhesive tape (27%) was found. None of these re-

sulted in sensor withdrawal. Similarly, in our study, all of the adverse events were mild. The CGMS were well tolerated and there was no evidence of infection or inflammation. The most frequent adverse event was also discomfort related to the adhesive tape (12.8%). The rate of local minor hemorrhage events was 2.1% (two resulted in sensor removal, two affected the sensor's accuracy and one did not affect the precision of the sensor). There were no incidences of a major hemorrhage or hematoma at the site of the sensor insertion. Most (89%) of the participants experienced no local adverse events, any adverse events that were reported did not result in sensor removal. The present study revealed that there were no increased risks of minor hemorrhage, major hemorrhage or hematoma at the site of the sensor insertion for STEMI patients undergoing p-PCI.

CGM of glucose concentration in interstitial fluid is a sophisticated method to control and regulate glucose metabolism. The substantial harm associated with stress hyperglycemia in patients with AMI suggests that glucose management strategies may improve outcomes in patients with hyperglycemia. CGMS could be used as a tool to show trends in glucose levels, predict impending glucose excursions (hypo- and hyperglycemia) and monitor glycemic variability. Further research is re-

quired to address the likely benefits of CGMS in STEMI patients undergoing p-PCI.

Study limitations

There are several limitations to this study. First, the number of patients participating was small, in part because studies using CGMS are difficult to implement with a large number of patients. Second, in order to assess the accuracy of CGMS and obtain more reliable data, we did not enroll diabetes patients and did not intervene on the hyperglycemia. Additionally, in the retrospective CGMS data analysis, asymptomatic hypoglycemia events were found but were not treated. Four patients had symptomatic hypoglycemia, and treatment with PO supplementation was utilized for hypoglycemic events. Third, the specific cause of spontaneous hypoglycemia in non-diabetic STEMI patients who were not treated with insulin or hypoglycemic therapies could not be definitively established. Fourth, because there were patients with unique needs, the dietary patterns of the participants were irregular; thus, we could not analyze the postprandial BG levels.

Conclusion

CGMS glucose values are relatively accurate and reliable. The use of CGMS was shown to be safe and feasible in STEMI patients undergoing p-PCI. CGMS could be used as a tool to detect trends in glucose levels and to predict impending glucose excursions (hypo- and hyperglycemia) in STEMI subjects.

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Author Disclosure Statement

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