Comparison of Space Glucose Control and Routine Glucose Management Protocol for Glycemic Control in Critically Ill Patients: A Prospective, Randomized Clinical Study

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Abstract

Background: The Space Glucose Control (SGC) system is a computer-assisted device combining infusion pumps with the enhanced Model Predictive Control algorithm to achieve the target blood glucose (BG) level safely. The objective of this study was to evaluate the efficacy and safety of glycemic control by SGC with customized BG target range of 5.8–8.9 mmol/L in the critically ill patients.

Methods: It is a randomized controlled trial of seventy critically ill patients with mechanical ventilation and hyperglycemia (BG ≥ 9.0 mmol/L). Thirty-six patients in the SGC group and 34 in the routine glucose management group were observed for three consecutive days. Target BG for both groups was 5.8–8.9 mmol/L. The primary outcome was the percentage time in the target range.

Results: The percentage time within BG target range in the SGC group (69 ± 15%) was significantly higher than in the routine management group (52 ± 24%; $P < 0.01$). No measurement was ≤2.2 mmol/L, and there was only one episode of hypoglycemia (2.3–3.3 mmol/L) in each group. The average BG was significantly lower in the SGC group (7.8 ± 0.7 mmol/L) than in the routine management group (9.1 ± 1.6 mmol/L, $P < 0.001$). Target BG level was reached earlier in the SGC group than routine management group (2.5 ± 2.9 vs. 12.1 ± 15.3 h, $P = 0.001$). However, the SGC group performed worse for daily insulin requirement (59.8 ± 39.3 vs. 28.4 ± 36.7 U, $P = 0.001$) and sampling interval (2.0 ± 0.5 vs. 3.7 ± 0.5 h, $P < 0.001$) than the routine management group did. Multiple linear regression showed that the intervention group remained a significant individual predictor ($P < 0.001$) of the percentage time in target range.

Conclusions: The SGC system, with a BG target of 5.8–8.9 mmol/L, resulted in effective and reliable glycemic control with few hypoglycemic episodes in critically ill patients with mechanical ventilation and hyperglycemia. However, the workload was increased.

Trial Registration: http://www.clinicaltrials.gov, NCT 02491346; https://www.clinicaltrials.gov/ct2/show/NCT02491346?term=NCT02491346&cond=Hyperglycemia&cntry1=ES%3ACN&rank=1.

Key words: Critical Illness; Glucose Control in Intensive Care; Hyperglycemia; Space Glucose Control; Enhanced Model Predictive Control

Introduction

Many critically ill patients have stress-induced hyperglycemia,[1] which is associated with an increased risk of morbidity and mortality.[1-3] Intervention trials[4-8] that aimed to normalize glycemic level have reported conflicting outcomes in the Intensive Care Unit (ICU). In 2001, the landmark Leuven study[8] demonstrated that tight glycemic control (TGC) reduced mortality in the surgical ICU. Nevertheless, another study performed by the same author in medical ICU failed to find any significant effect of TGC on overall mortality.[7] However, the NICE-SUGAR study[5] in 2009 reported an increase in mortality for the TGC group. One possible explanation for the conflicting results might be

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that TGC in critically ill patients was associated with a higher risk of severe hypoglycemia (up to 28.6%) compared with conventional glycemic control.[5,6,9-11] In addition, there was considerable variability in what constituted "conventional glycemic control." For example, in the studies by van den Berghe *et al*., the targeted blood glucose (BG) level in conventional group was 10.0–11.1 mmol/L,[7,8] whereas it was <10.0 mmol/L in the NICE-SUGAR study.[5] In consequence, these results called for a heightened focus on improving the quality and safety of BG management in the ICU.

Numerous BG control protocols have been developed to achieve TGC. Among these, the enhanced Model Predictive Control (eMPC) algorithm proved to be efficient and safe in several multicenter clinical studies.[12-16] Space Glucose Control (SGC) is a CE-certified device installed with the eMPC algorithm, and the first device on the market available for clinical medical use.

Although the effectiveness of SGC was verified by Amrein *et al*.,[17] six of forty patients experienced hypoglycemia (<3.3 mmol/L) and one had severe hypoglycemia (<2.2 mmol/L). Many randomized controlled trials have demonstrated that it is difficult to achieve low BG targets for TGC without increasing the risk of severe hypoglycemia.[5,6,9,10] Based on these reports, current guidelines advocate less strict glycemic control in the setting of critical illness. To prevent the high risk of hypoglycemia and comply with the current recommendations, we have implemented the BG target range of 5.8–8.9 mmol/L in our ICU.

The objective of this randomized controlled study was to investigate the efficacy of the SGC system, which has been customized to our BG target range, for glycemic control in critically ill patients with mechanical ventilation through comparison with routine glucose management protocol.

Methods

Ethical approval

The protocol was approved by the Peking Union Medical College Hospital Ethics Committee. Written informed consent was obtained from every patient or the next-of-kin when the patient was unable to provide consent before any trial-related activities. The study was conducted in accordance with the *Declaration of Helsinki*, and was registered at the Clinical Trials Database (ClinicalTrials.gov Identifier: NCT02491346).

Patients

The study was designed as a randomized controlled nonblind clinical trial at the 15-bed medical ICU in a tertiary teaching hospital. Patients admitted to the ICU were eligible for the trial if they had at least one blood sugar measurement of ≥9.0 mmol/L plus the following: (1) age ≥18 years; (2) mechanical ventilation; and (3) predicted ICU length of stay ≥72 h. Patients were excluded if they were admitted because of diabetic ketoacidosis or nonketotic hyperosmolar state, pregnant, allergic to insulin, or moribund and likely to die within 24 h.

Patients enrolled in the trial were randomized to the SGC group or the control group (routine glucose management of the ICU). The BG target range for both groups was 5.8–8.9 mmol/L. Randomization was accomplished through computerized randomization table by a specialized statistician.

Space Glucose Control system and routine glucose management

The SGC system is run at the bedside by the ICU nursing staff. It includes three infusion pumps and a touch screen, which are interconnected through the Space station. Two of the pumps are for enteral and parenteral nutrition (Infusomat® Space; B. Braun, Melsungen, Germany) and the other is for insulin (Perfusor® Space; B. Braun). Data communication between the pumps can be conducted through the touch screen, which is the central user interface. The SGC is implemented with the eMPC algorithm to perform blood management. As described previously,[14,18] glucose measurement, insulin perfusion rate, and infusion rate of specific enteral and parenteral nutrition are the input variables for the SGC. The insulin perfusion rate and time of the next glucose sample (between 30 and 240 min) are the outputs. The responsible nurse must confirm the advised insulin dose rate, which is then set automatically at the pump. Changes in enteral or parenteral nutrition are communicated directly to the eMPC by the corresponding pumps that are attached to the SGC, which automatically generates an insulin dose that requires confirmation by the nursing staff. The system can store and display all data on treatment and trends of all relevant information on the touch screen.

In the current study, insulin adjustment in the SGC group was guided by the SGC and carried out by the ICU nursing staff under the direction of ICU physicians. All participating nurses were instructed on the principle of the eMPC algorithm and trained at the bedside in handling the SGC system before the trial began. In the control group, the responsible physician, who had been trained extensively with regards to the BG management protocol adopted in our department, aimed to maintain BG within the target range. The BG management protocol was a modification of the Yale insulin infusion protocol.[19] In brief, insulin was administered by the physician via intravenous infusion or subcutaneous injection if BG level exceeded 9.0 mmol/L, and was titrated to maintain BG in the range of 5.8–8.9 mmol/L. Glycemic monitoring was performed via BG measurements at 1–4 h intervals, which should be shortened in case of severe glucose abnormality.

BG was measured with a glucometer using the Accu-Chek Performa test strip (Roche Diagnostics GmbH, Mannheim, Germany). Capillary BG was sampled from the patients' fingertips. In patients with shock or receiving vasopressors,

we recommended that blood samples should be withdrawn from an arterial line to measure BG. Insulin (40 U in 40 ml 0.9% sodium chloride; Wanbang Biopharmaceuticals, Xuzhou, Jiangsu, China) was infused intravenously using a standard syringe of the ICU (Perfusor® Space). In the control group, insulin was administrated through intermittent subcutaneous or intravenous infusion according to the discretion of the responsible physicians.

All trial-related treatments and observations were continued for 72 h, or until discharge from the ICU, or death. Other insulin formulations or oral antidiabetic drugs were not allowed during this trial. If the patient was discharged to a general ward, BG was controlled according to the physician's discretion. Feeding was prescribed in accordance with our routine departmental practice. We recommended that patients should receive adequate caloric and glucose intake, such as 200–300 g/day glucose for those without enteral or parenteral nutrition; enteral nutrition should be given as soon as possible; and patients should receive 25–35 kcal·kg^{-1}·day^{-1} energy intakes for nutrition. For those patients treated with renal replacement therapy (RRT), the daily intake of carbohydrates was 3–5 g/kg, as recommended by the European Society of Parenteral and Enternal Nutrition Guidelines.[20]

Data collection

Patients' demographic and clinical information was collected prospectively, including age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, baseline BG level, history of diabetes, RRT, vasoactive-inotropic score (VIS)[21] for patients treated with vasopressors, daily steroid dose expressed as prednisone equivalent, carbohydrate content of enteral and parenteral nutrition, and main diagnostic category for ICU.

Outcome measures

The primary outcome was the percentage of time in BG target range during the 72-h study period. The secondary outcomes were average glycemia level for the entire study; incidence of severe hypoglycemia (≤2.2 mmol/L); incidence of moderate hypoglycemia (2.3–3.3 mmol/L); percentage of time between 3.4 and 5.7 mmol/L with moderate risk of hypoglycemia; percentage of time >9.0 mmol/L, indicating hyperglycemia; standard deviation (SD) of mean BG, indicating variability; time to first BG measurement in target range; insulin dose; and sampling interval, indicating workload. The percentage of time in the BG target range was defined as the number of measurements in the target range in each patient.

Statistical analysis

We calculated the sample size as 54 patients (27 per group) to detect a 20% difference in the time with target range, assuming an SD of 22% for each group, two-tailed Type 1 error of 0.05, and power of 90%.[15,17,22,23] In view of possible consent withdrawal and data missing during the trial, we finally planned to enroll 70 patients. SAS statistical software package (version 9.2, SAS Institute, Cary, North Carolina, USA) was used for sample estimation.

Categorical variables were reported as absolute frequencies. Numerical data were reported as the mean ± standard deviation (SD) if not otherwise indicated. Comparison of categorical data was made via Chi-square or Fisher's exact test, and differences in continuous data were evaluated by Student's *t*-test or Mann-Whitney *U*-test. For the paired data from average blood values every 4 h, a paired *t*-test was used for comparison. For data in the same group at different times, repeated measures analysis of variance was performed. For BG control outcomes with significant difference between the two groups, multivariate linear regression was performed to determine if the type of intervention remained as an independent predictor after controlled for confounding factors, including age, BMI, APACHE II, baseline BG level, insulin dose, carbohydrate administration, sampling interval, time to target range, and vasopressor or steroid treatment. The method by which the independent variables entered the regression model was "enter." A value of $P < 0.05$ was considered statistically significant and was presented as two-tailed. SPSS Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Between December 22, 2014 and June 20, 2015, 262 patients were admitted and screened for eligibility of the study. After exclusion of 183 patients, 79 patients were recruited and randomized into the study: Forty allocated to the SGC group and 39 to the control group. Data of 9 patients were censored and distributed equally in the 2 intervention groups ($P = 0.737$). Finally, 36 patients in the SGC group and 34 in the control group were analyzed [Figure 1]. Baseline characteristics are shown in Table 1. There were no differences in age, gender, history of diabetes, BMI, baseline BG level, time from ICU admission to BG control, glucocorticoid use, vasopressors, or RRT, while the APACHE II score in the SGC group was significantly higher than in the control group (23.6 ± 5.8 vs. 18.5 ± 6.6, $P = 0.001$). The two groups did not differ significantly with regards to the primary admission diagnosis, which included pulmonary (58.6%), central nervous system (24.3%), infectious (10.0%), cardiovascular (4.3%), and other disorders (2.9%).

Glucose control

The result of glycemic control is shown in Table 2. Compared with control group, percentage time within target range during the 72-h study was significantly higher in the SGC group (69 ± 15% vs. 52 ± 24%; $P < 0.01$). Moreover, patients in the SGC group also showed better daily time with target range, 62 ± 23% versus 47 ± 32% ($P < 0.01$) for day 1; 71 ± 22% versus 54 ± 28% ($P < 0.01$) for day 2; and 74 ± 16% versus 53 ± 27% ($P < 0.01$) for day 3 [Table 3]. In addition, daily time within target range significantly improved in the SGC group ($P = 0.019$) but not in the control group ($P = 0.282$).

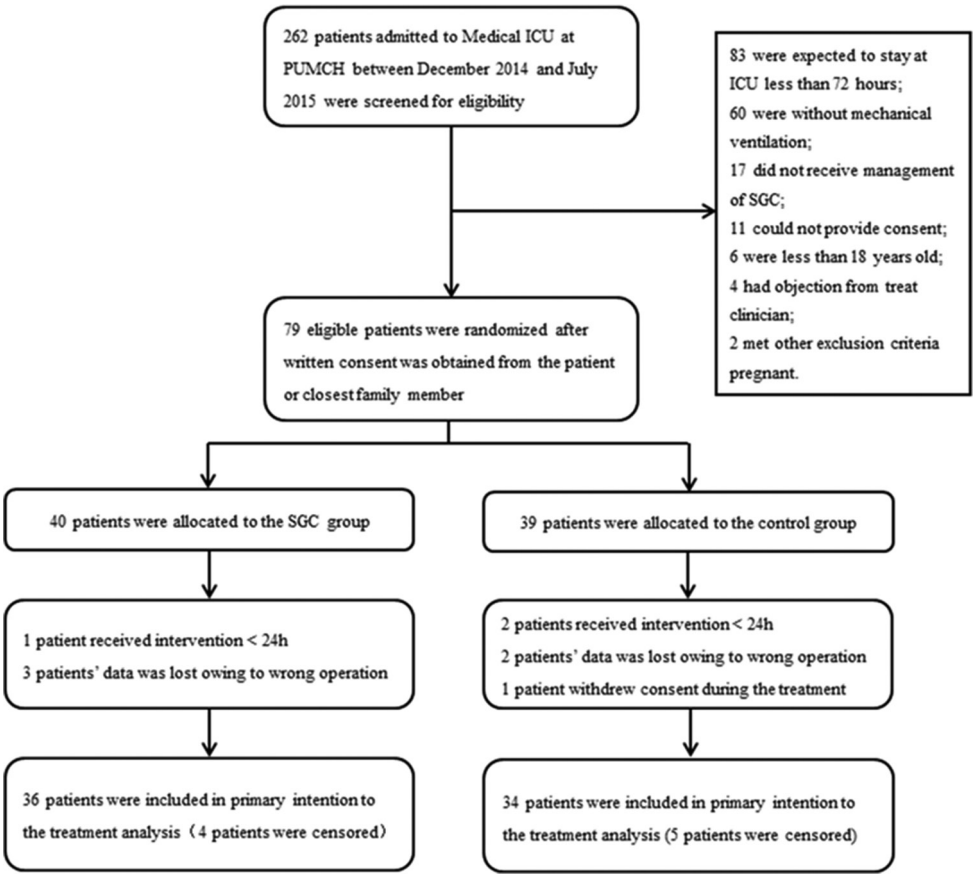

Figure 1: Trial flow diagram. ICU: Intensive Care Unit; PUMCH: Peking Union Medical College Hospital; SGC: Space Glucose Control.

Table 1: Patient baseline demographic and clinical characteristics

Characteristic	SGC group (n = 36)	Control group (n = 34)	Statistics	P
Age (years)	57.7 ± 18.9	54.6 ± 17.5	0.712*	0.479
Male sex, n (%)	18 (50)	21 (62)	0.981†	0.322
BMI (kg/m^2)	23.1 ± 4.1	23.5 ± 4.0	−0.423*	0.674
APACHE II	23.6 ± 5.8	18.5 ± 6.6	3.480*	0.001
History of diabetes, n (%)	4 (11)	5 (15)	0.202†	0.731
Steroid treatment, n (%)	26 (72)	21 (62)	0.867†	0.352
Vasoactive therapy, n (%)	24 (67)	16 (47)	2.745†	0.098
RRT, n (%)	6 (17)	4 (12)	0.343†	0.736
Baseline BG (mmol/L)	9.8 ± 2.6	9.2 ± 2.7	0.956*	0.342
Time from ICU admission to BG control (h)	49.6 ± 42.5	41.7 ± 23.9	0.945*	0.348
Diagnostic category, n (%)				
Respiratory	22 (61)	19 (56)	0.197†	0.657
Sepsis	5 (14)	2 (6)	1.245†	0.430
Neurologic	7 (19)	10 (29)	0.945†	0.331
Cardiovascular	2 (6)	1 (3)	0.291†	0.589
Others	0	2 (6)	NA	NA

Data are presented as means ± SD or n (%) as noted. *t values, †χ^2 values. SGC: Space GlucoseControl; BMI: Body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; RRT: Renal replacement therapy; BG: Blood glucose; NA: Not applicable; ICU: Intensive Care Unit.

During the 72-h study, the mean BG levels in the SGC group fluctuated within the target range most of time, whereas those in the control group were not [Figure 2]. Compared with the control group, patients in the SGC group had significantly lower average BG (7.8 ± 0.7 vs. 9.1 ± 1.6 mmol/L, P < 0.001), shorter time to reach target glucose level (2.5 ± 2.9 vs. 12.1 ± 15.3 h, P = 0.001), lower percentage of time >9.0 mmol/L (21 ± 14% vs. 42 ± 25%, P < 0.001), and higher percentage of time between 3.3 and 5.7 mmol/L (10 ± 6% vs. 5 ± 9%, P = 0.014). However, there were no episodes of severe hypoglycemia (<2.2 mmol/L) in either group, and only one episode of moderate hypoglycemia (2.2–3.3 mmol/L) in each group [Table 2]. The two groups showed no significant difference in BG

Table 2: Primary and secondary outcomes of blood glucose control according to treatment group

Outcome	SGC group (n = 36)	Control group (n = 34)	t	P
Percentage of time in target range (%)	69 ± 15	52 ± 24	3.509	0.001
Average BG (mmol/L)	7.8 ± 0.7	9.1 ± 1.6	−4.556	<0.001
Time to target range (h)	2.5 ± 2.9	12.1 ± 15.3	−3.643	0.001
Percentage of time ≥9 mmol/L (%)	21 ± 14	42 ± 25	−4.379	<0.001
Percentage of time 3.4–5.7 mmol/L (%)	10 ± 6	5 ± 9	2.510	0.014
Hypoglycemia episodes (≤3.3 mmol/L), n (%)	1 (2.8)	1 (2.9)		
Severe hypoglycemia episodes, n (%)	0	0	NA	NA
Standard deviation of mean BG (mmol/L)	1.8 ± 0.7	2.1 ± 1.1	−3.643	0.159
Insulin dose (U/24 h)	59.8 ± 39.3	28.4 ± 36.7	3.452	0.001
Sampling interval (h)	2.0 ± 0.5	3.7 ± 0.5	−14.710	<0.001

Data are presented as means ± SD or n (%) as noted. SGC: Space GlucoseControl; BG: Blood glucose; SD: Standard deviation; NA: Not applicable.

Table 3: Daily blood glucose control, carbohydrate administration, vasopressor and corticosteroid treatment according to treatment group

Parameters	Day 1				Day 2			
	SGC	Control	t	P	SGC	Control	t	P
Percentage in target (%)	62 ± 23	47 ± 32	2.374	0.020	71 ± 22	54 ± 28	2.855	0.006
Mean BG (mmol/L)	8.0 ± 1.1	9.5 ± 1.8	−4.252	<0.001	7.6 ± 1.0	8.8 ± 2.2	−2.980	0.004
Insulin dose (U)	70.6 ± 40.7	24.5 ± 34.5	5.083	<0.001	60.7 ± 45.4	32.2 ± 43.1	2.632	0.011
Sampling interval (h)	1.8 ± 0.5	3.8 ± 0.6	−15.357	<0.001	2.2 ± 0.7	3.7 ± 0.7	−9.298	<0.001
Total carbohydrate (g/d)	304.7 ± 140.0	315.2 ± 132.5	−0.321	0.750	359.9 ± 134.1	356.1 ± 119.8	0.123	0.903
VIS (μg·kg^{-1}·min^{-1})	22.6 ± 28.9	15.3 ± 20.5	1.226	0.225	20.9 ± 29.7	10.8 ± 17.0	1.692	0.097
Steroid dose (mg/d)	60.5 ± 70.6	49.6 ± 51.7	0.740	0.462	55.3 ± 72.1	54.7 ± 63.8	0.034	0.973

Parameters	Day 3			
	SGC	Control	t	P
Percentage in target (%)	74 ± 16	53 ± 27	3.707	<0.001
Mean BG (mmol/L)	7.5 ± 0.8	8.9 ± 1.8	−3.969	<0.001
Insulin dose (U)	63.8 ± 46.6	28.4 ± 37.5	3.373	0.001
Sampling interval (h)	2.2 ± 0.6	3.7 ± 0.5	−10.822	<0.001
Total carbohydrate (g/d)	353.3 ± 96.3	379.3 ± 124.8	−0.940	0.351
VIS (μg·kg^{-1}·min^{-1})	16.6 ± 25.9	11.3 ± 21.7	0.881	0.382
Steroid dose (mg/d)	48.9 ± 61.2	54.7 ± 62.6	−0.370	0.712

Data are presented as means ± SD. SGC: Space Glucose Control; BG: Blood glucose; VIS: Vasoactive-inotropic score; SD: Standard deviation.

variability, as shown by SD of mean BG (1.8 ± 0.7 vs. 2.1 ± 1.1 mmol/L, P = 0.159) [Table 2].

Insulin dose, sampling interval, nutrition intake, and concomitant medication

The daily insulin dose was significantly higher in the SGC group than the control group (59.8 ± 39.3 vs. 28.4 ± 36.7 U, P = 0.001) [Table 2]. The average sampling interval was notably shorter in the SGC group than the control group (2.0 ± 0.5 h vs. 3.7 ± 0.5 h, P < 0.001). The two groups did not differ significantly in daily energy supplied by enteral and parenteral nutrition [Table 3].

Twenty-four (66.7%) patients in the SGC group and 16 (47.1%) in the control group received vasopressors during the study, but this difference was not significant (P = 0.098). There were no significant differences between the SGC and control groups for VIS [Table 3]. Twenty-six patients (72.2%) in the SGC group and 21 (61.8%, P = 0.352) in the control group were treated with steroids, whereas the daily dose was comparable between the two groups [Table 3].

Multiple regression analysis

For the dependent variable of percentage time within target range during the 72-h study, multiple linear regression analysis showed that the significant confounding variables were sampling interval (P < 0.001), time to target range (P < 0.001), baseline BG (P = 0.02), insulin (P = 0.001), and steroid dose (P = 0.014). After we controlled for all the confounding variables, intervention group remained a significant individual predictor (P < 0.001) of percentage time within the BG target range [Table 4]. In the SGC group, sampling interval (P < 0.001), baseline BG (P = 0.006), and insulin dose (P = 0.009) were the individually significant predictors for time within target range [Table 5]. The time to target range (P = 0.001) and steroid dose (P = 0.025) were individually significant in the control group [Table 6].

Adherence to enhanced Model Predictive Control instruction

Throughout the trial, majority of the recommendations for SGC was followed, except when overruled by the nurse on one occasion in one patient. In that case, moderate hypoglycemia (2.8 mmol/L) developed during continuous infusion of insulin at a dose of 5.6 U/h. The treating physician prescribed an intravenous bolus of 10 g glucose, and increased delivery of enteral nutrition from 30 to 80 kcal/h. The responsible nurse overruled the SGC recommendation (i.e., adjust the insulin dose to 4 U/h), and reduced the insulin dose to 2 U/h after discussion with the treating physician.

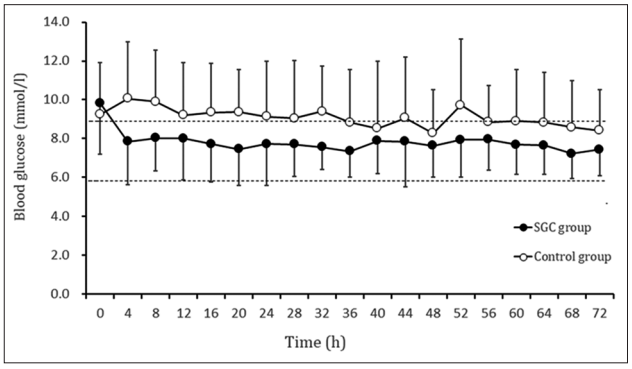

Figure 2: Comparison of groups for glycemic control in every 4-h. BG concentrations, expressed as means ± SD, every 4-h during this trail controlled by the SGC system (SGC group) showed significantly lower and for more time in target range than those by routine BG management protocol (control group). Black horizontal lines in the graph show the 5.8–8.9 mmol/L BG target range. BG: Blood glucose; SD: Standard deviation; SGC: Space Glucose Control.

Discussion

To the best of our knowledge, this is the first study to demonstrate the effectiveness of the SGC system with a BG target of 5.8–8.9 mmol/L in critically patients with mechanical ventilation. Compared with the routine glucose management, the SGC system significantly improved glycemic control, as suggested by a longer time within the target range, a shorter time to achieve the BG target, a lower mean BG concentration, and no evidence of increased risk of severe hypoglycemia, at the expense of increased workload for medical staff.

The time within target range in the SGC group in our study was inferior to those reported by Amrein *et al*., who

Table 4: Multiple regression analysis for individual predictors of percentage time within the target range

Independent variables	Regression coefficient (SE)	Standardized coefficients	*P* for regression coefficients	Adjusted R^2 for the model
Time to target range	−0.716 (0.145)	−0.394	<0.001	0.727
Group	−39.678 (6.582)	−0.927	<0.001	
Baseline BG	−1.438 (0.599)	−0.176	0.020	
Insulin dose	−0.161 (0.045)	−0.306	0.001	
Sampling interval	11.471 (3.268)	0.530	0.001	
Age	−0.123 (0.077)	−0.104	0.117	
APACHE II	−0.371 (0.260)	−0.115	0.159	
BMI	0.051 (0.372)	0.009	0.892	
Total carbohydrate	0.008 (0.014)	0.041	0.568	
VIS	−0.104 (0.072)	−0.106	0.151	
Steroid dose	−0.059 (0.230)	−0.168	0.014	

Dependent variable: Percentage of time within the range target. BMI: Body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; BG: Blood glucose; VIS: Vasoactive-inotropic score; SE: Standard error.

Table 5: Multiple regression analysis for individual predictors of percentage time within the target range in the SGC group

Independent variables	Regression coefficient (SE)	Standardized coefficients	*P* for regression coefficients	Adjusted R^2 for the model
Time to target range	0.200 (0.746)	0.039	0.791	0.763
Baseline BG	−2.374 (0.797)	−0.414	0.006	
Insulin dose	−0.122 (0.043)	−0.305	0.009	
Sampling interval	10.091 (3.865)	0.587	0.000	
Age	−0.047 (0.070)	−0.061	0.508	
APACHE II	−0.344 (0.260)	−0.136	0.197	
BMI	0.231 (0.376)	0.064	0.545	
Total carbohydrate	0.005 (0.014)	0.036	0.716	
VIS	−0.065 (0.057)	−0.108	0.267	
Steroid dose	−0.042 (0.230)	−0.185	0.084	

Dependent variable: Percentage of time within the range target. SE: Standard error; BG: Blood glucose; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index; VIS: Vasoactive-inotropic score.

Table 6: Multiple regression analysis for individual predictors of percentage time within the target range in routine management group

Independent variables	Regression coefficient (SE)	Standardized coefficients	*P* for regression coefficients	Adjusted R^2 for the model
Time to target range	−0.791 (0.196)	−0.501	0.001	0.665
Baseline BG	−0.571 (1.191)	−0.064	0.636	
Insulin dose	−0.178 (0.090)	−0.269	0.059	
Sampling interval	1.971 (5.950)	0.043	0.743	
Age	−0.111 (0.155)	−0.080	0.482	
APACHE II	−0.469 (0.502)	−0.127	0.360	
BMI	−0.522 (0.707)	−0.707	0.467	
Total carbohydrate	0.030 (0.028)	0.141	1.086	
VIS	−0.187 (0.171)	−0.139	0.284	
Steroid dose	−0.122 (0.051)	−0.290	0.025	

Dependent variable: Percentage of time within the range target. SE: Standard error; BG: Blood glucose; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index; VIS: Vasoactive-inotropic score.

conducted the only two studies up to now to investigate the performance of the SGC system in ICU settings.[17,24] These authors reported that the time within target range was 83.4% and 93.1%, respectively. ICU staffs in the above two studies had intensive hands-on simulated training and long-term routine use of branded pumps, and ICU nurses attended one-on-one training on virtual patients before enrolment of the first patient. In comparison, the training in our study was less extensive. In addition, the average study period was 6–7 days in the studies of Amrein *et al*., which was significantly longer than 3 days in our study. As shown in our study, the time within target range steadily increased from day 1 to day 3, indicating a process of self-learning through integration of previous data and treatment response. Other possible reasons for the difference in time within target range might include the lack of control group, and the different target range (default of 4.4–8.3 mmol/L vs. customized 5.8–8.9 mmol/L).

Interestingly, although the SGC system was developed based on eMPC algorithm, studies using the former system, including our study, observed a significantly longer time within target range, compared with 46.0–66.1% as reported in studies using the eMPC algorithm.[15,16,23,25] Previous studies examining the efficacy of the eMPC algorithm used a laptop, thus requiring manual input of data such as BG and calorie intake, which was prone to errors. In comparison, the SGC system had the advantage of automatic integration of a variety of confounders, e.g., insulin dose, and nutritional delivery.

We observed no cases of severe hypoglycemia, as well as only two cases of moderate hypoglycemia (one in each group), which was comparable to other studies of the eMPC and SGC system.[14-17,23,24] However, it was noteworthy that the current study did not have adequate power to detect any difference in severe/moderate hypoglycemia between the two groups. Further studies with a larger sample size are required to investigate whether a higher BG target range is associated with a better safety profile compared with traditional BG target range, i.e., 4.4–6.1 mmol/L.

In the current study, the average sampling interval in the SGC group was similar to previous reports about eMPC or SGC (1.5–2.3 h),[14-17,23,25] and almost half of that in the routine management group. This indicated a significant increase of workload. The main difference between the eMPC and other protocols is the nonfixed sampling interval of the eMPC algorithm, which provides unequivocal instructions regarding the time to next measurement. In reality, individual requests for glucose measurements can be easily postponed because of the fast pace of work in the ICU. A clear indication of time interval by the time counter of the eMPC can resolve the problem to some extent.

However, more frequent BG measurements in the SGC group might inevitably be associated with Hawthorne effect, meaning more care to the patients, and, therefore, longer time within target range. Multivariate linear regression analysis in all enrolled patients, as well as patients in the SGC group, found that longer sampling interval was associated with longer time within target range, which was contrary to the previous consensus[26] and reports.[27,28] Although inconclusive, these findings suggested that sampling interval was more affected by severity of acute illness, but not positively correlated with better glucose control.

We acknowledge the following limitations to our study. First, the original calculated sample size was designed to compare the difference in time within target range between two groups. However, the observed difference between the two groups (17%) was lower than predicted 20%. Furthermore, as discussed above, the current study was not designed to detect difference in safety profile, although we observed nonsignificant lower glycemic variability in the SGC group. Second, the current study was conducted in nonblinding approach due to feasibility issues, therefore prone to Hawthorne effect. However, the analyst was not involved in the conduct of the study, which might reduce the selection bias. Third, our results might only be applicable to population with similar characteristics. It is therefore important to note that the enrolled population in this study exclusively included mechanically ventilated patients with expected

ICU length of stay for >72-h. Thus, many postsurgical patients and individuals without mechanical ventilation or with life-threatening conditions were excluded. Fourth, there was no clinical trial to examine the influence of the customized target range of 5.8–8.9 mmol/L on clinical outcome. However, our results, along with previous studies, demonstrated that the SGC system had the advantage of being adaptable to customized target ranges in different clinical scenarios. Fifth, bedside glucometers used to measure BG had insufficient accuracy for glycemic control in critically ill patients, especially if anemia is present.[29,30] Nevertheless, the glucometers were nowadays widely used in many ICUs,[31,32] with routine calibration indicating an accepted difference of 10%. Moreover, to overcome the inaccuracy resulting from documented deviation between capillary and arterial BG measurement, a more prominent issue in critically ill patients requiring vasopressin[33-35] but not in other patients,[36] we performed BG measurement by sampling the arterial blood in these patients. A small pilot study had shown that combining the eMPC algorithm with continuous glucose monitoring was a feasible method for BG control in cardiac surgery patients.[37] A real closed loop system may achieve the desirable BG control in the future.

In conclusion, the customized SGC system with a BG target range of 5.8–8.9 mmol/L resulted in effective and reliable glycemic control with a low incidence of hypoglycemia in critically ill patients with mechanical ventilation. However, this system led to an increase in workload for the medical staff. Further development of the SGC system is required to decrease the staff workload without reducing the quality of BG management. Further multicenter, large, randomized studies are also necessary to determine the efficacy and safety of the SGC system on BG control.

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Conflicts of interest

There are no conflicts of interest.

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