Brain natriuretic peptide as a predictor of cardioembolism in acute ischemic stroke patients

- BNP stroke prospective study -

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Abstract

Background and purpose: Our previous retrospective study demonstrated that a brain natriuretic peptide (BNP) level of >140pg/ml on admission was useful to distinguish cardioembolism (CE) from non-CE. The aim of the present study was to prospectively investigate the utility of this predefined threshold.

Method: Two hundred and twenty-one consecutive patients were prospectively enrolled. Patients were measured BNP levels and on admission, and classified according to low BNP (≤140.0pg/ml) or high BNP (>140.0pg/ml) levels. Final diagnosis of stroke subtype on discharge was made using TOAST criteria. Measured parameters included the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CE in the High BNP group.

Results: There were 81 patients in the High BNP group and 140 patients in the Low BNP group. A total of 76(34.4%) patients were diagnosed with CE, including 59(72.8%) patients in the high BNP group and 17(12.1%) patients in the low BNP group ($p<0.001$). A BNP level >140.0pg/ml corresponded to a sensitivity of 77.6%, specificity of 84.8%, PPV of 72.8%, and NPV of 87.9% for a diagnosis of CE.

Conclusion: A BNP level of >140.0pg/ml on admission in patients with acute ischemic stroke is a strong biochemical predictor for CE.

Introduction

Brain natriuretic peptide (BNP), a 32-amino acid polypeptide containing a 17-amino acid ring structure that was isolated from porcine brain in 1988, is a diuretic factor with vasodilator activity(1). It is primarily released from ventricular myocardium and is useful for the assessment of cardiac dysfunction(2). A simple rapid BNP assay has recently been developed that can determine BNP levels at bedside about 15 minutes. Several authors have described the utility of this rapid assay in the emergency diagnosis of heart failure(3)(4).

BNP levels are elevated in patients with acute ischemic stroke(1, 5-8), particularly in those with atrial fibrillation (AF)(9). In a previous retrospective study, we reported that BNP level >140.0 pg/ml on admission in patients with acute ischemic stroke patients was a predictor of cardioembolism (CE) with high sensitivity (80.5%) and high specificity (80.5%)(10). The goal of the present study was to prospectively investigate the utility of this predefined threshold using a rapid BNP assay.

Subjects and Methods

Between January 2008 and December 2008, 221 consecutive patients with acute ischemic stroke within 24 hours of onset were prospectively enrolled. Blood samples were taken on admission for use in a rapid BNP assay within 1 hour after admission, and patients were classified according to low BNP (≤140.0 pg/ml) or high BNP (>140.0 pg/ml) levels on admission (Figure 1). The following factors were also assessed: age, gender, vascular risk factors, old myocardial infarction, renal dysfunction, blood pressure, National Institutes of Health Stroke Scale (NIHSS) score(11) on admission,

and ejection fraction (EF) on echocardiography. Hypertension was defined as the use of antihypertensive agents, systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg before stroke onset. Diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, fasting blood glucose level >126 mg/dl, or glycosylated hemoglobin level >6.4%. Hyperlipidemia was defined as the use of antihyperlipidemic agents or serum cholesterol level >220 mg/dl. Smoking habit was defined as a history of smoking during the preceding three months. AF was defined as a chronic AF or paroxysmal AF.

After admission, all patients underwent duplex carotid ultrasonography, transcranial Doppler, transthoracic echocardiography and/or transesophageal echocardiography, 12-lead electrocardiogram (ECG), continuous ECG monitoring, 24-hour Holter ECG, magnetic resonance angiography and/or computerized tomographic (CT) angiography and/or cerebral angiography.

Final diagnosis of stroke subtype was made according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) stroke classification(12), and patients were divided into two groups : those with cardioembolism (CE group) and those without (non-CE group).

This study followed the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Kawasaki Medical School Hospital.

Brain natriuretic peptide measurements

Whole blood sample were collected on admission into tubes containing ethylenediamine tetraacetic acid, and BNP levels were immediately measured using a fluorescent immunochromatographic assay (SHIONOSPOT® BNP, Shionogi & Co., Ltd., Osaka, Japan). This assay allows quantification of BNP within 15 minutes. The

normal BNP value at our institution is <18.4 pg/ml, and the assay detection limit is 5.9 pg/ml. The intra-assay coefficient of variation ranges from 4.2 to 9.8%, and the inter-assay coefficient of variation ranges from 7.0 to 8.1%.

Statistical analysis

Clinical characteristics were compared between the High BNP and Low BNP groups using the chi-squared and Mann-Whitney *U* tests. The Mann-Whitney *U*-test and linear regression analysis were used to examine factors associated with whole blood BNP level. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (positive LR), negative likelihood ratio (negative LR) and odds ratio for a diagnosis of CE were also calculated. Furthermore, the optimal cut-off points of BNP to discriminate the CE group from the non-CE group were obtained using receiver operating characteristics (ROC) curves. Multivariate logistic regression analysis was performed to determine factors independently associated with CE using variables with $p<0.1$ on univariate analysis. Furthermore, we divided the CE patients into two groups according to the time of blood sampling (≤12 hour and >12 hour). Statistical analysis was performed using a commercially available software package [SPSS, version 17 (SPSS Japan Inc., Tokyo, Japan)]. Differences were considered statistically significant at a level of $p<0.05$.

Results

A total of 221 patients (141 males; mean age, 72.9 years) were enrolled in the present study. The median [interquartile range (IQR)] of NIHSS score on admission was 6 (2-15.75). The mean ± SD interval of time from stroke onset to blood sample collection was 8.2±7.4 hours. The mean±SD BNP level was 214.5±358.3 pg/ml.

The High BNP group consisted of 81 (36.7%) patients, and the Low BNP group consisted of 140 (63.3%) patients (BNP level median of [IQR] was 321.8 [216.0-635.0] vs. 34.7 [5.9 - 66.2] pg/ml, $p<0.001$). BNP level positively correlated with several clinical variables, including age (r=0.194, $p=0.004$) and NIHSS score on admission (r=0.216, $p=0.001$).

Clinical characteristics of two groups are summarized in Table 1. The frequency of female gender (44.4% for High BNP group vs. 31.4% for Low BNP group, $p<0.001$), age (mean 77.7±12.0 vs. 70.1±12.1 years, <0.001), AF (46.9% vs. 6.4%, $p<0.001$), renal dysfunction (17.3% vs. 7.2%, p=0.026) and NIHSS score on admission (median [IQR] 12 [3-20] vs. 5 [2-11], $p<0.001$) were higher in the High BNP group than in the Low BNP group. In contrast, the median (IQR) EF was significantly lower in the High BNP group than in the Low BNP group (59 [50-64]% vs. 66 [61-68.25]%). There were no significant differences in frequency of hypertension, diabetes mellitus, hyperlipidemia, old myocardial infarction, blood pressure, and interval time from stroke onset to BNP measurement between the two groups.

Seventy-six (34.4%) patients were diagnosed with CE, while 145 patients (65.6%) were classified as non-CE (33 as small-vessel occlusion, 22 as large artery atherosclerosis, 74 as other strokes, and 16 as unknown). The mean±SD BNP level was higher in the CE group than in the non-CE group (508.3±461.2 vs. 44.5±37.6 pg/ml).

Sub-group analysis of the non-CE group showed BNP levels of 55.4 pg/ml in those with large artery atherosclerosis, 138.4 pg/ml in those with small-vessel occlusion, 125.5 pg/ml in those with other types of stroke, and 168.0 pg/ml in those with unknown-type stroke (Figure 2).

Of the patients with CE, 46 patients had chronic AF, 20 had paroxysmal AF, 6 had patent foramen ovale, 2 had left atrial myxoma, 1 had nonbacterial thrombotic endocarditis, and 1 had dilated cardiomyopathy. CE occurred in 59 (72.8%) patients in the high BNP group and in 17 (12.1%) patients in the low BNP group (p<0.001).

A BNP level >140.0 pg/ml was associated with a sensitivity of 77.6%, specificity of 84.8%, PPV of 72.8%, NPV of 87.9%, positive LR of 5.1, negative LR of 0.26 and odds ratio 19.4 (95% CI, 10.2 - 42.0) for a diagnosis of CE (Table 2).

Of the 17 patients with CE who had low BNP levels, 6 patients had paroxysmal AF, 5 had paradoxical brain embolism, and 1 had left atrial myxoma. Of the 21 patients without CE who had high BNP levels, 7 had chronic renal failure, 5 had old myocardial infarct, and 2 had Takotsubo cardiomyopathy (Table 3).

The ability of BNP to distinguish CE from non-CE was assessed using ROC curves analysis (Figure 3). A BNP level of 142.5 pg/ml was identified as the optimal cutoff value with a sensitivity of 77.6%, specificity of 84.8%, with an area under the curve of 0.858 (95% CI, 0.81-0.91). Seven variables identified on univariate analysis at p<0.1 were selected. Multivariate logistic regression analysis demonstrated that AF and BNP>140 pg/ml were independent factors associated with CE (Hosmer-Lemeshow 0.628) (Table 4.) .

With respect to the CE groups, the mean ± SD BNP value of patients with the blood sampling time ≤12 hour than that of 12 hours (358.3±51.4 pg/ml vs. 518.6±73.7 pg/ml,

p=0.011) .

Discussion

The present study demonstrated that a predefined threshold of a BNP >140.0 pg/ml was associated with a sensitivity of 77.6%, a specificity of 84.8%, a PPV of 72.8%, a NPV of 87.6%, a positive LR of 5.1, a negative LR of 0.26, and an odds ratio of 19.4 (95% CI, 10.2 - 42.0) for a diagnosis of CE.

In a previous study, we reported that a BNP level >140.0 pg/ml could discriminate CE from non-CE patients, which was incompatible with findings from other studies(5, 6). Montaner et al. demonstrated that the optimal cutoff point of BNP to distinguish between CE and non-CE was 76 pg/ml, which corresponded with a sensitivity of 72% and specificity of 68% (10). Similarly, Yukiiri et al. reported that the optimal cutoff point of BNP to distinguish between CE and non-CE was 77 pg/ml, which corresponded with a sensitivity of 75.8% and a specificity of 76.8%(6). The reason for this discrepancy between the present study and these previous studies may be attributed to various factors, including differences in the study population. Age correlates with BNP level(13), and the study population was older in the present study when compared with those previous studies. Furthermore, the half-life of BNP is approximately 20 minutes, and BNP level increase in the acute phase of stroke, and decline substantially thereafter(14)(15). In the present study showed that there is time-dependent difference in BNP levels in CE patients. Therefore, these time-dependent changes in BNP level may also account for difference between the present study and previous studies, as blood samples were obtained upon admission in the present study but were taken on the first morning after admission in a previous report(5).

Elevated BNP was a false-positive predictor of CE in patients with chronic renal failure, prior myocardial infarction, and Takotsubo cardiomyopathy, which is consistent

with reports describing elevation of BNP levels under these circumstances(16). Therefore, the presence of these conditions should also be considered in patients with high BNP levels on admission. Low BNP was a false-negative group predictor of non-CE in patients with paroxysmal AF. Okada et al.(17) reported that the optimal cutoff BNP level to distinguish newly diagnosed AF from non-AF patients was 85.0 pg/ml. Therefore, if BNP level is >85.0 pg/ml, a diagnostic workup with continuous ECG monitoring and repeated 24-hour Holter ECG should be performed to detect paroxysmal AF.

This study had several limitations. First, the presence of low BNP in five patients with CE could not be explained. Second, the study may have failed to detect some patients with paroxysmal AF in the High BNP group. Third, BNP level is not a component of the TOAST classification of risk of CE in the absence of AF or paroxysmal AF. Thus, further study to evaluate difference of BNP level within each TOAST classification of risk factors for CE would be of benefit. Finaly, the BNP level is affected by blood sampling time, old age, heart failure, old myocardial infarction, and renal dysfunction. Therefore, we should pay attention to such patients when BNP value is assessed.

In conclusion, a BNP level of >140.0 pg/ml on admission in patients with acute ischemic stroke is a strong biochemical predictor for CE.

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Figure legends

Figure 1. Algorithm of diagnostic stroke subtypes using whole blood BNP.

Figure 2. BNP level of stroke subtypes

CE = cardioembolism, LAA= large artery atherosclerosis, SVO= small-vessel occlusion

The mean±SD BNP level and stroke subtypes.

Figure 3.

ROC curve analysis. The optimal cut-off value, and sensitivity and specificity required to distinguish CE from non-CE was BNP 142.5 pg/ml, which corresponded with a sensitivity of 77.6% and a specificity of 84.8%, The AUC using BNP to predict CE was 0.858 ($p<0.001$)