Published in final edited form as:

Hosp Pract (1995). 2012 April ; 40(2): 22–30. doi:10.3810/hp.2012.04.966.

Diabetes and Stress Hyperglycemia in the Intensive Care Unit: Outcomes After Cardiac Surgery

Roma Y. Gianchandani, MD¹ [Assistant Professor], Nazanene H. Esfandiari, MD¹ [Assistant Professor], Jonathan W. Haft, MD² [Assistant Professor], Richard L. Prager, MD³ [Professor], and Rodica Pop-Busui, MD, PhD⁴ [Associate Professor]

¹Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI

²Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI

³Department of Cardiac Surgery, University of Michigan, Ann Arbor, MI

⁴Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, MI

Abstract

Background—Hyperglycemia is common in the post–cardiac surgery population and has been associated with increased mortality, surgical length of stay, and infection rates. Although hospitalized patients with diabetes are known to have more complications, recent studies in various hospital settings have reported worse outcomes in patients with stress hyperglycemia than in those with diabetes.

Aim—The primary objective of this study was to analyze 30- and 90-day mortality rates in post–cardiac surgery patients with stress hyperglycemia and diabetes who were managed to achieve similar moderate blood glucose goals using the University of Michigan Hospital (Ann Arbor, MI) insulin protocol between 2005 and 2008. The secondary outcomes were rates of postoperative complications, including hypoglycemia.

Methods—A standardized glucose management program was followed to treat all patients in the cardiac intensive care unit, with a blood glucose goal of 100 to 140 mg/dL. Data from 1973 patients with either diabetes or stress hyperglycemia were analyzed to identify associations between mean postoperative blood glucose levels and mortality, incidence of hypoglycemia, and complication rates.

Results—Mortality rates did not differ between patients with diabetes and stress hyperglycemia (3.4 and 2.3%; $P = 0.2$). Rates of severe hypoglycemia were low (1%) for both groups and were

Correspondence: Roma Y. Gianchandani, MD, Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48109. Tel: 734-647-5400, Fax: 734-936-9240, romag@umich.edu.

Conflict of Interest Statement

Roma Y. Gianchandani, MD, Nazanene H. Esfandiari, MD, Jonathan W. Haft, MD, Richard L. Prager, MD, and Rodica Pop-Busui, MD, PhD disclose no conflicts of interest.

not associated with an increase in mortality ($P=0.95$). Other complication rates were similar between patients with diabetes and stress hyperglycemia.

Conclusion—Maintaining a blood glucose range between 100 to 140 mg/dL in post-cardiac surgery patients was associated with a low mortality rate, low risk of hypoglycemia, and with complications rates that were similar in patients with diabetes and stress hyperglycemia.

Keywords

moderate glucose control; cardiac surgery hypoglycemia; stress hyperglycemia; diabetes; outcomes

Introduction

Hyperglycemia is common in the post-cardiac surgery population and has been associated with increased mortality, surgical length of stay (LOS), and infection rates, especially deep sternal wound infections (DSWIs).^{1–7} Stress associated with cardiac surgery causes blood glucose (BG) level elevations in patients with and without diabetes.⁸ Several observational intensive care unit (ICU) studies of these patients have reported higher rates of complications and mortality in patients with diabetes after cardiac surgery.⁹ Conversely, recent work on hospitalized patients with hyperglycemia raises the concern that patients with stress hyperglycemia (SH) have worse outcomes.^{10–12}

In 2002, Umpierrez et al¹⁰ reported that patients with newly diagnosed hyperglycemia have worse ICU and hospital outcomes than those with known diabetes. This finding has been reproduced in several other observational studies of mixed ICU populations,^{12,13} studies on post-acute myocardial infarction patients,¹⁴ and those on total parenteral nutrition administration.¹⁵ Additionally, several prospective studies have shown patients with SH to have improved morbidity and mortality, as well as better BG control.^{16,17} These studies suggest that elevated BG levels affect patients with both diabetes and SH, and that appropriate treatment may improve outcomes.

Blood glucose management goals in the ICU are currently evolving as large prospective trials update their results. Improvements in DSWI and mortality rates in patients with diabetes by lowering BG targets to < 200 mg/dL were first described by the Portland group.¹ An initial large trial¹⁶ in surgical ICU patients reported a significantly lower rate of morbidity and mortality by targeting euglycemia (BG, 80–110 mg/dL) compared with standard care. Several other multicenter trials that followed^{18–20} could not reproduce this finding and had worse mortality outcomes with tight BG control. Results of the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial¹⁹ led to a modification of BG targets in the ICU to 140 to 180 mg/dL.^{21–23} Lower ICU targets (110–140 mg/dL) were recommended by the American Diabetes Association²¹ if they could be safely achieved and in cardiac surgery patients who required > 3 days of ICU care (< 150 mg/dL).²³

Although these studies have addressed tight (ie, 80–100 mg/dL)¹⁶ and usual (ie, 140–180 mg/dL)¹⁹ BG ranges, data are still inadequate on safety and outcomes of targeting BG levels

in the moderate range (100–140 mg/dL) for patients with SH and diabetes separately.²⁴ Therefore, the objective of this study was to analyze and compare mortality and complication rates of cardiac surgery patients with either SH or diabetes managed to achieve similar moderate BG goals at the University of Michigan Hospital (Ann Arbor, MI). The incidence of hypoglycemia and its implications on the outcomes in this population were also assessed.

Methods

This is an observational study of 1973 patients who underwent cardiac surgery from 2005 to 2008, and were also followed by the Hospital Intensive Insulin Program (HIIP). A standardized institutional insulin infusion protocol was strictly implemented in the cardiothoracic ICU in late 2004, targeting a BG goal of 100 to 140 mg/dL. This protocol, derived partially from the Portland protocol,¹ was developed prior to initial inpatient recommendations from the American Diabetes Association and American Association of Clinical Endocrinologists,^{2,25} and was validated within this institution. Although at the program's initiation this BG goal was chosen as a prudent and safe starting point, it was later determined not to lower BG targets, as data on higher incidence of hypoglycemia with tighter BG goals began to emerge.^{18,26,27} This resulted in maintaining uniform BG ranges in all post-cardiac surgery patients at this level for several years.

Education on BG control, protocol nuances, as well as an insulin titration algorithm were provided to all health care providers in the cardiovascular ICU, including physicians, nurses, mid-level providers, medical assistants, and pharmacists. The use of the protocol (Appendix A) was mandated in the ICU. The HIIP provided oversight to ICU BG management by following all patients with diabetes and those with SH who were required to continue the insulin infusion for > 2 postoperative days. After admission to the ICU, BG surveillance was by point-of-care testing using ACCU-CHEK[®] monitors (Roche Diagnostics). Insulin infusions were initiated and typically continued for 3 days. Transition to subcutaneous insulin followed a basal-bolus algorithm initiated before discontinuing the insulin infusion.²⁸ Briefly, basal insulin was provided with either neutral protamine Hagedorn insulin for patients with SH, as previously described,²⁹ or glargine insulin for patients with diabetes. Insulin aspart was used as bolus insulin for meals and correction in both groups.

Patient Population

Patients who underwent cardiac surgery (eg, coronary artery bypass graft surgery, valve replacement, aortic root procedures, left ventricular assist device procedures, or a combination of these) at this institution were included in the analysis. Those who underwent initial surgeries at outside hospitals and were transferred for complication management were excluded.

BG Testing

Hourly BG tests were performed using hospital point-of-care ACCU-CHEK[®] monitors. Insulin infusion rates were titrated hourly until patients reached a stable BG level of 100 to 140 mg/dL for 3 successive hours, when titration frequency was reduced to every 2 hours.

Blood glucose samples were initially obtained through arterial catheters for the first 26 to 30 hours, and after loss of arterial access, capillary BG samples were obtained.

Data Extraction

Data were obtained by chart review and data mining of the hospital electronic medical record database from 2005 to 2008. Patients with diabetes were identified as those with known history of type 1 or type 2 diabetes and/or treated with oral medications and/or insulin at the time of surgery. Stress hyperglycemia was defined by absence of history of diabetes or hypoglycemic medication use, but with 2 consecutive postoperative BG levels 140 mg/dL 1 hour apart, or 1 BG level ≥ 200 mg/dL.²² We collected both point-of-care and laboratory BG levels from day of surgery until postoperative day 2. Blood glucose level variability during the insulin infusion was represented by the standard deviation over that day.

Outcome Measures and Definitions

The primary outcome measure of this study was 30- and 90-day postoperative mortality. Secondary outcome measures were the incidence of complications (eg, DSWI, postoperative atrial fibrillation, acute requirement of dialysis, cerebrovascular disease, or bacteremia or other infections) and the incidence of hypoglycemia in patients with diabetes and SH.

Mortality included both death during hospitalization and that occurring after discharge from the hospital within 30 and 90 days of the procedure. Deep sternal wound infections were defined according to the Centers for Disease Control and Prevention definition³⁰ and collected by the Department of Infection Control & Epidemiology. This was expansive, and all infections beyond wound drainage were captured, including all incisional and organ-space infections (ie, mediastinitis). Atrial fibrillation was defined as new-onset atrial fibrillation requiring treatment. Postoperative bacteremia with positive blood culture results was identified as bacteremia. Other infections, such as cellulitis, urinary tract infections, and cholecystitis, were collected by chart review of the discharge summary. Hypoglycemia was defined as a BG level ≤ 60 mg/dL and severe hypoglycemia as a BG level ≤ 40 mg/dL. Surgical LOS was calculated by subtracting the date of surgery from the date of discharge.

Statistical Analysis

The study was approved by the University of Michigan Institutional Review Board. Baseline characteristics were compared between the diabetes and SH groups using t tests for continuous variables and Fisher's exact test or a chi-square test for categorical variables. Because surgical LOS was not normally distributed, it was transformed to the square root of each observation prior to analysis. Patients with left ventricular assist devices have prolonged hospitalizations, and this group was excluded from the surgical LOS analysis. Multivariate analysis was performed to explore the association between statistically significant outcomes and the covariates of interest. The variables considered to be potential confounders from the univariate analysis were included in multiple regression models and then removed individually to examine the change in estimate of the exposure. Variables that changed the estimate by $> 10\%$ were retained and a final model was built. A *P* value of

0.05 was considered statistically significant. The statistical analysis was performed using both SPSS, version 17 and SAS, version 9.1 software.

Results

Demographic

Valid data were obtained from 1973 patients who underwent cardiac surgery and were included in this analysis. Of these, 33% (n = 648) had a preexisting diagnosis of diabetes (type 1 or type 2) and 67% (n = 1325) had SH. Table 1 compares the demographic characteristics, types of surgery, and glycemic profiles of these groups. Patients with diabetes were significantly older (63.2 ± 10.6 vs 61.2 ± 14.1 years; $P < 0.0001$), had greater body mass indices (29.2 ± 6.51 vs 26.4 ± 5.9 kg/m²; $P < 0.001$), and had more cardiovascular risk factors, such as smoking and hypertension. Thirty-seven percent of patients with diabetes were treated with subcutaneous insulin preoperatively and 67% were on oral hypoglycemic agents. Different types of surgical procedures predominated in the 2 groups; coronary artery bypass graft surgery was the most common procedure among patients with diabetes (54%) and aortic root procedures or valve replacements were most common in patients with SH (64%).

Mortality Outcomes

Mortality rates within the first 30 days after surgery were similar between the 2 groups (3.4% for patients with diabetes and 2.3% for patients with SH; $P = 0.2$), as were mortality rates at 90 days (4.6% for patients with diabetes and 3.5% for patients with SH; $P = 0.3$). Mortality was not statistically significant in patients who experienced severe hypoglycemia compared with patients without hypoglycemia ($P = 0.41$ and $P = 0.32$, respectively). There were no deaths in patients with diabetes or SH who experienced severe hypoglycemia (Table 2).

BG Profiles

Blood glucose levels achieved are shown in Table 1 and Figure 1. Mean BG levels on the day of surgery through postoperative day 2 were significantly higher in the diabetes compared with the SH group ($P < 0.0001$ for all days), as was the variability represented here by the standard deviation (Table 1). Approximately 60% and 80% of BG levels fell between the target of 100 to 140 mg/dL in the diabetes and SH groups, respectively (Figure 1), and 90% of BG levels were between 100 to 180 mg/dL in both groups. There was a very low rate (1%) of severe hypoglycemia (BG level < 40 mg/dL). The overall rate of BG level < 60 mg/dL was significantly higher in the diabetes group (16%, with mean BG level of 50.7 mg/dL) compared with the SH group (9%, with mean BG level of 49.7 mg/dL; $P < 0.0001$).

Postoperative Complications

Rates of DSWI were higher in patients with diabetes compared with those with SH in unadjusted analysis and after adjusting for type of surgery, (3.4% vs 1.6%; $P = 0.01$; Table 3). However, on multivariate analysis, presence of diabetes was no longer a significant factor in those with diabetes (Table 4). Body mass index and a high mean BG level, especially on postoperative day 2, were positively associated with DSWIs. Mean BG levels in patients

with DSWIs were not statistically significant when compared with those of patients without DSWIs (Table 5). Patients with SH had a higher rate of new-onset atrial fibrillation compared with those with diabetes (24.5% vs 19.9%; $P = 0.02$). There were no statistically significant differences in other postoperative complications, including bacteremia, acute renal failure requiring dialysis, cerebrovascular accidents, and other infections (Table 3).

Surgical LOS

Patients with diabetes had a longer mean surgical LOS than patients with SH (10.5 days vs 8.8 days; $P < 0.002$). However, after multivariate analysis, the difference in mean surgical LOS was no longer significant.

Discussion

In this study evaluating post-cardiac surgery patients, we demonstrate that using a standardized insulin protocol and targeting a moderate BG range of 100 to 140 mg/dL was associated with a low risk of hypoglycemia and low mortality rates in both diabetes and SH populations. Additionally, mortality and complication rates were not statistically different between the 2 groups. This was despite the patients in the diabetes group being older, as well as having higher body mass indices and postoperative BG levels. Therefore, a BG goal of 100 to 140 mg/dL using insulin titration via the University of Michigan Hospital protocol was a reasonable and safe approach for hyperglycemia management in both groups.

The results of this study are similar to those of Finney et al,³¹ who studied a mixed ICU population with and without diabetes, and whose cardiac surgery subset was also heterogeneous. The largest proportion of that study's survivor group had BG levels between 111 to 144 mg/dL, and accrued mortality benefits with a BG range of < 144 to 200 mg/dL (estimated upper limit of BG level at 145 mg/dL), similar to the BG goals used in our study. In 2 other studies^{32,33} of mixed ICU populations, the survivor groups had BG levels < 145 mg/dL; however, in contrast to our study, their SH group had a higher mortality rate than the diabetes group for similar BG targets. Several other observational retrospective studies^{10–12} have now shown that for any level of hyperglycemia, mortality rates are increased in SH groups. The mortality differences between the SH and diabetes groups could be secondary to the mixed nature of the ICU populations. Additionally, fewer patients with diabetes (only 20%–30%) spent their time in the < 145 mg/dL BG range, unlike our study, in which > 50% of the BG levels of patients with diabetes were within target range. Although the ratio of survivors to nonsurvivors in the 111 to 144 mg/dL range did not attain statistical significance, survival rate was still highest in this range.³²

The mortality rates and other complications in this study are similar to those reported in previous studies.^{9,31} Prior to the glucose management era, Herlitz et al³⁴ reported that postoperative complications, especially cardiac death and stroke, were increased in patients with diabetes up to 5 years after coronary artery bypass graft surgery. Schmeltz et al⁹ reported an overall higher mortality rate in patients with diabetes compared with those without diabetes (7.3% vs 3.3%, respectively) who were managed with tight BG control (BG level, 80–110 mg/dL) after cardiac surgery. They attributed these differences to preexisting renal failure, nonelective surgery, and female sex.⁹ Our approach of controlling BG levels to

a moderate range, as described, appears to “bridge the diabetes disadvantage gap,”¹ and equalize outcomes between the SH and diabetes groups. Our surgical LOS trended downward, especially with single-procedure surgeries, such as aortic root procedures, valve replacement, and coronary artery bypass graft surgery only. Surgical LOS had several other confounding factors. The valve replacements included younger patients with mitral and tricuspid valve repairs, and the aortic group, which included patients who had higher risks due to comorbidities. These contribute to the variable surgical LOS in our cohort.

The rates of DSWI were higher for patients with diabetes in unadjusted analysis, but the difference was no longer significant in multivariate analysis. The influence of several other factors must be considered for complication rates in patients with diabetes, although conclusive data on their effect are not yet available. Some of these include preoperative BG levels,^{35,36} glucose variability,³⁷ and post-ICU and post-discharge BG levels. A higher rate of atrial fibrillation noted in the patients with SH can be explained by the higher proportion of valve replacements performed in this group. Valvular abnormalities are associated with cardiac hypertrophy and left atrial dilation, which may lead to electrical excitability and arrhythmias.

Another important finding in this study is the low level of severe hypoglycemia (BG level 40 mg/dL) seen in the immediate postoperative period. Hypoglycemia in this population was not associated with increased mortality. Unlike the intensive or control arm of several recent large, prospective, multicenter trials in mixed ICU populations with higher hypoglycemia and mortality rates,^{18–20,24} our study data are strictly postoperative. This could suggest that hypoglycemia early in the postoperative period may not have the same clinical implication as that in the medical ICU. Stress hormones are maximally elevated after surgery and a further increase with hypoglycemia may have minimal effect on outcomes. Also, postoperative patients are not metabolically compromised for prolonged periods of time and maintain their responses to hypoglycemia.^{38,39} This could be part of the explanation for differences in rates of both hypoglycemia and mortality in the 2 Leuven studies.^{16,40} Several studies have evaluated the prevalence of hypoglycemia and mortality in different ICU populations.^{41–44} As in this study, Stamou et al⁴² found no independent association between hypoglycemia and mortality. This is unlike several studies of mixed ICU populations in which hypoglycemia and mortality were found to have some association.^{32,43,44} Analyzing an early ICU stay period similar to ours, an Australian study found high mortality rates with both hypo- and hyperglycemia.¹³ In this large Australian cohort, 24 ICUs were included, and therefore standardization of insulin protocols or ICU care was less likely. They also documented patients' mean admission-day BG levels, which usually has the largest excursion and an initial lag time before BG targets are reached.⁴⁵

Although recent studies have published moderate BG goals^{46,47} in the cardiac surgery population, this is the first study to evaluate SH and diabetes groups separately in this BG range. Other strengths of this study are that its large sample size is a well-characterized cohort, and that a standardized approach for managing BG levels was used. Like the study by Finney et al,³¹ various types of cardiac surgeries with different demographic characteristics were evaluated, and therefore a heterogeneous population was available for

analysis. In addition, BG data targeted to moderate BG goals over several years were available for analysis.

The study's limitations include issues related to conducting a retrospective review at a single medical center. The clinical data sets were created partly by chart review and partly by electronic data extraction. Before the HIIP was implemented, data on BG levels, diabetes history, and SH were not consistently gathered, and therefore a pre- and postintervention comparison was not possible. Information on disease severity and nutrition were not collected and thus could not be assessed. Because glycated hemoglobin levels were checked in only patients with diabetes, some patients assigned to the SH group may have had undiagnosed type 2 diabetes and therefore would have been misclassified. Finally, treatment improvements and initiatives would affect outcomes positively, while infection outbreaks would have a negative effect. These effects cannot be fully accounted for in an observational review.

Conclusion

Using a standardized institutional protocol and targeting a moderate BG range in early post-cardiac surgery patients maintained BG levels within target range for the SH and diabetes groups. Mortality and complication rates were low and hypoglycemia was not associated with mortality in either group. These data suggest that patients in different hospital populations (eg, surgical, medical, non-ICU) may need to be managed to achieve different BG goals, and provides basis for future randomized control trials.

Acknowledgments

Special thanks to Mary Fisher, MPH and Preethi Patil, MPH for setting up the database and statistical analysis, and to Tina Zrull, PAC and Lynda Mitgutsch, PAC for their work with the program and data collection. We would like to thank the cardiac surgery, critical care, and HIIP faculty, and physician assistants, nurses, and fellows who made this program possible. The HIIP was funded by the University of Michigan Clinical Innovations Fund. Rodica Pop-Busui, MD, PhD is funded by 1R01HL102334-01. This work utilized the Biostatistics and Economic Modeling core of the Michigan Diabetes Research and Training Center, funded by grant DK020572 from the National Institute of Diabetes and Digestive and Kidney Diseases. Some of these data were presented as a poster at the American Diabetes Association Scientific Sessions in June 2009 in Washington, DC.

Appendix A. Adult Insulin Infusion Protocol

(Not for use in patients with diabetic ketoacidosis or obstetric patients.) Indicate blood glucose goal: 100–140 mg/dL.

Patients with type 1 diabetes should always have basal insulin.

Always use clinical judgment when a situation does not fit the protocol.

Table 1

Regular Insulin Infusion Initiation

BG Level, mg/dL	Bolus Regular Insulin,	Initial Insulin Infusion	1) Recheck BG level every h when starting infusion and when changing vasopressors, steroids, TPN, PPN, enteral nutrition, or if patient receives NPO status.
-----------------	------------------------	--------------------------	--

	units/kg, IV Push	Rate, units/mL	
100–140	0	1	If BG level is 100–140 mg/dL for $\times 3$ consecutive h and is changing < 40 mg/dL per h, reduce BG level checks to every 2 h. 2) Monitor potassium levels per physician's order. 3) If patient begins to eat, start subcutaneous meal insulin in addition to infusion per Table 3. Obtain an order to advance to ADA diet. 4) No IV insulin boluses in patients with renal failure.
141–180	2	2	
181–220	3	2.5	
221–260	4	3	
261–300	6	3.5	
> 300	8	4.5	

Abbreviations: ADA, American Diabetes Association; BG, blood glucose; IV, intravenous; NPO, nothing by mouth; PPN, peripheral parenteral nutrition; TPN, total parenteral nutrition.

Table 2

Regular Insulin Infusion Titration

BG level, mg/dL	Insulin infusion (units per h)—regular insulin at concentration of 1 unit/dL
< 70	Hold infusion, administer 25 mL of 50% dextrose IV (1/2 vial). Recheck BG level in 15 min until BG level is > 70 mg/dL, then check every h.
70–79	Hold infusion. Recheck BG level every h $\times 2$, every 2 h $\times 2$, then every 4 h.
80–99	Decrease infusion rate by 50% of last rate. Recheck BG level in 1 h.
If infusion is held and BG level is > 120 mg/dL (ICU)/140 mg/dL (general care floor) on follow-up monitoring, restart infusion rate at 50% of last rate.	
100–140	No change. Unless BG level is reduced by > 20 mg/dL, decrease infusion rate by 50%. Recheck BG level every h. When BG level is 100–140 mg/dL for $\times 3$ consecutive h and is changing < 40 mg/dL per h, reduce BG level checks to every 2 h.
141–170	Increase infusion rate by 0.5 unit/h unless BG level is reduced by > 50 mg/dL since last check, then decrease infusion rate by 1 unit/h. Recheck BG level in 1 h.
171–200	Increase infusion rate by 1 unit/h unless BG level is reduced by > 50 mg/dL since last check, then decrease infusion rate by 1 unit/h. Recheck BG level in 1 h.
201–240	Increase infusion rate by 1 unit/h unless BG level is reduced by > 50 mg/dL since last check, then decrease infusion rate by 1 unit/h. Recheck BG level in 1 h.
241–280	Increase infusion rate by 2 units/h unless BG level is reduced by > 50 mg/dL since last check, then decrease infusion rate by 1 unit/h. Recheck BG level in 1 h.
281–320	Increase infusion rate by 2.5 units/h unless BG level is reduced by > 50 mg/dL since last check, then decrease infusion rate by 1 unit/h. Recheck BG level in 1 h.
321–360	Bolus 4 units regular insulin IV; increase infusion rate by 3 units/h. Recheck BG level in 1 h.
> 360	Bolus 5 units regular insulin IV; increase infusion rate by 4 units/h. Recheck BG level in 1 h.

Abbreviations: BG, blood glucose; ICU, intensive care unit; IV, intravenous.

Table 3

Additional Subcutaneous NovoLog[®] (Novo Nordisk)/Humalog[®] (Eli Lilly and Co) Meal and Snack Coverage (in addition to insulin infusion). NovoLog[®] Administered < 15 min Before or Just After Patient Finishes Eating Meal.

Infusion Rate, units/h	Ate $> 50\%$ Meal, units	Ate $< 50\%$ of Meal, units	Custom Order
0–0.5	2	0	
0.6–2	4	2	
2.1–4	6	3	
4.1–6	8	4	

Infusion Rate, units/h	Ate > 50% Meal, units	Ate < 50% of Meal, units	Custom Order
6.1–8	10	5	
> 8	12	6	

References

1. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg.* 1999; 67(2):352–360. discussion 360–352. [PubMed: 10197653]
2. Garber AJ, Moghissi ES, Bransome ED Jr, et al. American College of Endocrinology Task Force on Inpatient Diabetes Metabolic Control. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract.* 2004; 10(suppl 2):4–9. [PubMed: 15251633]
3. Brown JR, Edwards FH, O'Connor GT, Ross CS, Furnary AP. The diabetic disadvantage: historical outcomes measures in diabetic patients undergoing cardiac surgery—the pre-intravenous insulin era. *Semin Thorac Cardiovasc Surg.* 2006; 18(4):281–288. [PubMed: 17395023]
4. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc.* 2003; 78(12):1471–1478. [PubMed: 14661676]
5. 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(2):356–361. [PubMed: 9033300]
6. Herlitz J, Bang A, Karlson BW. Mortality, place and mode of death and reinfarction during a period of 5 years after acute myocardial infarction in diabetic and non-diabetic patients. *Cardiology.* 1996; 87(5):423–428. [PubMed: 8894264]
7. Herlitz J, Brandrup-Wognsen G, Haglid M, et al. Mortality and morbidity during a period of 2 years after coronary artery bypass surgery in patients with and without a history of hypertension. *J Hypertens.* 1996; 14(3):309–314. [PubMed: 8723983]
8. Doenst T, Wijeyesundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg.* 2005; 130(4):1144. [PubMed: 16214532]
9. Schmeltz LR, DeSantis AJ, Thiagarajan V, et al. Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. *Diabetes Care.* 2007; 30(4):823–828. [PubMed: 17229943]
10. 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; 87(3):978–982. [PubMed: 11889147]
11. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med.* 2009; 37(12):3001–3009. [PubMed: 19661802]
12. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Semin Thorac Cardiovasc Surg.* 2006; 18(4):317–325. [PubMed: 17395028]
13. Bagshaw SM, Egi M, George C, Bellomo R. Australia New Zealand Intensive Care Society Database Management Committee. Early blood glucose control and mortality in critically ill patients in Australia. *Crit Care Med.* 2009; 37(2):463–470. [PubMed: 19114915]
14. Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation.* 2005; 111(23):3078–3086. [PubMed: 15939812]
15. Cheung NW, Napier B, Zaccaria C, Fletcher JP. Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. *Diabetes Care.* 2005; 28(10):2367–2371. [PubMed: 16186264]

16. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001; 345(19):1359–1367. [PubMed: 11794168]
17. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*. 2004; 79(8):992–1000. [PubMed: 15301325]
18. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009; 35(10):1738–1748. [PubMed: 19636533]
19. Finfer S, Heritier S. NICE Study Management Committee and SUGAR Study Executive Committee. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: statistical analysis plan. *Crit Care Resusc*. 2009; 11(1):46–57. [PubMed: 19281445]
20. Brunkhorst FM, Engel C, Bloos F, et al. German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008; 358(2):125–139. [PubMed: 18184958]
21. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011; 34(suppl 1):S11–S61. [PubMed: 21193625]
22. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet*. 2009; 373(9677):1798–1807. [PubMed: 19465235]
23. 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(2):663–669. [PubMed: 19161815]
24. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009; 180(8):821–827. [PubMed: 19318387]
25. Clement S, Braithwaite SS, Magee MF, et al. American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004; 27(2):553–591. [PubMed: 14747243]
26. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med*. 2007; 35(10):2262–2267. [PubMed: 17717490]
27. 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(13):1283–1297. [PubMed: 19318384]
28. Schmeltz LR, DeSantis AJ, Schmidt K, et al. Conversion of intravenous insulin infusions to subcutaneously administered insulin glargine in patients with hyperglycemia. *Endocr Pract*. 2006; 12(6):641–650. [PubMed: 17229660]
29. Gianchandani, RY.; Mitgutsch, L. Bridging dose of insulin to transition from intravenous to subcutaneous therapy.. Presented at: 66th Annual Scientific Sessions of the American Diabetes Association; Washington, DC. June 9–13, 2006; Abstract 2055-PO
30. Centers for Disease Control and Prevention. [May 17, 2011] Surgical site infection (SSI) event.. Procedure-associated events. <http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSICurrent.pdf>.
31. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003; 290(15):2041–2047. [PubMed: 14559958]
32. Rady MY, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc*. 2005; 80(12):1558–1567. [PubMed: 16342648]
33. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med*. 2008; 36(8):2249–2255. [PubMed: 18664780]
34. Herlitz J, Wognsen GB, Karlson BW, et al. Mortality, mode of death and risk indicators for death during 5 years after coronary artery bypass grafting among patients with and without a history of diabetes mellitus. *Coron Artery Dis*. 2000; 11(4):339–346. [PubMed: 10860177]
35. Alserius T, Anderson RE, Hammar N, Nordqvist T, Ivert T. Elevated glycosylated haemoglobin (HbA1c) is a risk marker in coronary artery bypass surgery. *Scand Cardiovasc J*. 2008; 42(6):392–398. [PubMed: 18609043]

36. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schricker T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. *J Clin Endocrinol Metab.* 2010; 95(9):4338–4344. [PubMed: 20631016]
37. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med.* 2008; 36(11):3008–3013. [PubMed: 18824908]
38. Cerra FB, Siegel JH, Border JR, Peters DM, McMenamy RR. Correlations between metabolic and cardiopulmonary measurements in patients after trauma, general surgery, and sepsis. *J Trauma.* 1979; 19(8):621–629. [PubMed: 469974]
39. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med.* 1995; 98(1):75–84. [PubMed: 7825623]
40. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006; 354(5):449–461. [PubMed: 16452557]
41. Hermanides J, Bosman RJ, Vriesendorp TM, et al. Hypoglycemia is associated with intensive care unit mortality. *Crit Care Med.* 2010; 38(6):1430–1434. [PubMed: 20386307]
42. Stamou SC, Nussbaum M, Carew JD, et al. Hypoglycemia with intensive insulin therapy after cardiac surgery: predisposing factors and association with mortality. *J Thorac Cardiovasc Surg.* 2011; 142(1):166–173. [PubMed: 21397274]
43. Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc.* 2010; 85(3):217–224. [PubMed: 20176928]
44. 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(15):1556–1564. [PubMed: 19366775]
45. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. *Circulation.* 2008; 117(8):1018–1027. [PubMed: 18268145]
46. Lazar HL, McDonnell MM, Chipkin S, Fitzgerald C, Bliss C, Cabral H. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. *Ann Surg.* 2011; 254(3):458–463. discussion 463–464. [PubMed: 21865944]
47. Leibowitz G, Raizman E, Brezis M, Glaser B, Raz I, Shapira O. Effects of moderate intensity glycemic control after cardiac surgery. *Ann Thorac Surg.* 2010; 90(6):1825–1832. [PubMed: 21095319]

Abbreviations: BG, blood glucose; DOD, day of discharge; DOS, day of surgery; POD 1, postoperative day 1; POD 2, postoperative day 2.

Figure 1.

The number of patients with diabetes and stress hyperglycemia who had a BG level ranging between 100–180 mg/dL are shown by bars. Superimposed on the bars are percentages of patients with BG levels within the 100–140 mg/dL range for diabetes (triangle) and stress hyperglycemia (x).

Table 1**Patient Demographics: Diabetes Versus Stress Hyperglycemia**

Characteristic	Diabetes	SH	P Value
N	648	1325	–
Male ^a	408 (63)	902 (68)	0.04
Age ^b , years	63.2 ± 10.6	61.2 ± 14.1	< 0.0001
White ^a	525 (83)	1153 (88)	0.001
BMI ^b , kg/m ²	29.2 ± 6.51	26.4 ± 5.9	< 0.0001
H/O hypertension ^c , %	82	62.3	< 0.05
H/O smoking ^c , %	65.3	59.5	< 0.05
Elective surgery ^c , %	60.9	68.5	< 0.05
Cardiovascular procedure ^a			< 0.0001
Aortic root procedure	79 (12)	406 (31)	–
Coronary artery bypass graft surgery	352 (54)	445 (34)	–
Valve repair or replacement only	171 (26)	443 (33)	–
Left ventricular assist device implantation	46 (7)	31 (2)	–
Mean BG level on DOS ^b , mg/dL	148.2 ± 28.1	138.4 ± 23.1	< 0.0001
Mean BG level on POD 1 ^b , mg/dL	137.7 ± 17.8	128.9 ± 12.5	< 0.0001
Mean BG level on POD 2 ^b , mg/dL	141.4 ± 21.6	126.9 ± 14.0	< 0.0001
BG level 40 mg/dL ^a	7 (1)	17 (1)	–
BG level 60 mg/dL ^a	105 (16)	124 (9)	< 0.0001

Abbreviations: BG, blood glucose; BMI, body mass index; DOS, day of surgery; H/O, history of; POD 1, postoperative day 1; POD 2, postoperative day 2; SD, standard deviation; SH, stress hyperglycemia.

^aData presented as n (%)

^bdata presented as mean ± SD

^cdata from 2004–2007 only.

Table 2

Mortality at 30 and 90 Days After Surgery in Patients with and without Mild and Severe Hypoglycemia

Mortality	Mild Hypoglycemia (n = 229)	No Hypoglycemia (n = 1744)	P Value	Severe hypoglycemia (n = 24)	Mild/No Hypoglycemia (n = 1949)	P Value
30-Day mortality	6 (2.6)	47 (2.6)	0.95	0	53 (2.7)	0.41
90-Day mortality	11 (4.8)	66 (3.8)	0.32	0	77 (3.9)	0.32

Data are presented as n (%).

Table 3

Postoperative Complications Among Patients with Diabetes and Stress Hyperglycemia (Univariate Analysis)

Complication	Diabetes	Stress Hyperglycemia	P Value
Atrial fibrillation	129 (19.9)	324 (24.5)	0.02
Acute renal failure requiring dialysis	26 (4)	48 (3.6)	0.67
Cerebrovascular disease	1 (0.2)	5 (0.4)	0.39
Deep sternal wound infection	22 (3.4)	21 (1.6)	0.01
Bacteremia	13 (2)	19 (1.4)	0.34
Other infections	90 (13.9)	195 (14.7)	0.62
Mortality within 30 days	22 (3.4)	31 (2.3)	0.2
Mortality within 90 days	30 (4.6)	47 (3.5)	0.3

Data are presented as n (%).

Table 4

Multivariate Analysis of Deep Sternal Wound Infections

Variable	Odds Ratio	95% CI
Diabetes	1.45	0.75–2.84
BMI, kg/m ² (1-unit increase)	1.07	1.02–1.11
Mean BG level on POD 2 > 135 mg/dL	3.62	1.03–12.7

Abbreviations: BG, blood glucose; BMI, body mass index; POD 2, postoperative day 2.

Table 5

Patients with BG Levels < 180 mg/dL and 180 mg/dL, with and without DSWIs

Day, BG Level, mg/dL	Presence of DSWI, n (%)		P Value
	DSWI	No DSWI	
DOS			
< 180	38 (88)	1762 (93)	0.22
180	5 (12)	129 (7)	
POD 1			
< 180	43 (100)	1903 (99)	0.57
180	0	14 (0.7)	
POD 2			
< 180	43 (100)	1880 (98)	0.36
180	0	36 (2)	

Abbreviations: BG, blood glucose; DOS, day of surgery; DSWI, deep sternal wound infection; POD 1, postoperative day 1; POD 2, postoperative day 2.