Abstract (219words)

Background: There have been no large scale studies on the impact of diabetes mellitus (DM) on outcomes in Japanese patients undergoing coronary artery bypass grafting (CABG).

Methods: A multi-institutional retrospective cohort study was conducted in 14 Japanese centers. All adult patients who underwent isolated CABG from 2007 to 2008 were included (n=1,522; 1,177 males; mean age: 68.5 years). The definitions of DM were all patients admitted with diagnosis of DM and preoperative HbA1c$\geq$6.5%. Univariate and multivariable analyses were performed to identify the risk of morbidity and mortality.

Results: There were 849 DM and 572 non-DM patients. Preoperative, intraoperative and 3-day average postoperative blood glucose (BG) were 146mg/dl, 172mg/dl and 168mg/dl in the DM group, and 103mg/dl, 140mg/dl and 136mg/dl in the non-DM group (all p<0.0001). Although there were no significant differences in postoperative cardiovascular events, the incidence of infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, P=0.036). The all-cause death was also higher in the DM group than in the non-DM group (2.1% vs 1.1%, p=0.12), and this was likely related to infection.

Conclusions: DM patients had worse perioperative BG control, higher incidence of infection, and higher mortality than non-DM patients. These results indicate that perioperative BG control guidelines should be standardized to obtain better surgical outcomes in Japanese DM patients.

Key words: complication, coronary artery bypass grafting, diabetes mellitus, infection, mortality

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the last several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 million to 8.9 million in the last decade (a 29% increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal treatment for DM patients; some physicians favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4, 5]. However, it is well known that patients with DM who undergo CABG have worse early and late outcomes than CABG patients without DM [6, 7]. Also, it has been shown that intraoperative and postoperative blood glucose (BG) control has a significant effect on complications such as infection and mortality [8-10]. However, there have been no large-scale studies on Japanese DM patients undergoing coronary artery bypass grafting. To better understand the impact of DM on coronary artery surgery and to establish the optimal BG control method during cardiac surgery, we organized a multicenter/multidisciplinary research group, which we called the JMAP study group (Japanese Study to Explore the Impact of Diabetes on Cardiac Surgery for Optimal Glycemic

Control Protocol). Herein, we carried out a retrospective cohort study to identify the impact of DM and BG control on surgical outcomes in Japanese patients undergoing CABG.

Patients and Methods

From 2007 to 2008, a total of 1,522 patients underwent isolated CABG in 14 cardiac surgery centers in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. All the patient characteristics and operative data were extracted from the prospective national database (the Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in the North America. Other study-specific data like perioperative BG control, as well as other blood laboratory data and postoperative complications including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These two sets of data were merged and sent to a data center (the EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables are listed in Appendix I. Of note, the Japanese Diabetes Society (JDS) value of HbA1c (%) is converted into the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula according to the JDS guidelines [11]:

$$HbA1c\ (NGSP)\ (\%) = HbA1c\ (JDS)\ (\%) + 0.4\ (\%)$$

Postoperative variables were acute myocardial infarction (MI), cerebrovascular events, acute renal failure and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after PCI). Postoperative infection was categorized into deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, blood stream infection, urinary tract infection, and pneumonia. Details of the definitions of the clinical events are summarized in Appendix II. Hospital death included all-cause death within 30 days of operation or during initial hospitalization. All the aforementioned clinical events were evaluated at the participating centers, and then assessed by the independent clinical events evaluation committee (Appendix III). The primary composite endpoint was defined as a composite of acute MI, cerebrovascular accidents, other cardiovascular events, all infections and their related deaths. Although cardio-cerebrovascular events were thought to be important for DM patients, this prespecified primary composite endpoint was not related to DM. Thus, we added a new composite endpoint, which consisted of all infections, renal failure, and all cause deaths, and conducted an additional analysis.

DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Patients without a previous diagnosis of DM who had preoperative HbA1c $\geq$ 6.5% (NGSP) were also included [12]. The intraoperative BG was an average of 3-4 BG measurements taken during surgery. The postoperative 3-day BG average was a composite average of the daily mean BG levels (BG was measured up to 12 times per day following surgery) from the day of the surgery to postoperative day 3.

Perioperative BG control methods varied from hospital to hospital, however, in all the participating institutions, it was standard practice to treat hyperglycemia with continuous insulin infusion whenever BG exceeded 200mg/dl.

Statistical Analyses

Baseline characteristics of the DM and the non-DM groups are described as mean $\pm$ standard deviation for continuous variables and proportions for categorical variables. P-values were calculated by the t-test and the chi-squared test. We compared the proportions of primary and additional composite endpoints and their components between the DM and the non-DM groups. Risk ratios and associated 95% confidence intervals were calculated.

Logistic regression analyses were conducted to estimate the magnitude of the effect of DM on the additional composite endpoint, all infections, and all cause deaths adjusted by age (in 10-year increments), gender, body mass index, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction < 50%, operative status (elective vs urgent or emergency), bilateral internal thoracic artery use, and intraoperative steroid use. Of note, two patients undergoing CABG as salvage were excluded from the analyses. Odds ratios and their associated 95% confidence intervals were calculated. All analyses were performed with JMP 8.0 statistics software (SAS Institute Inc., Cary, NC, USA). The two-sided alpha level was set to 5%.

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1,522 enrolled patients were classified into two groups: the DM group (n=849) and the non-DM group (n=572). Because there were no preoperative HbA1c data for 101 patients without a previous diagnosis of DM, these patients were excluded from this study. Patients' baseline characteristics are shown in Table 1. There were no differences in terms of age, gender and body mass index (BMI). However, depressed left ventricular systolic function (ejection fraction < 50%), renal insufficiency, and peripheral artery disease were significantly higher in the DM group than in the non-DM group. On the other hand, chronic obstructive pulmonary disease was less common in the DM group. There was no difference in terms of usage of bilateral internal thoracic artery, however intraoperative administration of intravenous steroids was more common in the non-DM group. There were no differences in operative status. Off-pump techniques were used frequently in both groups (about 70% of patients in each group).

Preoperative fasting, intraoperative and 3-day average postoperative BG were 146mg/dl, 172mg/dl and 168mg/dl in the DM group, and 103mg/dl, 140mg/dl and 136mg/dl in the non-DM group, respectively. At all measurement points, DM patients had significantly higher BG levels ($p<0.0001$). As shown in Table 2, the all-cause deaths were 2.1% (n=18) in the DM group and 1.1% (n=6) in non-DM group ($p=0.124$). There was no significant difference in the primary composite endpoint, however, the additional composite endpoint was significantly higher in the DM group. In terms of complications, although there were no significant differences in the incidence of postoperative cardiovascular events and cerebrovascular accidents, the incidence of overall infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, P=0.036). In particular, the incidence of deep sternal wound infection was much higher in the DM group (2.0%) than in the non-DM group (1.1%) although this did not reach statistically significance (p=0.163). The cause of death in the DM group was predominantly related to infection (10/18), while in the non-DM group there was only one patient who died of infection (1/6). On multivariable logistic regression analyses, the statistically significant risk factors for the additional composite endpoint included female gender, BMI, renal insufficiency, and chronic obstructive pulmonary disease (Table 3). Also, the statistically significant risk factors for infection were female gender, BMI and renal insufficiency (Table 4). Finally, the statistically significant risk factors for all-cause death were renal insufficiency, congestive heart failure, and emergency surgery (Table 5). The presence of DM was not identified as a statistically significant risk factor for any of the endpoints and complications including infection by multivariable analyses.

Discussion

In 2009, the Society of Thoracic Surgeons Blood Glucose Management Task Force published their guidelines regarding BG management during adult cardiac surgery [13]. According to these guidelines, it is highly desirable to maintain BG < 180mg/dl during surgery and during the immediate postoperative period with intravenous insulin infusion in DM patients. Although it is unnecessary to use intravenous continuous insulin infusion in non-DM patients during surgery, both DM and non-DM patients benefit from maintaining BG < 180mg/dl in order to prevent morbidity and mortality [13]. Based on the current findings, our BG management approach seems to be reasonable given the intraoperative and postoperative 3-day average BG with 172mg/dl and 168mg/dl, respectively, in the DM group. This begs the question of how low the target should be. Furnary et al. reported from their prospective observational study that there was a highly significant relationship between mortality and postoperative glucose levels rising above 175mg/dl [10]. Our current BG levels in DM patients were barely below this cut-off value.

It has been reported that the presence of DM in patients undergoing CABG is a significant risk factor for hospital mortality and morbidity including stroke, deep sternal wound infection and length of hospital stay from the STS database analyses [13]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [6]. Our results show that DM has a significant influence on the additional composite endpoint consisting of all-cause death, infection and acute renal failure (10.8% vs 7.3%, p=0.027). Looking at each complication, infection was the most significant factor contributing to this result (9.2% in DM group vs 6.1% in non-DM group, p=0.036).

Also, DM patients tended to have higher mortality than non-DM patients (2.1% vs 1.1%, p=0.124). Moreover, DM patients tended to have a much higher incidence of deep sternal wound infection than non-DM patients (2.0% vs 1.1%, p=0.163), although this difference did not reach statistical significance. However, the complication of infection definitely influenced mortality rates because the majority of deaths were related to infection in the DM group. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high BMI, and worse renal function, all of which would contribute to worse short and long-term outcomes compared to non-DM patients. The Portland Diabetic Project, which is an on-going prospective study of over 5,000 DM patients, aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [15]. They showed that tight glucose control with a full 3 days of continuous insulin infusion (the Portland Protocol) significantly reduced mortality (by 65%), deep sternal wound infection (by 63%), and length of hospital stay (average 2-day reduction). Therefore, they concluded that DM is not the true risk factor for the seemingly unfair diabetic disadvantage in terms of increased mortality and morbidity. Since we showed that DM patients still have excess mortality and morbidity compared to non-DM patients in the current study, we might be able to reduce these excess complications by implementing tighter glucose control protocols.

It has been debated whether intensive BG control is better than conventional BG control. In a landmark paper, Van den Berghe et al. conducted the first prospective randomized trial comparing tight BG control (target 80-110mg/dl) with intensive insulin therapy to conventional BG control in critically ill surgical patients [16]. They demonstrated that tight BG control resulted in a significant reduction in mortality (10.6% with intensive treatment vs 20.2% with conventional treatment, p=0.005), exclusively in those patients who required ≥ 5 days of ICU care with multiorgan failure and sepsis. Also, cardiac surgical mortality was reduced in those patients requiring ≥ 3 days of ICU care. D'Alessandro et al. reported a propensity analysis that showed that strict BG control significantly reduced the EuroSCORE expected mortality in DM patients undergoing CABG, especially in moderate to high-risk patients [17]. Their BG target in the operating room and ICU were 150-200mg/dl and ≤ 140mg/dl, respectively. In terms of long-term outcomes, Lazar et al. showed that tight perioperative glucose control with glucose-insulin-potassium solution improved not only perioperative outcomes, but also long-term survival and freedom from recurrent angina [18]. These studies clearly demonstrate the superiority of tight BG control over conventional control, especially in critically ill patients. On the other hand, Gandhi et al. showed in a prospective randomized study on 400 patients undergoing CABG, including non-DM patients, that intraoperative intensive insulin therapy with a target range of 80-100mg/dl did not reduce perioperative mortality and morbidity, but rather increased stroke rate and mortality [19]. Furthermore, a meta-analysis of 29 randomized studies focusing on the benefits and risks of tight glucose control in critically ill adult patients concluded that tight glucose control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia [20]. To support these results, a recent prospective randomized multicenter trial (the NICE-SUGAR study) demonstrated that intensive BG control with a target of 81-108mg/dl increased mortality among adults in the ICU compared with conventional BG control with a target of 180mg/dl or less [21]. In this study, however, the mortalities in the intensive control group and conventional control group were 27.5% and 24.9% at 90 days after randomization, respectively. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90% of the patients who died. Also, it seems that severe hypoglycemia commonly occurred in the intensive BG control group of the study, which may raise the question of the safety and feasibility of the tight glucose control protocol itself. Because these patients in the study were so sick at the time of enrollment, it is difficult to compare the results of these studies with studies on regular cardiac surgery patients, given the current acceptable mortality after CABG of around 2%. It may be necessary to conduct a prospective randomized study to compare tight glucose control and conventional glucose control using more sophisticated protocols with a minimum risk of hypoglycemia in exclusively cardiac surgery patients to reach a definitive conclusion.

Perhaps, one of the other interesting features of this multi-center study is the fact that about 70% of all isolated CABG procedures were performed using the off-pump technique in both the DM and non-DM groups. This trend is far above the typical rates in the North America, given the fact that the adoption of off-pump CABG was only 21.8% in 2009 according to the STS database [22]. A systematic review and meta-analysis of propensity score analyses in more than 123,000 patients comparing off-pump and on-pump CABG demonstrated that off-pump provides favorable outcomes in mortality, stroke, renal failure, wound infection, blood transfusion, intraaortic balloon pump support and prolonged ventilation [23]. It will be interesting to see the impact of off-pump techniques in DM patients in terms of not only intraoperative and postoperative glucose control, but also in terms of postoperative complications and mortality. We are planning to perform a post-hoc subgroup analysis focusing on this in the near future.

There are several limitations to this study. This was a retrospective, observational study, and hence unknown patient selection processes may cause a bias. Our sample size was relatively large, however, it was not large enough to stratify the level of perioperative BG control as an indicator of risk events. Importantly, there was no standard BG control protocol across the participating hospitals.

Conclusions

DM patients had poor perioperative BG control and higher incidence of infection with a higher mortality rate than non-DM patients. Excess mortality and morbidity in DM patients may have been due to hyperglycemia during the perioperative period. These results highlight the need to initiate prospective studies to standardize perioperative BG control protocols to obtain strict BG control, which may yield better surgical outcomes in Japanese DM patients undergoing cardiac surgery.

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Table 1. Patients' baseline characteristics

Variables		DM Group (n=849)	Non-DM Group (n=572)	P value
Mean age (SD)		68.6 (8.4)	68.0 (10.1)	0.282
Age ≥ 75		208 (24.5%)	162 (28.3%)	0.107
Male gender		649 (76.4%)	451 (78.9%)	0.288
Mean body mass index (SD)		23.7 (3.3)	23.4 (3.1)	0.094
Steroid use		18 (2.1%)	8 (1.4%)	0.320
Congestive heart failure		131 (15.5%)	98 (17.1%)	0.397
Renal insufficiency		117 (13.8%)	45 (7.9%)	0.001
Chronic obstructive pulmonary disease		57 (6.7%)	64 (11.2%)	0.003
Peripheral artery disease		193 (22.7%)	101 (17.7%)	0.021
Left ventricular ejection fraction < 50%		212 (26.6%)	115 (20.5%)	0.010
Operative status				
	Elective	732 (86.2%)	484 (84.6%)	0.154
	Urgent	76 (9.0%)	67 (11.7%)	
	Emergency	41 (4.8%)	21 (3.7%)	
Bilateral internal thoracic artery use		400 (47.1%)	285 (49.8%)	0.316
Intraoperative steroid use		246 (29.0%)	200 (35.0%)	0.017
On-pump or off-pump				
	On-pump	214 (25.2%)	154 (26.9%)	0.754
	On-pump beating	43 (5.1%)	27 (4.7%)	
	Off-pump	592 (69.7%)	391 (68.4%)	

DM: diabetes mellitus