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Perioperative Hyperglycemia Is a Strong Correlate of Postoperative Infection in Type II Diabetic Patients after Coronary Artery Bypass Grafting

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Abstract. This study was planned to assess the relationship of perioperative glycemic control to the subsequent risk of infectious complications and to compare early clinical outcomes of coronary artery bypass surgery in diabetics with nondiabetics in a single center. A total of 1090 adults who underwent coronary artery surgery in a five year period were included in a retrospective cohort study based on available chart review. Of 1090 patients, 400 had type II diabetes mellitus. Intraoperative and postoperative blood glucose levels in diabetic group were manipulated by means of a continuous insulin infusion. Data of pre- and postoperative blood glucose levels were evaluated with respect to postoperative infection risk for diabetics. Risks of early mortality, cerebrovascular accident, and postoperative infection in diabetic patients were compared with the nondiabetic group. High preoperative mean glucose levels were the main risk factor for the development of postoperative infection ($p = 0.012$ and $p = 0.028$ for the mean glucose levels 1 and 2 days before operation, respectively). For diabetic group, of 400 patients 20 (5%) were diagnosed to have postoperative infection (superficial sternal wound in 3 (0.75%), donor site infection in 4 (1%), mediastinitis in 5 (1.25%), urinary tract infection in 6 (1.5%), and lung infection in 2 (0.5%) patients). The diabetic group had significantly higher prevalence of mediastinitis, donor site infection, urinary tract infection and total infection (p values were 0.048, 0.013, 0.009, and 0.044, respectively). Early mortality was higher among diabetics than in nondiabetics (1.73% vs 3%, $p = 0.048$) but the risk of cerebrovascular accident in diabetics was not greater than in nondiabetics in early period. In patients with diabetes who undergo coronary artery bypass surgery, preoperative hyperglycemia is an independent predictor of short-term infectious complications and total length of stay in hospital.

Key words: Preoperative hyperglycemia, Postoperative infection, Type II diabetes mellitus, Coronary artery bypass grafting, Deep sternal wound infection

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SEVERAL studies have reported an increased operative and postoperative morbitidy and mortality in patients with diabetes mellitus. Poststernotomy mediastinitis in diabetic patients after open heart surgical procedures increases operative mortality twofold to threefold [1, 2]. There is growing clinical and experimental evidence that hyperglycemia increases the risk of nosocomial infections and may actually be a causal factor in the development of these infections in critically ill patients [1, 3]. Hyperglycemia has a deleterious effect on macrophage or neutrophil function [4].

Prospective studies of the effect of strict blood glucose control in patients with type II diabetes mellitus have shown a reduction in mortality in intensive care unit after cardiac surgery [1, 4].

Early mortality after coronary artery bypass grafting (CABG), perioperative myocardial infarction, and pump failure were not more common in diabetic patients than in nondiabetic patients. The risk of late nonfatal myocardial infarction, recurrent angina,

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and chronic heart failure among diabetics are not higher either, but late mortality was [5].

Diabetes mellitus is a major risk factor for the development of ischemic stroke. Patients with diabetes are at least two times more prone to suffer from a stroke than nondiabetics [6].

The aim of this study was to determine whether diabetic patients undergoing CABG were at greater risk of early infection despite postoperative strict glycemic control than nondiabetics, and to determine the relationship between perioperative glycemic control and subsequent risk of infectious complications, total hospitalization period, and early mortality in a single center.

Patients and Methods

A total 1090 adults who underwent first time coronary artery surgery (off pump operations were excluded) in a five year period from January 1996 to November 2001 in the cardiac surgery service of our university hospital were included in a retrospective cohort study based on available chart review. The study group included 400 diabetic patients.

Historical, demographic, and surgical variables that might possibly be associated with infectious complications were collected in a common database. These variables included age, sex, body mass index (BMI), type of preoperative diabetic control (insulin, oral hypoglycemic, diet, or none), left ventricle end diastolic pressure (LVEDP) >12 mmHg, dialysis or elevated creatinin level (>2 mg/dL), chronic obstructive pulmonary disease (COPD), Society of Thoracic Surgeons operative status (elective, urgent, emergent salvage), cardiopulmonary bypass time, aortic clamp time, units of blood transfused, prolonged intubation (48 hours), inotropic use more than 48 hours, total hospitalization time, length of intensive care unit stay, duration of thoracal or mediastinal tubes stay (Table 1).

Patients were then screened for postoperative infectious complications or readmission for the same reason. Deep sternal wound infection (DSWI) involving the sternum or mediastinal tissues, including mediastinitis, superficial sternal wound infection (SSWI) involving the skin and subcutaneous tissues excluding the sternal bone, donor site infections (DSI) involving skin and subcutaneous tissues in harvested saphenous vein or radial artery site were noted.

Preoperative (capillary) and postoperative (arterial) blood glucose levels were monitored six times a day with Accu-check Easy (Boehringer Mannheim, Indianapolis, IN) and Roche Diagnostics (GmbH, D-68298 Mannheim, Germany, Roche/Hitachi 747–902) and recorded for diabetic patients. For purposes of data analysis, daily mean blood glucose levels were then calculated by averaging all glucose levels obtained clinically in the 2 days prior to the operation and postoperative 3 days.

Blood glucose levels in diabetic group were manipulated by means of a continuous insulin infusion (CII). The insulin drip was titrated to maintain blood glucose levels between 150 to 200 mg/dL (Novo Nordisk, Copenhagen, Denmark). Continous insulin infusion was started at least two hours before the operation according to fasting glucose levels together with dextrose infusion (conventional treatment) and continued postoperatively until the patient received oral nutrition.

Surgical infection prophylaxis remained constant throughout the entire study period. The cephalosporin class of antimicrobials was the agent of choice for prophylaxis of infection for coronary operations, and administered before skin incision and 3 hours after the first dose. All procedures were performed by the same surgical team.

Patients with associated valve replacement, those with simultaneous resection or plication of a left ventricular aneurysm and with concomitant or consecutive carotid artery surgery were included but reoperations were excluded. Either of the internal thoracic arteries was used as a graft in all of the patients. Anticoagulation was not routinely employed.

Statistical Methods: Data manangement and statistical analysis were performed using the SPSS for Windows program package. Categorical variables were compared with Fisher's exact test, Wilcoxon test, and continous variables with Student's t test. Mann-Whitney test was used as nonparametric test. Preoperative variables that were positively associated with postoperative outcome were studied with correlation tests (Pearson and Spearman's rho). All tests were two tailed and a level of significance was set at $p < 0.05$.

Table 1. Demographic and perioperative comparison of diabetic and nondiabetic group.

Variable	Diabetics (n = 400)	Nondiabetics (n = 690)	P value
Age (years)	61.6 ± 8.8	58.5 ± 11.1	0.56
Female Sex	182 (45%)	138 (20%)	0.4
LVEDP>12 mmHg	80.1%	77.6%	0.530
Urgent Surgery	5%	5.5%	0.7
Emergency Surgery	0.5%	0.7%	0.5
PVD	26 (6.5%)	20 (2.8%)	0.02*
Dialysis or creatinin >2 mg/dL	9%	5%	0.009*
COPD	2.8%	3%	0.12
BMI (kg/m2)	26.6 ± 3.7	25.6 ± 3.08	0.136
Chest tubes stay (day)	3.85 ± 1.80 (median = 2)	3.54 ± 1.46 (median = 2)	0.583
CABG + valve	10 (2.5%)	22 (3%)	0.12
CABG + Aneurysmectomy (Anterior LV)	20 (5%)	41 (5.9%)	0.09
CABG + carotid surgery (concomitant or consecutive)	10 (2.5%)	11 (1.5%)	0.09
CPB time (min)	80 ± 5	78 ± 4	0.7
Clamp time (min)	41 ± 4	38 ± 5	0.6
Inotropes >48 h	10%	9%	0.9
Ventilation >48 h	6%	5%	0.8
Transfusion PRBC (unit)	2.5 ± 1.2	2.6 ± 1.3	0.5
Length of stay (day)	15.6 ± 12.3 (median = 13)	13.0 ± 6.4 (median = 13)	0.089
ICU period (day)	5.8 ± 10.7 (median = 2)	4.9 ± 5.2 (median = 2)	0.097
Glucose level after operation (mg/dL) (day 1, day 2, day 3)	191 ± 36 169 ± 33 155 ± 27	140 ± 24 134 ± 20 128 ± 19	0.003*
Tube drainage (ml/24 h)	998 ± 265	1015 ± 284	0.09
Early mortality	12 (3%)	12 (1.73%)	0.048*

LVEDP, left ventricle end diastolic pressure; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; PRBC, packed red blood cells; ICU, intensive care unit. * significant p value.

Results

Between January 1996 and November 2001, 1090 patients underwent coronary artery bypass surgery through a median sternotomy. Four hundred of these patients were classified as diabetic at the time of admission and all were enrolled in the study. Mean age was 61.6 ± 8.8 years in diabetics and 58.5 ± 11.1 years in nondiabetics and 54% of diabetics and 80% of nondiabetics were men. There were no significant differences with respect to age, sex, procedures performed, cardiopulmonary bypass time (CPB), BMI, or blood transfusions.

Demographic and perioperative comparisons of the diabetic and nondiabetic group are shown in Table 1. The cardiac procedures performed in this diabetic cohort included CABG in 370 patients, CABG with valve replacements in 10 patients, and CABG with aneurysmectomy in 20 patients. Only left internal thoracic artery (ITA) was used in diabetic patients.

Of all diabetic patients, 20% were on insulin treatment, 60% were on oral agents, and the rest of them were on diet therapy in preoperative period. Mean preoperative glucose levels of diabetic patients in 2 days and 1 day prior to operation were 167 ± 37 mg/dL and 139 ± 31 mg/dL respectively. Postoperative 1st, 2nd and 3rd day mean glucose levels of diabetic patients were 191 ± 36 mg/dL, 169 ± 33 mg/dL, and 155 ± 27 mg/dL, respectively. Total duration of hospitalization, length of stay in intensive care unit were slightly higher in diabetic group although the difference was not significant (p = 0.08 and p = 0.09, respectively). There were significant correlations between mean glucose levels in 1st postoperative day and total duration of hospitalization (p = 0.003) and not significant correlation with the length of stay in intensive care unit (p = 0.063).

High preoperative mean glucose levels were the main risk factor for the development of postoperative infection (p = 0.012 and p = 0.028 for mean glucose levels 1 day and 2 days before operation, respectively). There was also significant correlation between the development of infection and the length of stay in intensive care unit and total duration of hospitalization (p = 0.006 and p< 0.001, respectively).

Tables 2 and 3 show that diabetics with infection and diabetics with DSWI have significantly higher preoperative mean blood glucose levels when they are compared with diabetics without infection and diabetics without DSWI. Chest tubes stay, ICU period, length of stay and mortality rate increased significantly in diabetics with infection or DSWI. Only postoperative mean glucose levels of diabetics with DSWI in 2nd day was higher significantly than those without DSWI.

In diabetic group, 20 (5%) patients were diagnosed to have postoperative infection (SSWI in 3 (0.75%), DSI in 4 (1%), DSWI in 5 (1.25%), urinary tract infection in 6 (1.5%), and lung infection in 2 (0.5%) patients). In nondiabetic group, only 14 of 690 patients (2%) developed postoperative infection (4 SSWI (0.57%), 2 DSI (0.28%), 4 DSWI (0.57%), 2 urinary tract infection (0.28%), and 2 lung infection (0.28%)) (Table 4). In diabetics, DSWI, DSI, urinary tract infection, and total infection were encountered more frequently than in nondiabetics (p values were 0.048, 0.013, 0.009, and 0.044, respectively).

The culprit infectious organism in diabetic patients with DSWI was Gram stain positive in 3 patients, Gram stain negative in 1, and unknown in 1. There were no anaerobic, fungal, or yeast infections.

Two diabetic patients (0.5%), 3 nondiabetic patients (0.43%) developed cerebrovascular accident,

Table 2. Demographic and perioperative comparison of diabetic patients with infection and those without infection.

Variable	Diabetics with infection (n = 20)	Diabetics without infection (n = 380)	P value
Age (years)	67.0 ± 9.73	60.44 ± 8.31	NS
Female sex	9 (45%)	173 (45%)	NS
BMI (kg/m2)	26.90 ± 1.7	26.6 ± 3.9	NS
Diabetic period (year)	9.79 ± 7.52	6.38 ± 6.43	NS
Glucose level 2 days prior to operation (mg/dL)	201 ± 47	165 ± 37	0.028*
Glucose level 1 day prior to operation	174 ± 36	136 ± 30	0.012*
Glucose level postop 1st day (mg/dL)	208 ± 41	190 ± 35	NS
Glucose level postop 2nd day (mg/dL)	156 ± 20	170 ± 33	NS
Glucose level postop 3rd day (mg/dL)	155.6 ± 32	154.2 ± 26	NS
Chest tubes stay (day)	5.86 ± 3.34 (median = 2.5)	3.41 ± 0.84 (median = 2)	0.001*
ICU period (day)	15.29 ± 23.39 (median = 5.5)	3.78 ± 1.21 (median = 2)	0.006*
Length of stay (day)	33.86 ± 21.40 (median = 23)	11.69 ± 2.44 (median = 12)	< 0.001*
Mortality (%)	10 (mediastinitis)	2.6	0.01*

NS, not significant, *significant p value.

Table 3. Comparison of perioperative mean glucose levels between diabetics with DSWI and diabetics without DSWI

Variables	Diabetics with DSWI (n = 5)	Diabetics without DSWI (n = 395)	P value
Glucose level 2 days prior to operation (mg/dL)	221 ± 10.50	166 ± 36.83	0.006*
Glucose level 1day prior to operation (mg/dL)	181 ± 9.45	138 ± 30.53	0.009*
Glucose level postop 1th day (mg/dL)	217 ± 30.35	189 ± 36.36	NS
Glucose level postop 2nd day (mg/dL)	210 ± 31.34	168 ± 33.38	0.012*
Glucose level postop 3rd day (mg/dL)	156 ± 2.08	154 ± 27.45	NS

NS, not significant, *significant p value.

Table 4. Infection rates in diabetic and nondiabetic group.

INFECTIONS	Diabetics (n = 400)	Nondiabetics (n = 690)	P value
DSWI	5 (1.25%)	4 (0.57%)	0.048*
SSWI	3 (0.75%)	4 (0.57%)	NS
DSI	4 (1%)	2 (0.28%)	0.013*
Urinary tract infection	6 (1.5%)	2 (0.28%)	0.009*
Lung infection	2 (0.5%)	2 (0.28%)	NS
Total	20 (5%)	14 (2.0%)	0.044*

DSWI, deep sternal wound infection (mediastinitis); SSWI, superficial sternal wound infection; DSI, donor site infection; NS, not significant. *significant p value.

but this risk in diabetics was not greater than in nondiabetics in early period ($p > 0.05$).

Hypoglycemia (defined as blood glucose level below 40 mg/dL) which was associated with sweating and agitation occurred in 3 patients during CII. There was no instance of hemodynamic deterioration or convulsion.

Twelve deaths in diabetic (two of them with mediastinitis) and 12 deaths in nondiabetic group were recorded. Early mortality was higher among diabetics than in nondiabetics (1.73% vs 3%, $p = 0.048$).

Discussion

Deep sternal wound infection has been reported to occur in 1% to 4% of patients after CABG. In our study this rate was 0.8%. It carries a mortality rate of nearly 14–25% [7–9]. In the present study, mortality rate of mediastinitis was 22%.

Diabetic patients (total of 148400 patients) underwent cardiac surgical intervention with nearly a 2% risk of developing DSWI in USA (2968 potential DSWIs) [1,10,11]. In our center this risk was 1.2%.

Diabetes mellitus (DM) afflicts 1 of 5 coronary bypass patients and is an independent risk factor for wound infection [12]. In our study, wound infection rate (including DSWI, SSWI, and DSI) was 3% in diabetic patients. The presence of DM is another patient characteristic that has been associated with postoperative mediastinitis [6, 13, 14], especially in patients requiring insulin [1]. In addition to the microvascular changes seen in diabetic patients, elevated blood glucose levels may impair wound healing. The use of a strict protocol aimed to maintain blood glucose levels < 200 mg/dL by CII has been shown to significantly reduce the incidence of deep sternal wound infection in diabetic patients [1, 2, 7]. The risk for DSWI is halved by aggressive perioperative glucose control by using a continuous intravenous insulin infusion (0.9%) when compared with intermittent subcutaneous insulin treatment (1.9%) ($p = 0.04$) [1]. In the present study, CII was performed to maintain postoperative blood glucose levels between 150 and 200 mg/dL in diabetic patients.

Studies have consistently associated obesity and reoperation with DSWI, while other risk factors such as use of one or both ITAs, duration and complexity of operation, and the presence of diabetes have been reported inconsistently. Obesity is a strong correlate of mediastinitis after CABG [1, 6]. In our study, these risk factors were no different in either group. Reoperations and CABG with both ITAs were excluded. Homologous blood transfusions after coronary bypass are correlated in a dose-related fashion to increased risk for viral and bacterial infections, increased length of stay, antimicrobial use, and mortality through transfusion related immunomodulation [15, 16]. In our study, blood transfusions were not different in the two groups.

Preoperative antibiotic administration reduces the risk of postoperative infection 5-fold [17]. Prophylactic antimicrobial efficacy is dependent on adequate drug tissue levels before microbial exposure [18, 19]. The cephalosporin class of antimicrobials is currently the agent of choice for prophylaxis of infection for coronary operations. Usual cephalosporin pharmacokinetics mandates administration within 30 minutes of incision and redosing if the operation exceed 3 hours [18]. A practical failsafe guideline to assure proper timing is the administration of the cephalosporin by the anesthesiologist after induction but before skin incision, same protocol was used in our patients. Some of the literature support the result of the present study: Diabetes mellitus with a preoperative blood glucose level of 200 mg/dL or more (odds ratio = 10.2) and staple use for skin closure (odds ratio = 4) were independent risk factors for deep sternal wound infection [20]. According to another study, preoperative hyperglycemia is an independent risk factor for radial artery harvested site infection if preoperative glucose levels are higher than 200 mg /dL in diabetics [21]. Skin staples were not used in our operations and only one radial artery harvest site infection developed.

A recent study reported that the conventional blood glucose control in which goal is to achieve blood glucose level less than 200 mg/dL was clearly insufficient to decrease the risk of critical patients in ICU. They revealed that the use of exogenous insulin blood glucose at level no higher than 110 mg/dL reduced morbidity and mortality among critically ill patients in the surgical intensive care unit, regardless of whether they had a history of diabetes [4]. Intensive insulin therapy also reduced the use of intensive care resources and the risk of complications that are common among patients requiring intensive care, including episodes of septicemia and corresponding need for prolonged antibiotic therapy. The higher risk in the conventional treatment group may reflect the deleterious effects of hyperglycemia on macrophage or neutrophil function or insulin induced trophic effects on mucosal and skin barriers. Intensive insulin treatment also prevented acute renal failure and may reduce the risk of cholestasis and polyneuropathy. They showed that the mortality in the patients with conventional and intensive glucose control after various cardiac surgery procedures (most of them were CABG) was 5.1% and 2.1%, respectively [4]. In the present study mortality rate was 3% in diabetic patients and 1.73% in nondiabetics. Overall mortality was 2.2% in our study in which only the patients undergoing CABG were included. This may be the explanation for the difference between mortality rates for conventional treatment. The mortality rate rises up to 10% in diabetic patients with infection because of mediastinitis. Preoperative mean blood glucose levels in diabetics with infection were significantly higher than in diabetics without infection (Table 2). Especially DSWI (mediastinitis) is a very devastating complication in cardiac surgery. In our study, preoperative mean blood glucose levels in diabetics with DSWI were more pronounced than in diabetics without DSWI (Table 3).

In conclusion, blood glucose regulation in preoperative period is as necessary as in postoperative period to reduce postoperative infectious complications in diabetic patients undergoing coronary artery bypass surgery.

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