

# Continuous insulin infusion is associated with a reduced post-surgical length of stay, but not with the complication rate, in patients with diabetes mellitus undergoing coronary artery bypass graft

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**ABSTRACT. Objective:** To establish if glucose management with continuous intravenous insulin infusion (CII) in the early post-operative period after coronary artery bypass graft (CABG) surgery is associated with complication rate and length of hospital stay (LOS) in patients with diabetes mellitus (DM). **Research design and methods:** We reviewed the records of 587 patients with DM who underwent CABG from January 1999 until January 2008; 316 patients were placed on CII, while 271 patients were treated with subcutaneous insulin. We examined patient age, glycated hemoglobin (HgbA1c), 24- and 72-h post-operative average capillary blood glucose (CBG), length of stay (LOS), and the rate of compli-

cations. **Results:** There was no difference in HgbA1c between the groups. Mean CBG values at both 24 h and 72 h remained the same in the CII group (167 mg/dl), while in the non-CII group they were 194 mg/dl and 189 mg/dl, respectively ( $p < 0.001$  between the groups). Post-surgical median LOS was 6 days in the CII group and 6.5 days in the non-CII group ( $p = 0.003$ ). Complications occurred at similar rate (in 10% and 11% of patients) in the two groups. **Conclusions:** CII is associated with a reduced post-surgical LOS in patients with DM who undergo CABG.

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## INTRODUCTION

It is well known that patients with diabetes undergoing coronary artery bypass graft (CABG) surgery are at higher risk of poor surgical outcomes than individuals without diabetes. These patients have increased perioperative mortality (1, 2), prolonged length of stay (LOS) in hospital (3, 4), increased hospitalization costs (5), and a higher incidence of deep sternal wound infections (6-8) and of post-surgical stroke (9-11).

Intravenous insulin infusion is often used in critically ill patients in surgical or medical intensive care units (12). Early trials have demonstrated that strict glycemic control with continuous intravenous insulin infusion (CII) in diabetic patients after cardiac surgery positively affects the rates of post-operative atrial fibrillation (13), mediastinitis (6, 14), as well as LOS (5), and mortality (15, 16). The use of intensive insulin regimens to lower blood glucose concentrations has been shown to decrease mortality in diabetic patients with myocardial infarction (17). However, recent publications either failed to reproduce similar beneficial effects (18, 19) or have reported that

outcomes associated with intensive glycemic control were less favorable than outcomes in patients with less intensive glycemic management (20, 21).

We examined whether post-CABG glucose management with CII in diabetic patients influenced the rate of immediate post-operative complications and length of hospital stay, when compared to subcutaneous (SC) insulin regimens.

## RESEARCH DESIGN AND METHODS

We conducted a retrospective review of the records of all patients who underwent CABG surgery at Beth Israel Medical Center in New York City from January 1999 to January 2008. Records of 587 patients known to have a history of diabetes (Type 1 or Type 2) were reviewed. Patients with stress-induced hyperglycemia after surgery, which we defined as capillary blood glucose (CBG)  $> 150$  mg/dl on two or more readings without known history of diabetes, were excluded from the study.

Selection criteria differed by year of surgery. Patients hospitalized from January 1999 to 2003 either received sliding scale SC rapid acting insulin therapy plus long-acting insulin or an intravenous insulin infusion (CII) for a minimum of 3 days post-operatively. Patients who had at least one post-operative CBG  $> 150$  mg/dl during the first 4 h after surgery were placed on CII, while patients with CBG  $< 150$  mg/dl during this period were placed on the SC insulin therapy.

All patients with a known history of diabetes who underwent CABG starting January 2003 were placed solely on CII protocol post-operatively for a minimum of 24 h. Insulin infusion was initiated and titrated according to the results of CBG testing with

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the goal of maintaining the blood glucose between 90 mg/dl and 150 mg/dl. Patients on the SC insulin regimen had their CBG values taken at a minimum of every 4 h post-operatively. Patients in the CII group had their CBG measured every 1 h post-operatively while on CII. All patient regimens were converted to basal-bolus insulin therapy with a long- and a rapid-acting insulin preparation prior to transfer out of the intensive care unit. Average CBG values were calculated for the first 24 h and 72 h post-CABG. Glycated hemoglobin A1c (Hgb A1c) values available during hospital stay were recorded. Hgb A1c values were excluded in patients who previously received a blood transfusion during the admission.

We evaluated the efficacy of glycemic management in both treatment groups by examining the following:

- 1) Average CBG at 24-h and 72-h post-operatively;
- 2) Post-CABG complications: stroke (new neurological deficit), transmural myocardial infarction (new Q-waves) or non-transmural myocardial infarction (no new Q-waves), deep sternal wound infection (bone-related), heart block requiring permanent pacemaker placement, sepsis, endocarditis, renal failure (including the requirement of hemodialysis), and respiratory failure. Patients with bleeding requiring re-operation, gastro-intestinal complications (bleeding, perforation, infarction), intra-aortic balloon placement (IABP) during or after surgery, and with phrenic nerve palsy were excluded since these complications were not thought to be associated with hyperglycemia. Patients who died during hospitalization were also excluded from the length of stay and complication analysis. The list of complications was obtained for all patients from existing cardiothoracic surgery databases.
- 3) Total LOS and LOS after surgery were obtained for all included patients. When analyzing LOS after surgery, we included patients with LOS of 100 days or less.

Data were described in terms of mean $\pm$ SD in the case of normally distributed continuous variables (e.g., age). Categorical data (e.g., complications) were reported in terms of frequency (percentage). Skewed continuous data (e.g., LOS) were described in terms of median (minimum, maximum) based on the recommendation of Bland and Altman (22). Since mean LOS is subject to significant influence by outliers, median LOS is the more appropriate descriptor in outcome analysis studies (23). Two group tests of differences were performed using the Student's t-test for normally distributed continuous variables; the Mann-Whitney non-parametric test for skewed data, and either the chi-squared test or the Fisher's exact test for categorical data.

The database was not comprehensive enough in terms of possible risk factors to allow for modeling length of stay similar to the Society of Thoracic Surgeons (STS) models that have been previously published (24). Data for first time CABG vs redo surgery, left ventricular ejection fraction, coronary anatomy, associated valvular or mechanical disease, and carotid lesions were not available. There was no specific data available on individual patients regarding on or off pump surgery, but <3% of CABG procedures in our patients were carried out off pump. Generalized linear modeling (GLIM) was used to identify all significant univariate predictors of LOS. These were then entered into a multivariate model in order to determine whether each predictor remained significant after controlling for the other predictors in the model. All analyses were carried out using SAS 9.1 (SAS Inc., Cary, NC). A level of significance <0.05 was used for all statistical tests.

## RESULTS

A total of 587 patients were identified from records, 271 (46%) in the non-CII group and 316 (54%) in the CII group. A total of 61 patients were excluded due to complications which were not thought to be related to glycemic control, as discussed in the "Methods". Of these, 36 (13%) were in the non-CII group and 25 (8%) were in the CII group ( $p=0.04$ ). Eighteen patients were excluded due to mortality, 6 (2%) in the non-CII group, and 12 (4%) in the CII group ( $p=0.34$ ). Some patients were excluded as the result of a combination of complications not related to glycemic control and mortality (3 in the non-CII group, 6 in the CII group). The final sample for analysis consisted of 232 patients in the non-CII group and 285 patients in the CII group.

The population was predominately male; females comprised 34% of the non-CII group and 31% of the CII group ( $p=0.45$ ). Mean age was 65 yr in the CII group and 66 yr in the non-CII group ( $p=0.09$ ). There was no significant difference in mean Hgb A1c between the groups (7.8% in CII and 7.7% in non-CII groups,  $p=0.75$ ) (Table 1).

Patients in the non-CII group had a higher body mass index (BMI) compared with those in the CII group (29.5 vs 27, respectively,  $p<0.001$ ). Mean CBG values at 24 h and 72 h in the CII group were both 167 mg/dl, while in the non-CII group they were 194 mg/dl and 189 mg/dl, respectively ( $p<0.001$  between the groups).

There were no significant differences in overall complication

Table 1 - Characteristics of non-continuous intravenous insulin infusion (CII) and CII patients.

Characteristic	Non-CII (no.=232)	CII (no.=285)	p
Time frame (yr)*	1999-2003	1999-2008	
Age (yr)	66.4 $\pm$ 10.4 <sup>a</sup>	64.9 $\pm$ 9.8	0.09
Female (no.)	79 (34%) <sup>b</sup>	88 (31%)	0.45
BMI (kg/m <sup>2</sup> )*	29.5 $\pm$ 5.0	27.6 $\pm$ 5.7	<0.001
Hgb A1C (%)	7.7 $\pm$ 1.8	7.8 $\pm$ 2.0	0.75
Mean CBG 24 h (mg/dl)	193.9 $\pm$ 39.7	166.9 $\pm$ 31.9	<0.001
Mean CBG 72 h (mg/dl)	189.1 $\pm$ 39.8	166.8 $\pm$ 32.1	<0.001
Minimum frequency of CBG (h)*	4	1	
Complications (no.)	24 (10%)	30 (11%)	1.00
Number of complications			
0	208 (90%)	255 (89%)	0.75
1	19 (8%)	20 (7%)	
2	4 (2%)	7 (3%)	
3	1 (0%)	3 (1%)	
Stroke (Intra-op to 24 h)	1 (0.4%)	5 (2%)	0.23
Stroke (After 24 h)	3 (1%)	2 (0.7%)	0.66
Q wave MI	3 (1%)	2 (0.7%)	0.66
Deep sternal wound infection	3 (1%)	2 (0.7%)	0.66
Sepsis or endocarditis	7 (3%)	10 (4%)	0.81
Renal failure	8 (3%)	8 (3%)	0.80
Respiratory failure	4 (2%)	14 (5%)	0.06
Unplanned cardiac reoperation or interventional procedure	1 (0.4%)	0 (0%)	0.45
Total LOS (days)	9 (2, 4) <sup>c</sup>	9 (3, 9)	0.47
LOS after surgery (days)	6.5 (2, 4) <sup>c</sup>	6.0 (1, 8)	0.003

<sup>a</sup>mean $\pm$ SD; <sup>b</sup>frequency (percentage); <sup>c</sup>median (minimum, maximum); \*values which differed between the two groups at baseline.

rates between the groups (10% in the non-CII group and 11% in the CII group,  $p=1.00$ ), with no recorded instances of new non-transmural myocardial infarction or heart block requiring permanent pacemaker placement (Table 1). Similarly, there were no significant group differences in the rates of any individual complication or in the number of patients with one or more than one complications.

Median LOS after surgery was longer in the non-CII group than in the CII group (6.5 days vs 6 days,  $p=0.003$ ) (Table 1). The generalized linear modeling of LOS after surgery showed that CII ( $p=0.003$ ), occurrence of complications ( $p<0.001$ ), and age ( $p=0.001$ ) were significant univariate predictors of longer LOS after surgery. When all of these were examined in a single multivariate model, all 3 factors (CII, complications, and age) remained significant ( $p<0.001$ ), indicating that all 3 factors constituted independent predictors of LOS (Table 2). BMI was not a significant univariate predictor of LOS after surgery. When included in the multivariate model with CII, complications and age, BMI did become a significant predictor of LOS after surgery ( $p<0.001$ ).

## DISCUSSION

In this relatively large retrospective cohort study, we have focused on determining the complication rate and length of hospital stay among patients with diabetes undergoing CABG. There was no difference in the complication rates between the groups, but a shorter length of stay after surgery was related to the implementation of the continuous insulin infusion, thus indicating a benefit for patients in this group.

Several possible explanations have been proposed for the beneficial action of lower glucose level and of insulin itself in patients with diabetes undergoing CABG. Perioperative hyperglycemia, especially in the setting of cardiopulmonary bypass, is thought to produce negative outcomes via direct and indirect mechanisms. Directly, it interferes with neutrophil and monocyte function, inducing the expression of proinflammatory cytokines and acute-phase proteins, and thus potentiating an inflammatory response and worsening wound infection or sepsis (25, 26). Indirectly, it reflects impaired insulin signaling and chronic insulin resistance state that is considered to be a serious risk factor for a diabetes-related cardiomyopathy and coronary-artery disease (27). Additionally, endogenous release of cortisol and catecholamines during surgery augments inhibition of glycolysis, increases the concentration of free fatty acids (FFA), and decreases production of ATP, which may result in myocardial and endothelial membrane instability (28, 29).

Insulin itself inhibits several cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and migration-inhibitory factor (MIF) (30, 31), and decreases circulating FFA levels (32). Besides glucose-lowering effects, insulin's anti-apoptotic and anti-inflammatory properties may produce cardioprotective effects in patients undergoing open heart surgery. CII inhibits nitric oxide release which may prevent endothelial injury that can contribute to end-organ damage. Nitric oxide, when produced in excessive amounts, can contribute to reperfusion injury following a period of ischemia (28). In addition, by protecting mitochondrial function, CII helps prevent multi-organ failure frequently seen in critical illness (33).

Our study supports the beneficial effects of insulin infusion in patients undergoing CABG as these effects relate to the LOS. However, the reasons for the reduced LOS in the CII group in our study remain obscure. It is possible that any of the above beneficial effects of insulin infusion may have contributed to the reduction of length of stay, but it is somewhat surprising that the effect on the LOS was observed without any effect on the rates of recorded complications. Perhaps, the rates of complications that were not examined in our study were affected by CII. Alternatively, because of the already low rates of complications, with individual complication rates ranging from 0-4%, a much larger study would be needed to demonstrate any further improvement.

It is also possible that we were unable to demonstrate any difference in complication rates because our study, as other retrospective studies, has a number of limitations. Most importantly, ours was not a randomized prospective controlled trial and there were some baseline differences between the groups.

One such difference was in BMI, which was higher in the non-CII group. Several studies have examined the association between the BMI and post-operative complications in patients undergoing CABG surgery. Wang et al., have shown that BMI  $>30$  kg/m<sup>2</sup> was one of the independent predictors of the long-term post-CABG mortality among patients with and without diabetes who also had a severe left ventricular dysfunction (34). In 2003, McAlister et al. demonstrated that more diabetic patients have suffered from the post-operative complications if they had higher BMI, despite the fact that the vast majority of them were managed with the intravenous insulin drip (35). More recently, Deaton et al. have shown that in the multivariate analysis, BMI was the only independent predictor of re-hospitalization 3 months after the CABG surgery (36). On the other hand, several studies have shown that, in spite of comorbidities associated with obesity, BMI was not an independent predictor of mortality and morbidity after CABG (37-39). In fact, underweight patients may be at higher risk for post-CABG mortality and morbidity (38, 39). Thus the role of BMI in the post-operative outcomes after CABG remains controversial. In our study, BMI was not used as a criterion for the choice of treatment.

In terms of length of stay, to our knowledge, no consistent association has been reported regarding LOS and BMI. In Engel et al., linear regression models indicated that hospital LOS and intensive care unit (ICU) stay were longest for patients with underweight BMI values (39). In our univari-

Table 2 - Univariate and multivariate results based on generalized linear modeling (GLIM) of length of stay after surgery.

Predictor	Univariate		Multivariate	
	B Coefficient	p	B Coefficient	p
Non-CII	0.02	0.003	0.02	<0.001
Complications	0.09	<0.001	0.06	<0.001
Age	0.002	<0.001	0.002	<0.001

ate analysis, BMI on its own was not a significant predictor of LOS after surgery. Thus, the role of BMI in determining LOS in patients undergoing CABG needs to be explored in longer prospective controlled studies.

Another difference between the two study groups involved the frequency of CBG testing. In the CII group, CBG was tested hourly, while in the SC insulin group CBG was measured every 4 h or more frequently, if the CBG was elevated. In previous studies involving intensive insulin regimens, frequency of CBG testing varied from every 30 min to 2 h post-operatively (15), to hourly, or every 2 to 4 h based on stability (40). However, to our knowledge, there are no studies which assessed the independent impact of the frequency of testing on postoperative complications or on LOS in CABG patients. Thus, we are unable to conclude with certainty whether the frequency of CBG monitoring on its own may have had an effect on the outcomes. This factor should be examined in future studies in a controlled fashion.

The general level of surgical and post-operative care has changed within the decade that the data were collected. With the advancement of percutaneous coronary interventions, the overall volume of cardiac bypass surgery has declined. In our hospital, no formal policy was adapted during the study interval for selecting patients for CABG or stenting, but there was a substantial decline in CABG procedures, with 381 in 1999 and 245 in 2007 (41). These changes could have affected our data and contributed to the margin of error. Adjusting for the year of surgery has allowed us to address this issue. In our multivariate analysis, year of surgery was not associated with LOS.

In our study, more patients with complications unrelated to hyperglycemia were excluded from the SC therapy group than from the CII group. However, when data analysis which included all patients was carried out, results were the same (data not shown).

Patients with stress-induced hyperglycemia were excluded from our study. When compared to non-diabetic patients and hyperglycemic diabetic patients, hospitalized patients with stress-induced hyperglycemia may have a higher risk of adverse outcomes (42) such as increased risk of in-hospital mortality (43, 44), and longer LOS (45). Thus, these patients constitute a distinct group which should be examined in detail and on its own in future studies.

An important indicator of insulin therapy in patients with diabetes, hypoglycemia rate, was not recorded. Although definitions of hypoglycemia in hospitalized patients vary widely (12), severe hypoglycemia is known to be detrimental to clinical outcomes. The Leuven (40) and Krinsley (45) studies both showed independent relationships between single episodes of severe hypoglycemia and mortality in ICU settings. Bagshaw et al. (46) confirmed these findings by showing that a single episode of hypoglycemia (<40 mg/dl) increased the risk-adjusted mortality by a factor of 2.6. In a study by Turchin et al hypoglycemia during hospitalization lead to an increase in the LOS (47). However, since in our study the frequency of hypoglycemic episodes was likely to be higher in the CII group than in the SC insulin therapy group (40), adjusting for hypoglycemia would have further magnified the difference in LOS between the two groups in favor of the CII group, and thus would have only strengthened our conclusions.

We targeted glucose level of 90-150 mg/dl. Despite the

lack of uniform guidelines defining the standards for glycemic control among hyperglycemic patients undergoing open heart surgery, there is still a trend in favor of the relatively "tight" glucose management (12, 48). Numerous clinical studies, which evaluated blood glucose control among patients undergoing CABG, have failed to arrive at generally accepted post-operative glucose standards. Target blood glucose for the first 72 h after the surgery has shifted within the past decade from below 200 mg/dl (14, 6), to 80-110 mg/dl (40), 100-150 mg/dl (15), 120-200 mg/dl (49), and <130 mg/dl (50). The recent combined American Association of Clinical Endocrinologists and American Diabetes Association consensus statement (51) did not recommend a specific target, noting simply that the previously recommended target of 80 to 110 mg/dl was too stringent. Recent Society of Thoracic Surgeons Practice Guidelines have recommended keeping blood glucose <180 mg/dl for patients without complications and <150 mg/dl for complicated patients spending more than 3 days in ICU (52). Therefore, the capillary blood glucose of 90-150 mg/dl targeted in our study appears to be in a generally acceptable range.

We conclude that patients with diabetes who undergo CABG and receive intravenous insulin infusion appear to exhibit shorter post-surgical LOS. In addition, as in other recent studies, the mean CBG was not a predictor of surgical outcome. These data need to be confirmed in large prospective randomized controlled trials.

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## Disclosure

The authors do not have any conflict of interest to disclose.

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