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ORIGINAL ARTICLE

Plasma B-type natriuretic peptide in predicting outcomes of elective coronary artery bypass surgery

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Abstract The risks of surgery and its clinical outcome are of great importance for both patients and physicians when choosing coronary artery bypass (CABG) surgery for coronary artery disease. The purpose of the current study was to clarify the relationship between serum B-type natriuretic peptide (BNP) and patient clinical outcome. Seventy-six eligible patients who underwent CABG were enrolled into the prospective study. Venous blood samples were drawn for serum BNP and N-terminal (NT)-proBNP levels measurement on preoperative Day 1, postoperative Day 1, and postoperative Day 7. Clinical end points were: (1) intensive care unit (ICU) stay longer than 4 days postoperatively and/or hospital stay longer than 13 days postoperatively; (2) major complications and poor outcomes. Patients who had prolonged ICU stay and hospitalization had significantly higher postoperative Day 1 BNP and postoperative Day 1 NT-proBNP level ($p = 0.02$ and 0.005, respectively). Age was significantly older in patients with prolonged ICU stay and hospitalization than those without prolonged ICU stay and hospitalization ($p = 0.03$). Serum creatinine level was also significantly increased in patients with prolonged ICU stay and hospitalization ($p = 0.009$). However, age was the only remaining factor that correlated with prolonged ICU stay and hospitalization in the multivariate logistic regression model. These results suggest that research using BNP and NT-proBNP for predicting ICU stay and hospitalization in patients who have undergone CABG must adjust risk factors to present a more appropriate estimation of its clinical outcome.

Introduction

Coronary artery disease is currently the major cause of cardiovascular-related death in the modern world as well as

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in developing countries [1]. The cost of coronary artery bypass graft (CABG) surgery has been rising, making a review of outcome and cost-effectiveness imperative. Among major adverse events, prolonged hospitalization and/or prolonged intensive care unit (ICU) stay are the most common causes of costly medical expenses other than death related to surgery. It is known that there are many factors that can affect the outcome. Therefore, preoperative factors have been grouped into a scoring system to predict the possible risk of surgical mortality and morbidity [2–4]. However, there is no gold standard prediction model for length of hospital stay, surgical complications, and outcomes [5]. Furthermore, scoring systems are often cumbersome, which means an additional predicting system is necessary. The B-type natriuretic peptide (BNP) is a neurohormone mainly secreted from cardiac ventricles by increasing ventricular wall stress and volume expansion [6]. There are several previous studies that demonstrated that serum BNP concentration significantly increased after CABG surgery and was associated with increasing postoperative mortality and cardiac events [7,8]. Furthermore, ProBNP, a serum protein comprising 108 amino acids, can be cleaved into physiologically active BNP and biologically inactive N-terminal proBNP (NT-proBNP), whose plasma concentration reflects the activity of *de novo* synthesis and may have even greater specificity to cardiac activity than BNP [9]. NT-proBNP is also more stable, which makes its measurement more reliable [10]. Studies demonstrated that NT-proBNP can be used in diagnosing left ventricular dysfunction and acute coronary syndrome [11,12]. Theoretically, the elevation of serum NT-proBNP concentration may also reflect the higher mortality and complication rates after CABG surgery. However, there were studies suggesting that several variables of general population such as female sex, old age, and impaired renal function were also significantly associated with higher BNP and NT-proBNP levels [9,13]. The variables may possibly affect the predictability by BNP and NT-proBNP levels alone. Therefore, the purposes of the current study are to assess whether BNP and NT-proBNP are correlated with postoperative complications and outcomes after adjusting for risk factors.

Methods

The study was first reviewed and approved by the hospital's ethics committee, and then written informed consent was obtained from each patient. Ninety-four patients who underwent CABG surgery of a single surgeon were enrolled into the prospective study between January 2006 and June 2007. Among the 94 patients, 10 patients with uremia, five patients with inappropriate sample collection, and three patients who underwent emergency operation were excluded from the study. The remaining 76 patients all received elective cardiac bypass surgery, including conventional CABG surgery (single aortic cross-clamping, deep hypothermia 23–25°C, and crystalloid cardioplegia) in 54 patients, off-pump CABG surgery (median sternotomy, normothermia) in 11 patients, and minimally invasive direct CABG surgery (lateral thoracotomy with short segment of 5^{th} rib resection) in 11 patients. Left ventricular ejection fractions (LVEFs) were measured by echocardiography on preoperative Day 1 and postoperative Day 7. The serum BNP and NT-proBNP levels were measured on preoperative 1 Day, postoperative Day 1, and postoperative Day 7. Venous blood samples were drawn for BNP and NT-proBNP analysis after patients rested for 30 minutes. The venous samples were placed into chilled ethylenediaminetetraacetic acid tubes and placed on ice. After centrifugation, the plasma samples were stored at −80°C until assay. During the procedure, Roche Elecsys, Roche Diagnostics, Indianapolis 1010/2010 kits and Modular analytics, Roche Diagnostics, Indianapolis E170 immunoassay analyzers were used for the quantitative determination of NT-proBNP. The Abbott AxSYM (R), Abbott Laboratories, Illinois automated immunoassay instrument system was used for BNP measurement. All data were collected afterward.

Clinical end points were: (1) ICU stay longer than 4 days postoperatively and/or hospital stay longer than 13 days postoperatively; (2) major complications and poor outcomes, including new-onset atrial fibrillation, ventricular tachycardia, ventricular fibrillation, requirement of intra-aortic balloon pump (IABP) support, unscheduled cardiac-related readmission to the hospital, and late cardiac mortality within 1 year.

Data were analyzed using SPSS software (version 11.0.0, SPSS Inc., Chicago, IL, USA) and expressed as the mean with standard deviation. Categorical variables were presented as counts and percentages. The student *t* test and χ^2 test were used to examine differences in continuous and categorical variables, respectively. Multivariate logistic regression analyses were used to calculate odds ratios and 95% confidence intervals, with adjustment for potential confounders such as age, sex, creatinine level, heart failure class, NYHA, and LVEF. A value of $p < 0.05$ was considered statistically significant.

Results

Patients' mean age was 64.0 $\pm$ 10.2 years, and 85.5% were male. There were 5% of patients with preoperative New York Heart Association functional class III or IV. Most patients (76.3%) had triple vessel disease or left main disease. The mean serum creatinine level was 1.2 $\pm$ 0.38 mg/dL. The mean LVEF was 61.0 $\pm$ 11.2 in preoperative evaluation and 61.6 $\pm$ 9.5 in postoperative examination. There were no significant differences between preoperative and postoperative LVEF ($p = 0.52$). Thirty-day surgical mortality and in-hospital mortality was zero.

Fig. 1 shows the BNP and NT-proBNP changes. The mean BNP was 103.8 $\pm$ 184.0 pg/mL, 361.9 $\pm$ 463.7 pg/mL, and 261.9 $\pm$ 402.4 pg/mL at preoperation, postoperative Day 1, and postoperative Day 7, respectively. There were significant differences between preoperative BNP and postoperative Day 1 BNP ($p < 0.001$), and, preoperative BNP and postoperative Day 7 BNP ($p = 0.001$). The mean NT-proBNP was 621.3 $\pm$ 1050.7 pg/mL, 2869.8 $\pm$ 3252.6 pg/mL, and 1358.5 $\pm$ 1632.3 pg/mL at preoperation, postoperative Day 1, and postoperative Day 7, respectively. The postoperative Day 1 and Day 7 NT-proBNP concentrations were significantly higher than preoperative NT-proBNP concentrations ($p < 0.001$, respectively). Linear regression with 95%

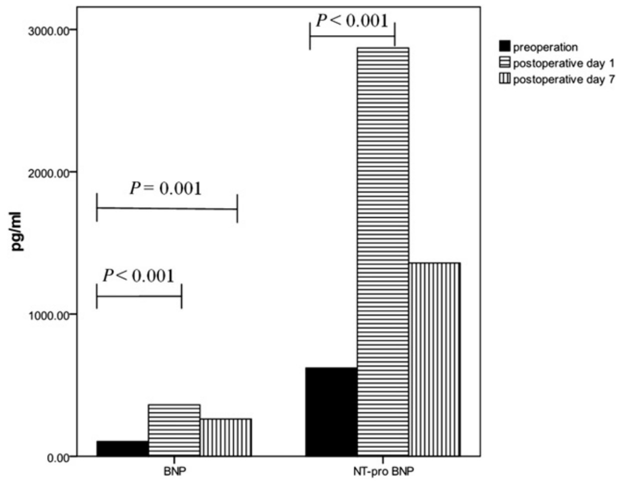

Figure 1. Changes in B-type natriuretic peptide (BNP) and NT-proBNP.

individual prediction interval was used for the determination of the relationship between BNP and NT-proBNP concentrations. The correlations between BNP and NT-proBNP were all apparent at preoperation, postoperative Day 1, and postoperative Day 7 (r = 0.64, 0.84, and 0.89; $p < 0.001$, respectively).

The values of BNP and NT-proBNP in on-pump and off-pump CABG surgery are shown in Table 1. The BNP and NT-proBNP concentrations were higher in on-pump CABG surgery than those in off-pump CABG surgery. However, there were no significant differences.

The mean ICU stay was 3.9 ± 1.6 days and mean hospitalization was 12.8 ± 4.9 days. There were 38 patients staying in the ICU >4 days and/or admitted to hospital >13 days. IABP was administered in nine patients during surgery due to unstable hemodynamic status. New-onset arrhythmia occurred in three patients. A total of five patients experienced readmission to the hospital and mortality within 1 year, including one death and four readmissions due to cardiac complications. Table 2 shows BNP and NT-proBNP concentrations in patients with and without clinical complications and outcomes. The postoperative Day 1 NT-proBNP and postoperative Day 1 BNP were significantly higher in patients with prolonged ICU stay and hospitalization (p = 0.03 and 0.01, respectively). Preoperative BNP and preoperative NT-proBNP also were higher with prolonged ICU stay and hospitalization. However, there were no significant differences (p = 0.34 and 0.12, respectively). Major complications and poor outcomes included new-onset atrial fibrillation, ventricular tachycardia, ventricular fibrillation, requirement of IABP support, unscheduled cardiac-related readmission to the hospital, and late cardiac-related mortality within 1 year. Patients who suffered from major complications and poor outcomes had higher preoperative BNP and NT-proBNP, postoperative Day 1 BNP and NT-pro BNP, postoperative Day 7 BNP and NT-proBNP concentrations. However, there were no significant differences.

Table 3 presents patient characteristics with and without prolonged ICU stay and hospitalization. Age was significantly older in patients with prolonged ICU stay and hospitalization than those without prolonged ICU stay and hospitalization (p = 0.03). Serum creatinine levels were also significantly increased in patients with prolonged ICU stay and hospitalization (p = 0.009).

Multivariate logistic regression analyses were used to adjust for potential confounders such as age, sex, creatinine level, heart failure class, and LVEF. Age was the only factor that was still significantly correlated with prolonged ICU stay and hospitalization (Table 4).

Discussion

Although the technology and the facility of percutaneous coronary intervention are improving dramatically, CABG surgery is still frequently the inevitable solution for many critically ill patients. Thus, it has become more important to be able to predict the associated risk of CABG surgery for the cardiac surgeon, the cardiologist, and families. It is as important to understand the possible relationship between the various clinical parameters and the possible cost-effective benefits. Therefore, there are many different scoring systems to assess the postoperative hospital stay, morbidities, and mortality after cardiac surgery. However, even with all these efforts, currently there is no gold standard to be followed [5,14]. In clinical practice, BNP and NT-proBNP are simple laboratory tests with the results easily reproduced and corroborated. Several investigators demonstrated that plasma BNP and NT-proBNP concentrations are good predictors for outcome of cardiac surgery [8,15]. Eliasdottir et al. [15] showed that preoperative NT-proBNP concentration was significantly higher in patients with prolonged ICU stay, death within 28 postoperative days, required inotropic agents or IABP, and new development of postoperative renal failure. They also found a good correlation between NT-proBNP and euroSCORE. However,

Table 1 The values of BNP and NT-proBNP in on-pump and off-pump coronary artery bypass surgery.

Coronary artery bypass surgery	On-pump (n = 54)	Off-pump (n = 22)	p
Preoperative BNP (pg/mL)	111.2 ± 229.8	90.1 ± 168.4	0.48
Postoperative day 1 BNP (pg/mL)	373.1 ± 504.8	322.9 ± 286.3	0.84
Postoperative day 7 BNP (pg/mL)	299.2 ± 441.8	163.8 ± 196.2	0.09
Preoperative NT-proBNP (pg/mL)	663.7 ± 1120.8	515.8 ± 778.6	0.51
Postoperative day 1 NT-proBNP (pg/mL)	3132.2 ± 3547.8	2312.2 ± 1681.6	0.36
Postoperative day 7 NT-proBNP (pg/mL)	1520.1 ± 1781.8	963.8 ± 741.9	0.11

BNP = B-type natriuretic peptide.

Table 2 BNP and NT-proBNP concentrations in patients with and without clinical complications and outcomes (values are shown as mean ± SD).

Clinical end points	Yes	No	*p*
Prolonged ICU stay and hospitalization (*n* = 38)			
Preoperative BNP	124.2 ± 199.4	83.3 ± 167.3	0.45
Postoperative day 1 BNP	508.2 ± 546.6	215.6 ± 305.0	0.01
Postoperative day 7 BNP	272.6 ± 367.8	251.4 ± 278.7	0.76
Preoperative NT-proBNP	812.3 ± 1334.0	430.3 ± 619.2	0.23
Postoperative day 1 NT-proBNP	3734.9 ± 3530.3	2004.6 ± 2728.5	0.03
Postoperative day 7 NT-proBNP	1425.4 ± 1289.8	1293.2 ± 1240.1	0.58
Major complications and poor outcomes (*n* = 15)			
Preoperative BNP	109.6 ± 2 08.6	101.2 ± 179.4	0.41
Postoperative day 1 BNP	556.1 ± 437.8	357.5 ± 433.7	0.74
Postoperative day 7 BNP	378.3 ± 613.9	255.9 ± 251.6	0.38
Preoperative NT-proBNP	1350.1 ± 1528.5	603.3 ± 667.4	0.14
Postoperative day 1 NT-proBNP	3677.1 ± 3638.5	2817.1 ± 3186.9	0.76
Postoperative day 7 NT-proBNP	2139.1 ± 1893.4	1289.6 ± 1614.3	0.13

Major complications and poor outcomes include new onset atrial fibrillation, ventricular tachycardia, ventricular fibrillation, requirement of intra-aortic balloon pump support, unscheduled cardiac readmission and late cardiac mortality within 1 year.
BNP = B-type natriuretic peptide; ICU = intensive care unit; SD = standard deviation.

Hutfless et al. [8] demonstrated that preoperative and peak postoperative BNP levels were associated with prolonged hospital stay and mortality within 1 year. However, these two studies were not adjusted for the risk factors that could influence the BNP level, NT-proBNP level, morbidity, and mortality. In our study, we demonstrated that postoperative Day 1 BNP and NT-proBNP concentrations were significantly higher in patients with prolonged ICU stay and hospitalization. However, the correlation became insignificant after adjusting for age, sex, renal function, and LVEF. Advanced age revealed good correlations with prolonged ICU stay and hospitalization in both univariate and multivariate logistic regression models. Interestingly, Khan et al. [16] have suggested that models for predicting outcome after CABG should be tested for potential interactions between age and risk factors. In our previous series, we also found that older patients had prolonged ICU stay and hospitalization following CABG surgery [17]. Moreover, Olsen et al. [18] recommended that cardiovascular risk prediction by NT-proBNP was affected by age. Therefore, we strongly suggest that risk factor adjustment be taken into consideration when using BNP and NT-proBNP in predicting outcome for patients who have undergone CABG surgery.

The BNP and NT-proBNP are mainly produced from the cardiac ventricles by increased ventricular wall stress and volume expansion. Morimoto et al [19]. showed that BNP concentration reached its peak during the 24 hours after surgery. They also demonstrated that peak BNP level was correlated with cardiac index, dopamine infusion rate, and cross-clamping time. However, the mechanism of the elevated postoperative BNP and NT-proBNP concentrations remains unclear. Plasma BNP concentration was found to increase remarkably in graft failure and heart failure after CABG surgery [7]. BNP level also was associated with endothelin-1 concentration in failing human hearts [20]. It is suspected that peak BNP concentrations reflect the condition of vascular circulation after CABG surgery. It is explained that high postoperative Day 1 BNP and NT-proBNP

Table 3 Patient characteristics in prolonged intensive care unit stay and/or hospitalization.

Variables	Yes (*n* = 38)	No (*n* = 38)	*p*
Age, y	68.2 ± 8.3	60.3 ± 10.4	0.03
Cr, mg/dL	1.3 ± 0.4	1.1 ± 0.3	0.009
LVEF, %	61.0 ± 10.9	61.1 ± 11.6	0.72
Off-pump surgery, *n* (%)	10 (26.3)	12 (31.5)	0.67
NYHA functional III and IV, *n* (%)	4 (10.5)	2 (5.2)	0.16
Male, *n* (%)	30 (78.9)	35 (92.1)	0.06
Preoperative BNP (pg/mL)	124.2 ± 199.4	83.3 ± 167.3	0.45
Postoperative day 1 BNP (pg/mL)	508.2 ± 546.6	215.6 ± 305.0	0.01
Postoperative day 7 BNP (pg/mL)	272.6 ± 367.8	251.4 ± 278.7	0.76
Preoperative NT-proBNP (pg/mL)	812.3 ± 1334.0	430.3 ± 619.2	0.23
Postoperative day 1 NT-proBNP (pg/mL)	3734.9 ± 3530.3	2004.6 ± 2728.5	0.03
Postoperative day 7 NT-proBNP (pg/mL)	1425.4 ± 1289.8	1293.2 ± 1240.1	0.58

BNP = B-type natriuretic peptide; Cr = creatinine; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 4 Multivariate correlation with prolonged intensive care unit stay and hospitalization.

Variables (n = 76)	Odds ratio (95% confidence interval)	p
Age, y	1.08 (1.01–1.16)	0.027
Cr, mg/dL	5.15 (0.92–28.72)	0.062
Postoperative day 1 BNP, pg/mL	1.00 (1.00–1.00)	0.809
Sex, male	0.41 (0.08–2.09)	0.283
LVEF, %	1.00 (0.96–1.06)	0.809

BNP = B-type natriuretic peptide; Cr = creatinine; LVEF = left ventricular ejection fraction.

concentrations were found in the current study. However, the high postoperative Day 1 BNP and NT-proBNP concentrations did not show significant correlation with prognosis after other risk factor adjustments in the current study.

Patients had emergent conditions including cardiogenic shock, emergent operation, severe left ventricular dysfunction, and congestive heart failure that increased morbidity and mortality after CABG surgery [3]. Emergent conditions were also associated with a higher BNP concentration [9]. Because elective CABG surgery was a prerequisite for enrollment in the current study, only 5% of patients revealed New York Heart Association functional class III and IV. Therefore, our preoperative BNP and NT-proBNP concentrations were lower than those in previous studies [8,15]. This may explain why preoperative BNP and NT-proBNP are not significantly associated with outcomes in the current study.

Limitations of study

The current study demonstrated that age was the most important factor for predicting prolonged ICU stay and hospitalization. Although BNP and NT-proBNP were used in predicting outcomes for patients who have undergone CABG surgery, we strongly suggest that risk factor adjustment be taken into consideration. However, the small sample size may result in statistical bias. Moreover, the long-term prognosis is unclear due to the 1-year follow-up period in the current study. Therefore, a large-scale study and long-term follow-up should be performed in the future.

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