Original Article

RISK OF POSTOPERATIVE HYPOGLYCEMIA IN CARDIOVASCULAR SURGICAL PATIENTS RECEIVING COMPUTER-BASED VERSUS PAPER-BASED INSULIN THERAPY

Samuel E. Crockett, MD[1]; Jorge Suarez-Cavelier, MD[2]; Kevin D. Accola, MD[2]; Lori A. Hadas, MSN[3]; Darcey L. Harnage, BSN[3]; Paul R. Garrett, MD[1]; Kathy A. Butler, MPH[1]; Zuber D. Mulla, PhD[4]

ABSTRACT

Objective: To evaluate the safety and efficacy of replacing a paper-based protocol with a computer-guided glucose management system (CGMS) for the treatment of postoperative hyperglycemia in the cardiovascular intensive care unit (CVICU).

Methods: With use of a before-and-after analysis, adult patients (≥18 years) discharged from the CVICU and treated with the paper protocol were compared with patients discharged from the CVICU and treated with the CGMS. Of the 1,648 patients analyzed, 991 were in the CGMS group. Clinical end points were evaluated by using the Wilcoxon test. Unadjusted and adjusted hazard ratios (HRs) for each hypoglycemic end point were calculated from Cox models with use of the proportional hazards regression procedure, and clinical end points were adjusted for potential confounders.

Results: Patients treated with the paper protocol were 6 times as likely to experience clinical hypoglycemia (blood glucose ≤70 mg/dL) as patients treated with the CGMS (adjusted HR = 6.06; *P*<.0001) and more than 7 times as likely to experience severe hypoglycemia (blood glucose ≤40 mg/dL) (adjusted HR = 7.59; *P* = .01). Despite the increased risk of hypoglycemia, no significant difference in length of stay or mortality was observed between the groups.

Conclusion: CGMS treatment of postoperative hyperglycemia in CVICU patients can successfully attain goal glucose levels with a significant reduction in hypoglycemia in comparison with a paper protocol. This association persists after controlling for covariates. **(Endocr Pract. 2012; 18:529-537)**

Abbreviations:
BG = blood glucose; **BMI** = body mass index; **CGMS** = computer-guided glucose management system; **CVICU** = cardiovascular intensive care unit; **HRs** = hazard ratios; **LOS** = length of stay; **POC** = point-of-care; **RCTs** = randomized controlled trials

INTRODUCTION

Inpatient hyperglycemia, particularly in patients admitted to an intensive care unit, is associated with increased morbidity and mortality (1-8). Studies in patients who have hyperglycemia with or without diabetes report that increased fasting blood glucose (BG) levels before cardiac surgical procedures, and persistently elevated BG levels during and immediately after such operations, predict increased perioperative morbidity and mortality (1-6). Appropriate treatment of hyperglycemia with avoidance of hypoglycemia is vital to successful patient outcomes (1-4). The optimal glucose goal in the cardiovascular intensive care unit (CVICU) is an area of ongoing investigation. A consistent finding in all outcome studies is the increased incidence of hypoglycemia associated with glucose control (9-13).

Guidelines for managing adult patients undergoing cardiac surgical procedures have been published in the United States by the Society of Thoracic Surgeons (4). These guidelines recommend use of continuous intravenously

Submitted for publication November 1, 2011
Accepted for publication February 22, 2012
From the [1]Adventist Health System, Orlando, Florida, [2]Department of Cardiovascular Surgery, Florida Hospital, Orlando, Florida, [3]Florida Hospital, Orlando, Florida, and [4]Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center, El Paso, Texas.
Address correspondence to Dr. Zuber D. Mulla, Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center at El Paso, 4800 Alberta Avenue, El Paso, TX 79905. E-mail: Zuber.Mulla@ttuhsc.edu.
Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on March 22, 2012. DOI:10.4158/EP11337.OR
To purchase reprints of this article, please visit: www.aace.com/reprints.

administered insulin without specifying an exact protocol or method to attain safe and effective glucose control. Numerous intravenous insulin protocols to control glucose levels after cardiac surgical procedures have been published (3,14,15). For use of these protocols, individual nursing interpretation is required. Use of computer-guided glucose management systems (CGMS) has been described for the postoperative management of hyperglycemia in CVICU patients (16-18). Improved glucose control, less glucose variability, and shorter mean time to target glucose level have been reported with CGMS use in the CVICU (17,18).

Florida Hospital in Orlando, Florida, part of the Adventist Health System, is a 874-bed community teaching hospital with an active cardiovascular program that includes 27 CVICU beds. Intravenously administered insulin has been an integral part of CVICU postoperative treatment of hyperglycemia for more than 25 years. In 2004, Florida Hospital initiated a standardized, intravenous insulin algorithm (a paper protocol) for the treatment of hyperglycemia in the CVICU. This algorithm allowed for individual nursing interpretation and flexibility in its application. In 2008, predicated on published data that CGMS use can result in less hypoglycemia and improved patient outcomes, a CGMS was implemented in the Florida Hospital CVICU. This system was designed to assist the bedside nurse in determining the appropriate intravenously administered dose of insulin and to provide a uniform method of glucose control, thereby removing provider individualization of treatment. This observational study evaluates the safety and efficacy of a CGMS versus a paper protocol in treating patients with hyperglycemia in the CVICU.

PATIENTS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board for the Protection of Human Subjects of the Texas Tech University Health Sciences Center, El Paso, Texas, and the Florida Hospital Institutional Review Board.

This study of 1,648 patients compares outcomes by a before-and-after analysis of 657 patients discharged from the Florida Hospital CVICU between December 1, 2007, and September 14, 2008, and treated with a paper protocol versus 991 patients discharged from the Florida Hospital CVICU between September 15, 2008, and September 30, 2009, and treated with a CGMS. Two primary hypoglycemic end points were evaluated in this study. The literature uses multiple cut points to define hypoglycemia (8-10,18). In this study, hypoglycemia is defined as severe (BG ≤40 mg/dL) and clinical (BG ≤70 mg/dL). These 2 primary end points were evaluated by using various regression techniques: time to first episode of severe hypoglycemia (BG ≤40 mg/dL) and time to first episode of clinical hypoglycemia (BG ≤70 mg/dL). In addition, intravenous administration of corticosteroids, length of stay (LOS) in the CVICU, hospital LOS, and hospital mortality were analyzed. The paper protocol was initiated for BG levels >150 mg/dL, with a treatment goal of 110 to 150 mg/dL.

Blood samples obtained from arterial lines in the acute postoperative setting (<24 hours in the intensive care unit) and by finger-stick method when the patient's condition was stable were measured on a point-of-care (POC) device (Accu-Chek, Roche Diagnostics, Indianapolis, Indiana). The frequency of glucose monitoring was hourly in both study groups unless more frequent measurement was clinically indicated. The paper protocol was initiated as follows: after an initial POC BG level >150 mg/dL, the patient was given a regular insulin intravenous bolus of 0.1 U/kg, and an intravenous insulin infusion was started at a rate of 0.1 U/kg of body weight per hour. Hourly POC BG levels were measured, and the insulin infusion rate was adjusted hourly as follows. If the POC BG level was ≥150 mg/dL, the infusion was increased (current rate × 1.25); if the POC BG value was ≤150 mg/dL and ≥80 mg/dL, the rate was decreased (current rate ÷ 1.25). If, however, the POC BG level was increasing or decreasing by >40 mg/dL per hour, the insulin infusion was adjusted by a factor of 1.5 (current rate × 1.5 or current rate ÷ 1.5). If the BG levels were >150 mg/dL for 3 consecutive hours, despite increasing insulin dosages, the insulin infusion rate was doubled for 1 hour. If the next BG level was still >150 mg/dL, an endocrine consultation was obtained. For BG levels <80 mg/dL, the infusion was discontinued and then resumed when the BG level was again ≥150 mg/dL, with use of an insulin infusion rate that was half the last infusion rate before POC BG was <80 mg/dL (last infusion rate ÷ 2). A columned worksheet was used by the nursing staff to simplify the hourly adjustments. The insulin infusion was continued through the second postoperative day or until the patient was eating.

The implemented CGMS (EndoTool, Hospira, Inc., Lake Forest, Illinois) is a software system that recommends intravenous insulin dosing, including bolus doses, and BG measurement frequency for patients who have BG levels greater than a selected value (>150 mg/dL in our CVICU). It recommends a bolus of 50% glucose in water as appropriate for hypoglycemia. The CGMS requires that goal BG variables be programmed into the system, which in our CVICU was defined as 100 to 150 mg/dL. The frequency of BG measurements is determined by the CGMS software. This software regulates a quadratic insulin dosing relationship up and down on the basis of entered glucose readings from a POC device. It uses engineering control mathematics in which the previous 4 BG levels are considered for regulation of the dosing relationship (18,19).

Both the paper protocol and the CGMS groups received carbohydrate supplementation with 10% glucose in water at 30 mL per hour. Additional carbohydrates were received

from other infusions mixed in 5% glucose in water and, in some cases, enteral or parenteral nutrition.

Adult patients (age ≥18 years) with specific *International Classification of Diseases, Ninth Revision* procedure codes were included in the analysis (Table 1). In a number of patients, values for height were missing, and the body mass index (BMI) could not be calculated. For patients with missing values for BMI, multiple imputations with use of a Markov chain Monte Carlo approach were used to generate plausible BMI values (20,21).

Statistical Analysis

Data were analyzed with use of SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina). Demographic and clinical characteristics were analyzed. BG levels including the average value of the first BG specimen obtained in the CVICU, the average BG value between starting the insulin intervention and ending the insulin intervention, and the average time from starting the insulin intervention to reaching a BG level of 150 mg/dL were examined.

Kaplan-Meier survival curves were generated for the 2 hypoglycemia end points. For each end point, the survival curve for the CGMS group was compared with that for the paper protocol group by using the Wilcoxon test. Unadjusted and adjusted hazard ratios (HRs) for each hypoglycemic end point were calculated from Cox models by using the proportional hazards regression procedure. The assumption of proportional hazards was violated for both time-to-hypoglycemia outcomes for the glucose control strategy variable (the paper protocol versus the CGMS). To account for this violation, we included an interaction term, created by multiplying the glucose control strategy variable by time, in the multivariate Cox models. The small number of severe hypoglycemic events in combination with the use of multiple covariates (listed subsequently) could lead to bias in variable estimation. For reduction of the chance of bias, the Firth penalized maximum likelihood estimation was used when the adjusted HR for severe hypoglycemia was calculated. HRs were reported with 95% confidence intervals and *P* values. Unadjusted and adjusted variable estimates comparing patients managed with the paper protocol versus patients treated with use of the CGMS were calculated for 2 continuous outcomes—LOS in the CVICU and overall hospital LOS—by using linear regression. Unadjusted and adjusted odds ratios comparing patients managed with the paper protocol and those managed with the CGMS were calculated for hospital mortality with use of logistic regression. Odds ratios were reported with 95% confidence intervals and *P* values.

Possible Confounders

We controlled for the following variables: age divided into quartiles (22 to 59 years, 60 to 67.5 years, 67.6 to 76 years, and 77 to 95 years), race, sex, obesity, receipt of intravenously administered corticosteroids during the CVICU stay, and a history of diabetes (yes/no).

RESULTS

Demographic and clinical characteristics of the study population are reported in Table 2. The mean age of the patients in both the paper protocol and CGMS groups was approximately 67 years. The prevalence of diabetes was higher in the group managed with the paper protocol than in the CGMS group (47.6% versus 41.0%, respectively;

Table 1
International Classification of Diseases, Ninth Revision
Procedure Codes Included in the Analysis

Code	Description
36.10 to 36.19	Coronary bypass
36.2	Heart revascularization by arterial implant
35.10 to 35.14	Valvuloplasty without replacement
35.20 to 35.28	Replacement of heart valve
35.00 to 35.04	Valvotomy
35.31 to 35.39	Operations on structures adjacent to heart valves (papillary muscle, chordae tendineae, etc)
35.41	Enlargement of existing atrial septal defect
35.42	Creation of septal defect
35.50 to 35.54	Repair of septal defect with prosthesis
35.60 to 35.63	Repair of septal defect with tissue graft
36.91	Repair of aneurysm of coronary vessel

P = .01). Values for BMI were missing for 394 patients (145 in the paper protocol group and 249 in the CGMS group). These values were ascribed by using multiple imputation. The prevalence of obesity (BMI ≥30 kg/m^2) was similar in the 2 groups.

Target goal glucose ranges differed between the 2 groups, being 110 to 150 mg/dL in the paper protocol group and 100 to 150 mg/dL in the CGMS group. The effect of this difference on the clinical outcome is unknown; however, potentially the lower target BG range of 100 to 150 mg/dL for the CGMS group is a design problem that favors the paper protocol, in that the lower limit of the CGMS target (100 mg/dL, versus 110 mg/dL for the paper protocol) is more likely to predispose to hypoglycemia.

The initial mean BG value in the CVICU was higher in the CGMS group in comparison with the paper protocol group (192.0 mg/dL versus 175.3 mg/dL, respectively; *P*<.0001). The mean CVICU BG value during insulin infusion was 141.1 mg/dL versus 143.5 mg/dL (*P* = .01), respectively, in the paper protocol and CGMS groups. Clinical hypoglycemia (BG ≤70 mg/dL) in the CVICU was significantly more frequent in the paper protocol versus the CGMS group, as was severe hypoglycemia (BG ≤40 mg/dL). Significantly more patients in the CGMS group than in the paper protocol group received intravenously administered corticosteroids: 23.1% versus 17.5%, respectively (*P* = .01) (Table 2).

The patients in the paper protocol group were compared with those in the CGMS group for occurrence of hypoglycemia. The CGMS group of patients had a greater number of days free of severe and clinical hypoglycemia in comparison with those managed by the paper protocol. Kaplan-Meier curves for the cumulative probability of being free of severe and clinical hypoglycemia are shown in Figures 1 and 2. The outcome is time (in days) to the first episode of hypoglycemia while receiving insulin therapy. In Figure 1, the mean time spent free of severe hypoglycemia (BG ≤40 mg/dL) was 7.0 days in patients in the CGMS group and 1.1 days for those in the paper protocol group. The difference in survival curves between the 2 groups was statistically significant (Wilcoxon test; *P* = .003). The results for clinical hypoglycemia (BG ≤70 mg/dL) are displayed in Figure 2. The mean time spent free of clinical hypoglycemia was 5.8 days in patients treated with use of the CGMS and 2.8 days in patients managed with the paper protocol. The difference in survival curves between the 2 groups was statistically significant (Wilcoxon test; *P*<.0001).

Table 2
Patient Demographic and Clinical Characteristics, Stratified by Glucose Control Strategy

Characteristic	Paper protocol	CGMS	*P* value
No. of patients	657	991	
Mean age, y (SD)	66.9 (11.0)	66.8 (11.8)	.79
Sex, no. (%)			.56
Female	230 (35.0)	333 (33.6)	
Male	427 (65.0)	658 (66.4)	
Race or ethnicity, no. (%)			.14
Asian, Pacific Islander, or Native American	8 (1.2)	15 (1.5)	
Black non-Hispanic or black Hispanic	42 (6.4)	54 (5.5)	
White Hispanic	78 (11.9)	139 (14.0)	
White non-Hispanic	456 (69.4)	705 (71.1)	
Other	73 (11.1)	78 (7.9)	
Diabetes, no. (%)	313 (47.6)	406 (41.0)	.01
Obesity			
Mean BMI before CVICU admission,[a] kg/m^2 (SD)	29.3 (6.8)	28.7 (6.3)	.11
Obese (BMI ≥30 kg/m^2),[a] no. (%)	228 (44.5)	303 (40.8)	.19
IV corticosteroids while in CVICU, no. (%)	115 (17.5)	229 (23.1)	.01

Abbreviations: BMI = body mass index; CGMS = computer-guided glucose management system; CVICU = cardiovascular intensive care unit; IV = intravenously administered; SD = standard deviation.
[a] In 394 patients, values for body mass index were missing. These values were imputed by using multiple imputation.

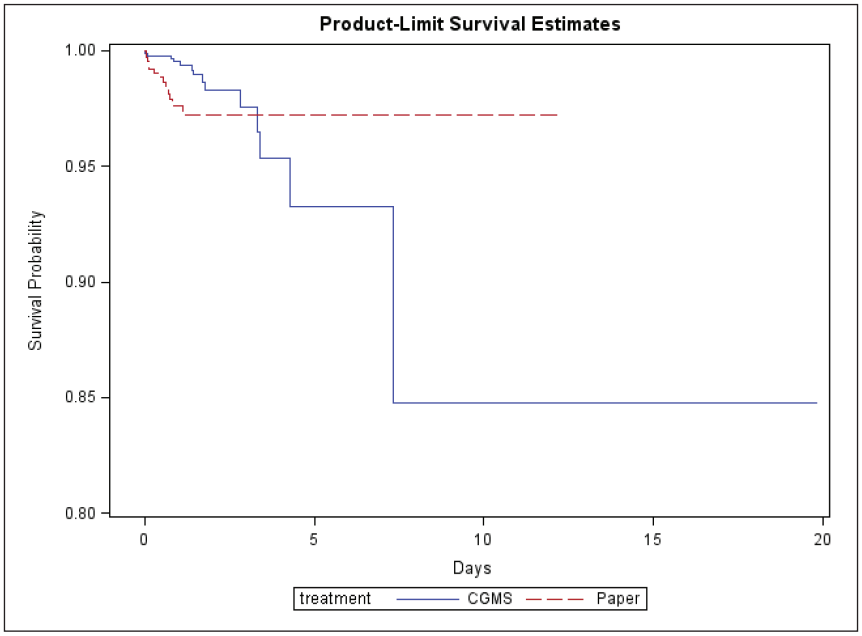

Fig. 1. Comparison of days free of severe hypoglycemia (blood glucose level ≤40 mg/dL) in 2 study groups in a cardiovascular intensive care unit—one managed by a paper protocol (*Paper*) and the other treated with use of a computer-guided glucose management system (*CGMS*) (Wilcoxon test; $P<.003$). The y-axis does not start at 0. See text for further details.

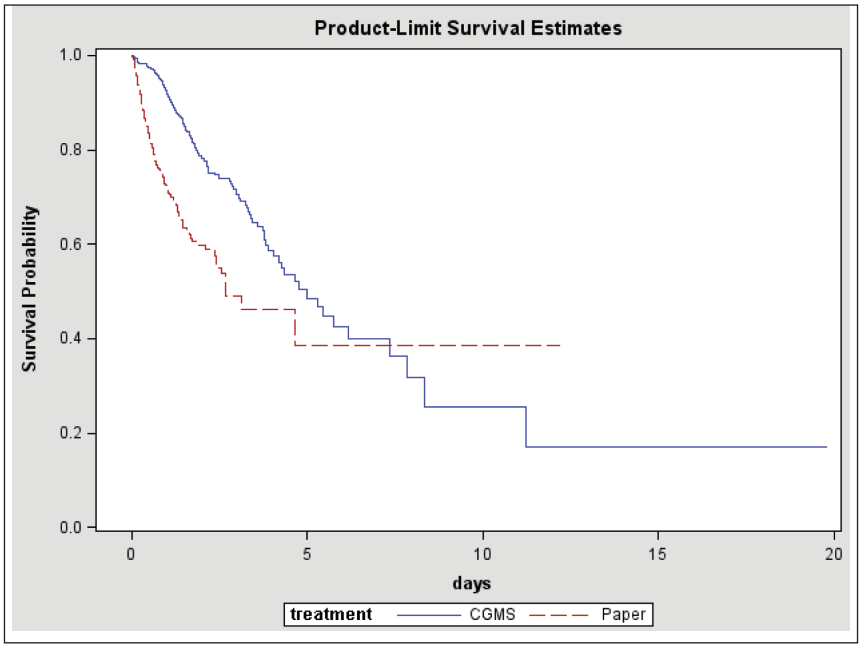

Fig. 2. Comparison of days free of clinical hypoglycemia (blood glucose level ≤70 mg/dL) in 2 study groups in a cardiovascular intensive care unit—one managed by a paper protocol (*Paper*) and the other treated with use of a computer-guided glucose management system (*CGMS*) (Wilcoxon test; $P = .0001$). See text for further details.

The effect of use of the CGMS on LOS in the CVICU and overall hospital LOS was evaluated by using simple and multiple linear regression, and statistically significant associations were not found with either LOS measure (data not shown). The mean CVICU LOS was 4.8 days for the paper protocol group and 5.1 days for the CGMS group ($P = .28$) (Table 3). The mean overall hospital LOS for the corresponding groups was 13.8 days and 14.0 days, respectively ($P = .67$) (Table 3). The unadjusted hospital mortality rate was 3.7% in both groups. No relationship

between glucose control strategy and hospital mortality was detected with use of multiple logistic regression (data not shown).

The unadjusted and adjusted HRs for the outcomes of clinical and severe hypoglycemia are presented in Table 4. Patients treated with the paper protocol were 6 times as likely to experience clinical hypoglycemia as patients treated with the CGMS (adjusted HR = 6.06; *P*<.0001) and more than 7 times as likely to experience severe hypoglycemia (adjusted HR = 7.59; *P* = .01).

DISCUSSION

CVICU management of hyperglycemia is complex and requires a treatment approach that facilitates safe practices and reduces the risk of errors (7,8,10,22). Lability of glucose control after cardiovascular surgical procedures affects patients with and without diabetes (17,23-25). Hyperglycemia is mediated by the release of inflammatory cytokines (such as tumor necrosis factor-α and interleukin-6) and elevated concentrations of catecholamines, growth hormone, glucagon, and glucocorticoids. These factors induce changes in metabolism of fat and carbohydrates that alter peripheral glucose uptake and utilization, increase gluconeogenesis, depress glycogenesis, and induce insulin resistance and glucose intolerance (26,27). Treatment with intravenous infusion of insulin and glucose ameliorates these changes and results in improved carbohydrate and free fatty acid metabolism (28,29). This scenario translates into lowering or normalization of BG levels and reported resultant decreases in sternal wound infections, morbidity, and mortality (1-6,30). The key to glycemic management is normalization of BG levels without occurrence of hypoglycemia. Hypoglycemia can increase morbidity and mortality (22,30-32).

After years of successful use of a nurse-driven paper protocol in the Florida Hospital CVICU, conversion to a CGMS was accomplished easily and safely in a brief time. The CVICU nursing staff is highly trained with extensive clinical experience in treating postoperative cardiovascular patients. At the time of CGMS institution, the nursing staff received intensive on-site education in the application of the CGMS and had additional "as needed" backup from nurses experienced in CGMS use.

Randomized controlled trials (RCTs) comparing the use of CGMS versus manual insulin titration protocols have been reported (33-35). Both RCTs and other studies that used a CGMS, such as the Specialized Relative Insulin and Nutrition Tables (SPRINT) system, the Glucose Regulation for Intensive Care Patients (GRIP) system, and the Glucommander system, have demonstrated improved achievement of target glucose with reduced or no increase

Table 3
Outcomes of Study Patients, Stratified by Glucose Control Strategy

Characteristic	Paper protocol	CGMS	*P* value
No. of patients	657	991	
Glucose variables			
Mean first glucose value in CVICU,[a] mg/dL (SD)	175.3 (45.8)	192.0 (44.3)	<.0001
Mean glucose value during insulin drip in CVICU, mg/dL (SD)	141.1 (18.7)	143.5 (15.7)	.01
Mean hours to target glucose: 150 mg/dL (SD)	3.2 (2.6)	5.0 (3.6)	<.0001
Outcomes			
Severe hypoglycemia (≤40 mg/dL) during insulin infusion in CVICU, no. (%)	13 (2.0)	14 (1.4)	.003[b]
Clinical hypoglycemia (≤70 mg/dL) during insulin infusion in CVICU, no. (%)	204 (31.1)	183 (18.5)	<.0001[b]
Mean LOS in the CVICU, days (SD)	4.8 (5.5)	5.1 (5.7)	.28
Mean LOS in the hospital, days (SD)	13.8 (9.7)	14.0 (10.9)	.67
Hospital mortality, no. (%)	24 (3.7)	37 (3.7)	.93

Abbreviations: CGMS = computer-guided glucose management system; CVICU = cardiovascular intensive care unit; LOS = length of stay; SD = standard deviation.
[a] First glucose value was missing in 6 patients (2 in paper protocol group and 4 in CGMS group).
[b] Wilcoxon *P* values for comparison of the complete paper protocol Kaplan-Meier curve with the complete CGMS Kaplan-Meier curve.

Table 4
Hazard Ratios for Time to Clinical and Severe Hypoglycemia Comparing Patients Managed With Use of a Paper Protocol Versus Patients Treated With Use of a Computer-Guided Glucose Management System in the Cardiovascular Intensive Care Unit Setting

	Unadjusted			Adjusted[a]		
Outcome	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval	*P* value
Clinical hypoglycemia (blood glucose ≤70 mg/dL)	2.63	2.15 to 3.23	<.0001	6.06	4.16 to 8.85	<.0001
Severe hypoglycemia (blood glucose ≤40 mg/dL)	2.28	1.05 to 4.97	.04	7.59	1.62 to 35.60	.01

[a] Adjusted for age in quartiles, race (other, white non-Hispanic, and white Hispanic), sex, obesity (body mass index ≥30 kg/m^2), diabetes, receipt of corticosteroids, and a glucose control strategy (paper protocol versus computer-guided glucose management system) variable by time interaction term. Missing values for body mass index in 394 patients were imputed.

in hypoglycemia (17,35-42). In a review of tight glycemic control (BG levels 80 to 110 mg/dL) with use of a CGMS, 17 peer-reviewed studies on implementation and outcomes were reported. Of the 17 studies, 2 were prospective RCTs studying fewer than 100 patients, 7 were prospective observational or controlled studies, 6 were retrospective analyses, and 2 were observational without mention of the study design (40). Most comparative CGMS studies have been accomplished in a mixed medical-surgical or medical intensive care unit population and have included fewer than 800 patients.

The current observational study presents the clinical application of a particular CGMS (EndoTool) in a large cohort of 991 CVICU patients in comparison with a CVICU cohort managed with use of a paper protocol. The demographics of the studied CGMS and paper protocol groups were similar with the exception of a greater number of patients with diabetes in the paper protocol group and a greater use of corticosteroids in the CGMS group. The effect of these differences on outcomes is unknown. Both cohorts attained essentially similar glucose levels; however, the mean BG value during insulin therapy in the paper protocol group was statistically significantly lower than that in the CGMS group. We found no significant difference in mean LOS in the CVICU, mean overall hospital LOS, or mortality. The CGMS cohort had a higher initial mean BG value and a greater use of corticosteroids, which may have influenced the significant increase in mean hours to achievement of target glucose observed in this group. Use of the CGMS resulted in a greater reduction of mean BG concentrations than did use of the paper protocol, and patients in the CGMS group experienced a longer time free of clinical and severe hypoglycemia than did patients managed with the paper protocol. This association persisted after controlling for covariates.

This study demonstrates that glucose control in the CVICU in conjunction with reduced hypoglycemia is attainable by using a CGMS with programmable glucose control variables in contrast with a paper protocol. The CGMS used in the current study adjusts insulin dosing by mathematical modeling in order to treat the frequently changing BG levels in an individual patient. Trends in BG readings are analyzed and modeled to determine a patient-specific insulin-resistance curve. Adjustments are made in the dosing curves in accordance with predictive mathematical models to prevent episodes of hypoglycemia and hyperglycemia. The ability to analyze past BG readings mathematically to determine slopes and standard deviations from slopes is complex and beyond the training of most nurses and physicians to use at the bedside in the CVICU. The concept of a computer program to model glycemic control is appropriate in light of the complex relationships that prevail when patients are under the stress of acute illness. Although similar to other paper protocols in design and the associated incidence of severe hypoglycemia, our paper protocol was unique to our institution. Generalization of our comparative results to other paper protocols or other CGMS equipment may not be valid.

CONCLUSION

There are limitations to this investigation. This study is a single-center, retrospective analysis and thus subject to limitations inherent in this type of investigation. Although our analysis adjusted for many baseline variables and perioperative characteristics, other unmeasured variables

could affect the association with outcomes and, therefore, confound the results.

Currently, a CGMS is a treatment modality that facilitates attainment of appropriate glucose goals by using advanced mathematics amenable to bedside use and with the potential of a low incidence of hypoglycemia and improved patient safety. More research is needed to determine whether a CGMS can be used in situations in which tighter glucose control without the occurrence hypoglycemia is sought (42,43).

ACKNOWLEDGMENT

We thank Anne Gentry, PharmD, for assistance in manuscript preparation.

DISCLOSURE

Dr. Mulla's employer was compensated for the time he spent analyzing this data set. The other authors have no multiplicity of interest to disclose.

REFERENCES

1. **McAlister FA, Man J, Bistritz L, Amad H, Tandon P.** Diabetes and coronary artery bypass surgery: an examination of perioperative glycemic control and outcomes. *Diabetes Care*. 2003;26:1518-1524.
2. **Gandhi GY, Nuttall GA, Abel MD, et al.** Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med*. 2007;146:233-243.
3. **Furnary AP, Gao G, Grunkemeier GL, et al.** Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:1007-1021.
4. **Lazar HL, McDonnell M, Chipkin SR, et al (Society of Thoracic Surgeons Blood Glucose Guideline Task Force).** The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. *Ann Thorac Surg*. 2009;87:663-669.
5. **O'Brien JE Jr, Marshall JA, Tarrants ML, Stroup RE, Lofland GK.** Intraoperative hyperglycemia and postoperative bacteremia in the pediatric cardiac surgery patient [with discussion]. *Ann Thorac Surg*. 2010;89:578-584.
6. **Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, Koch CG.** Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. *Anesthesiology*. 2010;112:860-871.
7. **Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE.** Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;53:978-982.
8. **Krinsley JS.** Association between hyperglycemia and hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;78:1471-1478.
9. **Van den Berghe G, Wouters P, Weekers F, et al.** Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001; 345:1359-1367.
10. **Van den Berghe G, Wilmer A, Hermans G, et al.** Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449-461.
11. **Finfer S, Chittock DR, Su SY, et al (NICE-SUGAR Study Investigators).** Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009; 360:1283-1297.
12. **Wiener RS, Wiener DC, Larson RJ.** Benefits and risks of tight glucose control in critically ill adults: a meta-analysis [published correction appears in *JAMA*. 2009;301:936]. *JAMA*. 2008;300:933-944.
13. **Arabi YM, Dabbagh OC, Tamim HM, et al**. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med*. 2008;36:3190-3197.
14. **Markovitz LJ, Wiechmann RJ, Harris N, et al.** Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract*. 2002;8:10-18.
15. **Zimmerman CR, Mlynarek ME, Jordan JA, Rajda CA, Horst HM.** An insulin infusion protocol in critically ill cardiothoracic surgery patients. *Ann Pharmacother*. 2004; 38:1123-1129.
16. **Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF.** Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. *J Am Med Inform Assoc*. 2005;12:172-180.
17. **Halpin L, Henry L, Dunning E, et al.** Comparison of blood glucose management strategies to achieve control following cardiac surgery (computerized versus paper). *AACN Adv Crit Care*. 2010;21:146-151.
18. **Saager L, Collins GL, Burnside B, et al.** A randomized study in diabetic patients undergoing cardiac surgery comparing computer-guided glucose management with a standard sliding scale protocol. *J Cardiothorac Vasc Anesth*. 2008;22:377-382.
19. EndoTool Glucose Management System. Hospira, Inc. 2008. http://www.hospira.com/Products/endotool.aspx. Accessed for verification March 8, 2012.
20. **Mulla ZD, Seo B, Kalamegham R, Nuwayhid BS.** Multiple imputation for missing laboratory data: an example from infectious disease epidemiology. *Ann Epidemiol*. 2009;19:908-914.
21. **Yuan Y.** Multiple imputation for missing data: concepts and new development. In: *Proceedings of the Twenty-Fifth Annual SAS Users Group International Conference*. Cary, North Carolina: SAS Institute, Inc, 2000: 1410-1419.
22. **Krinsley JS, Grover A.** Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med*. 2007;35:2262-2267.
23. **Krinsley JS.** Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36:3008-3013.
24. **Egi M, Bellomo R, Stachowski E, French CJ, Hart G.** Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. 2006; 105:244-252.
25. **Dossett LA, Cao H, Mowery NT, Dortch MJ, Morris JM Jr, May AK.** Blood glucose variability is associated with mortality in the surgical intensive care unit. *Am Surg*. 2008;74:679-685.
26. **Dungan KM, Braithwaite SS, Preiser JC.** Stress hyperglycaemia. *Lancet*. 2009;373:1798-1807.

27. **Hirsch IB.** Effect of insulin therapy on nonglycemic variables during acute illness. *Endocr Pract*. 2004;10(suppl 2): 63-70.
28. **Vanhorebeek I, Langouche L, Van den Berghe G.** Intensive insulin therapy in the intensive care unit: update on clinical impact and mechanisms of action. *Endocr Pract*. 2006;12(suppl 3):14-22.
29. **Dandona P, Chaudhuri A, Ghanim H, Mohanty P.** Proinflammatory effects of glucose and anti-inflammatory effect of insulin: relevance to cardiovascular disease. *Am J Cardiol*. 2007;99(4A):15B-26B.
30. **Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A.** Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg*. 1997;63:356-361.
31. **Fischer KF, Lees JA, Newman JH.** Hypoglycemia in hospitalized patients: causes and outcomes. *N Engl J Med*. 1986;315:1245-1250.
32. **Kosiborod M, Inzucchi SE, Goyal A, et al.** Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA*. 2009;301:1556-1564.
33. **Newton CA, Smiley D, Bode BW, et al.** A comparison study of continuous insulin infusion protocols in the medical intensive care unit: computer-guided vs. standard column-based algorithms. *J Hosp Med*. 2010;5:432-437.
34. **Hovorka R, Kremen J, Blaha J, et al.** Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. *J Clin Endocrinol Metab*. 2007;92:2960-2964.
35. **Cavalcanti AB, Silva E, Pereira AJ, et al.** A randomized controlled trial comparing a computer-assisted insulin infusion protocol with a strict and a conventional protocol for glucose control in critically ill patients. *J Crit Care*. 2009;24:371-378.
36. **Dortch MJ, Mowery NT, Ozdas A, et al.** A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *J Parenter Enteral Nutr*. 2008;32:18-27.
37. **Kanji S, Singh A, Tierney M, Meggison H, McIntyre L, Hebert PC.** Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose control in critically ill adults. *Intensive Care Med*. 2004;30:804-810.
38. **Lonergan T, Compte AL, Willacy M, et al.** A pilot study of the SPRINT protocol for tight glycemic control in critically ill patients. *Diabetes Technol Ther*. 2006;8:449-462.
39. **Boord JB, Sharifi M, Greevy RA, et al.** Computer-based insulin infusion protocol improves glycemia control over manual protocol. *J Am Med Inform Assoc*. 2007;14:278-287.
40. **Eslami S, Abu-Hanna A, de Jonge E, de Keizer NF.** Tight glycemic control and computerized decision-support systems: a systematic review. *Intensive Care Med*. 2009;35:1505-1517.
41. **Juneja R, Roudebush C, Kumar N, et al.** Utilization of a computerized intravenous insulin infusion program to control blood glucose in the intensive care unit. *Diabetes Technol Ther*. 2007;9:232-240.
42. **Finfer S, Delaney A.** Tight glycemic control in critically ill adults. *JAMA*. 2008;300:963-965.
43. **Klonoff DC.** Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care*. 2005;28: 1231-1239.