Prognostic value of B-type natriuretic peptide in patients with chronic mitral regurgitation undergoing surgery: mid-term follow-up results

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Received 7 June 2012; received in revised form 10 August 2012; accepted 16 August 2012

Abstract

OBJECTIVES: The prognostic value of B-type natriuretic peptide (BNP) for surgical outcome in patients with mitral regurgitation (MR) has not been studied. The purpose of this study was to determine the prognostic value of BNP in patients with chronic severe MR, undergoing mitral valve surgery.

METHODS: In total, 117 patients with chronic severe MR undergoing surgery were evaluated from the MR registry of Seoul National University Hospital. Patients were excluded if they had acute MR or acutely decompensated heart failure, and significant renal, pulmonary, coronary or other significant valvular heart disease. The plasma BNP level assay and echocardiographic studies were done before surgery. Study endpoint was a composite of cardiac death and cardiac hospitalization during follow-up.

RESULTS: The median duration of the follow-up was 4.5 years, and the study endpoint was reached in 11 (9.4%) patients. Receiver-operating characteristic curve analysis yielded an optimal cut-off point of 125 pg/ml for BNP that distinguished patients with poor prognosis. Kaplan-Meier survival analysis with the log-rank test and multivariate Cox proportional hazards model showed that patients with BNP \geq 125 pg/ml had a worse clinical outcome after surgery (log rank 7.606, \textit{P} = 0.006; adjusted hazard ratio = 5.536 [95% confidence interval 1.189–25.788], \textit{P} = 0.029).

CONCLUSIONS: Among patients with chronic severe MR undergoing mitral valve surgery, BNP independently predicts the poor clinical outcome. The BNP measurement should be considered in the risk stratification of these patients.

Keywords: B-type natriuretic peptide • Mitral regurgitation • Mitral valve surgery

INTRODUCTION

In patients with severe mitral regurgitation (MR), surgery is the only way to improve long-term survival, preserve left ventricular (LV) function and improve exercise tolerance [1]. Therefore, determining surgical timing is critical in these patients. Although surgery is usually recommended based on clinical symptoms and/or LV function [2–4], the timing of surgery is still controversial [5]. This is partly due to the limitation of current load-dependent echocardiographic indicators and demonstrates the need for a new reliable parameter representing LV functional status.

B-type natriuretic peptide (BNP) is mainly secreted from the cardiac ventricles in response to volume and pressure overload [6]. Plasma levels of BNP are elevated with heart failure and can be a useful tool to distinguish cardiac causes of dyspnoea and to facilitate risk stratification such as predicting mortality and re-admission [7, 8]. In addition, BNP measurement is useful in patients with valvular heart disease. In patients with aortic valve disease including stenosis and regurgitation, increased levels of BNP correlate with severity, providing prognostic information [9, 10]. In patients with MR, plasma BNP levels increased with symptoms and severity, and the activation of BNP correlated with poor functional capacity and outcome [11–13]. A few studies have shown the prognostic value of plasma BNP levels in patients undergoing heart surgery, but the results were inconsistent and long-term prognosis was not included [14–17]. The aim of this study was to determine the prognostic value of BNP in patients with chronic severe MR undergoing mitral valve surgery.

MATERIALS AND METHODS

Study design and data collection

This was an observational single-centre study, and all patients were fully informed about the procedure and gave written informed consent. The study was carried out according to the principles of the Declaration of Helsinki and approved by the Clinical Research Institute of Seoul National University Hospital.
We evaluated 117 patients with chronic, organic, severe MR who were admitted for mitral valve surgery from 2006 to 2011 from our MR registry. The definition of severe MR was either regurgitant fraction (RF) ≥50% calculated by Doppler measurements with the regurgitant area ≥40% of the total left atrial (LA) area or wall-impinging jet swirling in the LA on colour Doppler as by the current guidelines [1]. Patients with MR <6 months or acutely decompensated heart failure were excluded. Patients were also excluded from the study if they had significant pulmonary disease, coronary artery disease, renal insufficiency (serum creatinine >1.5 mg/dl) or other significant valvular heart disease apart from tricuspid regurgitation (TR).

Baseline demographic data on gender, age, height, weight, body mass index (kg/m²), smoking status, diabetes mellitus (DM), hypertension, stroke, atrial fibrillation (AF) and valvular heart disease were collected at entry. Functional status based on New York Heart Association (NYHA) classification and echocardiographic parameters were assessed before and 6 months after surgery.

B-type natriuretic peptide assay

All the venous blood samples for the measurement of BNP levels were collected in ethylenediaminetetraacetic acid tubes within 1 week before surgery. Assays for BNP were performed with a Triage BNP test (Biosite Diagnostics Inc., San Diego, CA, USA), which is a fluorescence immunoassay for the quantitative determination of BNP in whole-blood and plasma specimens, with a turnaround time of 15 min and measurement range of 5–5000 pg/ml. This method correlates the fluorescence measurement to BNP concentration by using an internal calibration curve. All BNP samples were collected at rest just before echocardiographic measurement.

Echocardiography

All patients underwent standard two-dimensional and Doppler echocardiography before and 6 months after surgery. Echocardiographic examinations were performed with commercially available equipment (Vivid 7, GE Medical System, Horten, Norway). LA dimension, LV end-diastolic dimension (LVEDD) and end-systolic dimension (LVESD), and LV wall thickness were measured using M-mode tracings according to American Society of Echocardiography recommendations [18]. The biplane Simpson’s method was used to measure the LV ejection fraction (LVEF). Quantitation of MR was performed by the quantitative Doppler method using mitral and aortic stroke volumes (SV). Regurgitant volume was calculated from the difference between total and forward SV, and RF was calculated as the ratio of regurgitant volume to total SV. Pulmonary artery systolic pressure (PASP) was derived from TR jet velocity and right atrial pressure estimated at rest by the response of the inferior vena cava to deep inspiration.

Outcome data

The endpoint of the study was a composite of cardiac death and cardiac hospitalization during follow-up, as represented by independent patients. Patients who died during the follow-up period were not included in the cardiac hospitalization event. If a patient experienced multiple hospitalization events for cardiac diseases, only the first admission event was counted. Data were obtained until March 2012, and follow-up was 100% complete in all patients by clinic visit or phone calls.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± standard deviations (SD) or medians with interquartile ranges (IQR). Group comparisons were performed with Student’s t-test, the matched-pair t-test or the Mann–Whitney U-test. The χ² test or Fisher’s exact test was used for categorical variables. Pearson’s correlation coefficient was used to assess the relationship between BNP and echocardiographic parameters, and linear regression analysis was used to check the multicollinearity. The cut-off values for BNP or other continuous variables were set according to the receiver-operating characteristic (ROC) curve analysis, and the value showing the maximum likelihood ratio in the curve was established as the cut-off point. Survival analysis was assessed using the Kaplan–Meier method with the log-rank test and adjusted Cox proportional hazards model for the comparison of time to the event. The Cox proportional hazards assumption was checked by the goodness-of-fit test. Univariate Cox regression analysis was performed to identify independent predictors of poor outcome, and all univariate predictors with P-value <0.2 were entered into the multivariate analysis. Univariate and multivariate predictors were also applied for patients with NYHA functional class I or II, as the decision for surgery is critical in these asymptomatic or mildly symptomatic patients. All statistical analyses were performed with software SPSS 18.0 (SPSS Inc., Chicago, IL, USA), and a P-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of the study population are summarized in Table 1. Aetiology of MR was: degenerative in 85 (72.6%) patients, rheumatic in 24 (20.5%) and others in 8 (6.8%). The median BNP value of all 117 patients was 95 pg/ml (IQR 46–204.5). Seventy-five (64.1%) patients underwent mitral repair, and 42 (35.9%) underwent mitral replacement. Forty-three (36.8%) patients underwent tricuspid annuloplasty for concomitant TR.

Patients were divided according to the cut-off level of BNP, which was assessed by ROC curve analysis to predict the occurrence of the study endpoint. The area under the ROC curve was 0.679, and the optimal cut-off level of BNP was 125 pg/ml (P = 0.05). Patients with BNP level ≥125 pg/ml had a higher prevalence of AF (54.9 vs 22.7%, odds ratio = 4.139 [95% confidence interval, CI 1.865–9.187], P < 0.001) and were slightly older and more symptomatic; however, the differences were not statistically significant. Gender, hypertension, DM, type of mitral surgery and tricuspid surgery were not different.

Correlations between BNP and echocardiographic parameters were investigated. LA dimension (r = 0.389, P < 0.001) and PASP...
who was resuscitated.

sudden cardiac arrest due to ventricular heart failure in 7 (6.0%), ventricular tachycardia in 1 (0.9%) and (7.7%) patients were readmitted for cardiac disease including cause of death was sudden cardiac death for both patients. Nine of deaths during the follow-up period was 2 (1.7%), and the study endpoint occurred in 11 (9.4%) patients. Total number LVEF and LVESD were not correlated with BNP.

For survival analysis, the BNP level was dichotomized according to the cut-off value. Among 66 patients with BNP <125 pg/ml, 2 (3.0%) patients met the study endpoint when compared with 9 (17.6%) patients of the group with BNP ≥125 pg/ml. The result of the Kaplan–Meier analysis showed significant difference in event-free survivals between the two groups (log rank 7.606, P = 0.006; Fig. 1).

Subgroup analysis was performed for 95 (81.2%) patients who were asymptomatic or mildly symptomatic (NYHA functional class I or II; Fig. 2). The result showed a significant tendency for patients with BNP level ≥125 pg/ml to be more prone to develop cardiac events (log rank 4.169, P = 0.041).

### Predictor of worse outcome

Table 2 shows the results of univariable Cox regression analyses. Univariate markers of the worse clinical outcome were LVEF ≤50% (hazard ratio [HR] = 4.643 [95% CI 1.228–17.548], P = 0.024) and BNP ≥125 pg/ml (HR = 6.518 [95% CI 1.406–29.220], P = 0.017). LVESD >55 mm (HR = 3.951 [95% CI 0.852–18.314], P = 0.079) showed marginal significance. Multivariable Cox regression analysis demonstrated that BNP ≥125 pg/ml (HR = 5.536 [95% CI 1.189–25.788], P = 0.029) was an independent determinant of event-free survival (Table 3).
NYHA functional class, LVESD, LA dimension and PASP were significantly improved 6 months after surgery in both groups, whereas LVEF was decreased (Table 4).

**DISCUSSION**

In the present study, we showed that elevated plasma BNP levels in patients with chronic severe MR undergoing surgery predict the poor postoperative outcome. Although some studies have reported the relationship of BNP with the severity and outcome of MR, this may be the first study that investigated preoperative plasma BNP levels with the postoperative mid-term clinical outcome.

Since the first discovery of BNP, it has attracted much attention for its various clinical implications, and the possible roles of BNP in patients with MR have been intensively studied. In a
study by Sutton et al. [11], the BNP level was higher in symptomatic patients and was associated with RF, MR score and width of the vena contracta. Detaint et al. [12] investigated 124 patients with chronic organic MR, of whom about 70% were asymptomatic. In that study, a higher BNP level independently predicted the poor clinical outcome during 5 years of the follow-up, but BNP activation in organic MR was not a surrogate for MR degree, but rather, reflected primarily ventricular and atrial consequences [19]. Pizarro et al. [13] reported that BNP discriminates prognosis better than the echocardiographic parameters, in a well-designed prospective study. In that study, the independent prognostic markers were BNP level, LVESD index and effective regurgitant orifice area. The significance of that study was the incremental prognostic value of BNP and its possible application to risk stratification.

Although these studies indicated the clinical usefulness of BNP in patients with chronic MR, the relationship between BNP level and surgical outcome has received little attention. Few studies focused on the postoperative prognostic value of BNP, but they have significant drawbacks. Huttfluss et al. [15] investigated the utility of BNP for predicting the postoperative outcome in 98 patients undergoing open heart surgery, but the clinical outcome in that study was limited to 1 year after surgery, and only 4 underwent mitral surgery. In a study of Filsoffi et al. [17], long-term prognosis was not included and even the relationship between BNP level and immediate postoperative outcome was not definite. Krishnaswami et al. [20] conducted an observational study in 52 patients with severe MR, and concluded that there was no significant change in BNP activation 3–6 months after corrective surgery. Although they reported the association between postoperative BNP levels and LVEF, suggesting the clinical importance of BNP in patients with severe MR, more direct data are required. In contrast, all patients in our study underwent successful surgery and the median follow-up duration was 4.5 years, which was much longer than that of previous studies.

The results of our study could have a significant clinical implication for risk stratification in patients with chronic severe MR. American College of Cardiology/American Heart Association guidelines and other recent studies recommend surgery for patients with MR who present symptoms or LV dysfunction [1, 21]. However, after development of symptoms or LV dysfunction, worse postoperative outcome is predicted [2–4, 22]. Moreover, for patients with asymptomatic severe MR, there is scarce evidence for objectivizing the best treatment strategy regarding early surgery vs watchful waiting. These uncertainties provoked controversies on the optimal timing of surgery and led to the need for novel and reliable prognostic markers. As BNP ≥125 pg/ml was an independent predictor of poor prognosis in our study, BNP measurement should be considered for assessing postoperative outcome and might be useful for facilitating the timely decision for surgery. Additionally, we compared the clinical outcome among patients with no or minimal symptoms, and elevated BNP levels were associated with poor prognosis in these patients (Fig. 2). This result lends support to the usefulness of BNP measurement even in patients without severe symptoms.

In the multivariate analysis, LVEF showed a marginally significant P-value for the study endpoint. LVEF is a well-known preoperative predictor of the surgical outcome in MR, and the result of our study is in accordance with previous studies [2–4]. LVESD and preoperative symptoms, which have been validated for their prognostic values by many previous studies [13, 22], were not significant predictors in our study. However, these results should not be interpreted as LVESD and preoperative symptoms are not important predictors. This is partly because the majority of our patients had normal LVESD and had no or minimal symptoms.

**Study limitation**

The present study was subject to the following limitations. First, the sample size was relatively small, which is an inevitable shortcoming in the field of valvular heart disease. Although we could not evaluate many probable predictors because of the infrequent study endpoint, the strong predictive value of BNP levels was confirmed by univariate and multivariate analyses. Secondly, the duration of follow-up was diverse. It arises from the characteristic of our study design. However, the median follow-up duration of this study was 4.5 years, which was sufficient to estimate the mid-term postoperative outcome. Thirdly, although other significant valvular heart diseases were excluded, patients with concomitant TR were not excluded and 43 (36.8%) patients underwent tricuspid annuloplasty. These patients might have influenced the result of our study, as TR in patients with mitral valve disease is associated with poor prognosis [23], and elevated BNP levels is known as an independent predictor of outcome after tricuspid valve surgery [24]. However, in the present study, it was not statistically significant whether concomitant surgery for TR was done or not. The influence of tricuspid annuloplasty on study endpoint was not significant in univariate analysis, and the result of multivariate analysis remained unchanged after adding this factor. Fourthly, our study was not a randomized trial and only included the patients who underwent successful surgery. We were able to draw a conclusion that measurement of BNP could help discriminating patients with poor outcome, but it needs to be confirmed by the larger study or randomized controlled trial [25].

**Conclusion**

Among patients with chronic severe MR undergoing surgery, a preoperative BNP level ≥125 pg/ml independently predicts poor clinical outcome. BNP measurements should be considered in risk stratification of these patients.

**ACKNOWLEDGEMENTS**

The authors thank Ha-Young Joo, a research nurse, for her valuable help.

**Funding**

This study was supported by the National Research Foundation of Korea (NRF), grant funded by the Korean government (MEST; 2010-0021554, 2011-0025796).

**Conflict of interest:** none declared.
REFERENCES


