Factors Affecting the B-Type Natriuretic Peptide Levels in Stroke Patients
Ayhan Saritas, Zeynep Cakir, Mucahit Emet, Mustafa Uzkeser, Ayhan Akoz, Hamit Acemoglu

Abstract
Introduction: This study aims to evaluate the relationship between increased B-type natriuretic peptide (BNP) levels in stroke patients and clinical parameters such as age, sex, medical history, blood pressure, Glasgow Coma Score (GCS) and National Institutes of Health Stroke Scale (NIHSS). Materials and Methods: This is a prospective study of 123 stroke patients at the Emergency Department. The patients were divided into 3 groups according to the NIHSS scores. The analysis of the mean difference between continuous variables and plasma BNP levels was assessed using the Mann-Whitney and Kruskal-Wallis. Spearman correlation analysis was performed for BNP and other clinical parameters. Results: The BNP levels of patients who had a medical history of hyperlipidaemia, chronic obstructive pulmonary disease, diabetes mellitus and coronary artery disease were significantly higher than in patients without these diseases. Patients who had atrial fibrillation (AF) in their electrocardiography had significantly higher BNP levels than patients with sinus rhythm. A positive correlation was found between plasma BNP levels with age, blood urea nitrogen (BUN) and NIHSS and a negative correlation was found between plasma BNP levels and GCS. There was a significant difference between the BNP levels of NIHSS groups. Conclusion: We consider that plasma BNP levels could help us in interpreting the general clinical severity, functional capacity and clinical progress of stroke patients at the time of admission in the Emergency Department. In evaluating the high BNP levels in stroke patients, we must keep in mind that age, AF, BUN and medical history can affect the BNP levels.

Key words: Emergency Department, Progress, Relationship

Introduction
The term “stroke” comprises all diseases in which a region of the brain is transiently or continuously affected by ischaemia or haemorrhage, and/or in which there are pathologies in the vessels nourishing the brain. Besides being a serious health problem due to its high mortality and morbidity, stroke is a very significant social and economical problem.

B-type natriuretic peptide (BNP), which has diuretic, natriuretic and vasodilatory effects, is a peptide-structured neurohormone released from cardiac ventricles in response to volume and pressure loads. Studies performed in the last few years have shown that the plasma BNP level has an important place in the diagnosis and treatment of cardiovascular diseases, especially in cardiac failure and acute coronary syndrome. The level of BNP correlates with sex, age, renal functions, wide left ventricular diameter, atrial fibrillation (AF), acute coronary syndrome and high pulmonary pressure. The BNP levels can be measured at the bedside, rendering the follow-up of patients at the emergency unit and the ward easy.

Due to its biological features, BNP is thought to possess a significant role in the haemodynamic regulation in the acute phase of stroke. Comparable evidence supports that acute stroke patients can exhibit several cardiac abnormalities such as myocardial necrosis and arrhythmia. These cardiac changes may be related to the increased BNP production by the heart. In this prospective study, we aimed to evaluate the relationship between increased BNP levels in stroke patients and clinical parameters such as age, sex, medical history, blood pressure, Glasgow Coma Score (GCS) and National Institutes of Health Stroke Scale (NIHSS).

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Materials and Methods

Stroke patients who were admitted to our emergency department within the first 4 to 12 hours of symptom onset were included as the study group. The diagnosis of stroke was established both clinically and radiologically [brain computed tomography (CT)]. Past and present clinical history, including medication, was obtained by interviewing the patient or a family member in cases where patients were aphasic or unconscious. The hospital records were also reviewed for the medical history. Patients were monitored closely. All patients underwent a comprehensive clinical evaluation, standard electrocardiography (ECG), chest X-ray, blood pressure measurement, complete blood count and routine biochemical analyses such as liver and renal function tests. The stroke patients underwent CT of the brain and scoring of the neurological deficits on the GCS and NIHSS. The patients were divided into 3 groups according to the NIHSS scores (0-6 points: good prognosis, 7-15 points: intermediate, 16-42 points: bad prognosis).

The blood samples for the analysis of BNPs were taken in admission through an intravenous cannula into EDTA vacuum tubes. The level of plasma BNP was measured by the fluorescence immunoassay method.

This is a prospective study of patients with stroke who were admitted at the emergency department between June 2006 and February 2009. Data were analysed using the SPSS-15 software. Data were given as numbers, percentages and standard deviation. The analysis of the mean difference between continuous variables and plasma BNP levels was assessed using the Mann-Whitney and Kruskal-Wallis. Spearman correlation analysis was performed for BNP and other clinical parameters. $P < 0.05$ was considered statistically significant.

Results

A total of 123 patients, with a mean age of 65 ± 14 years (range, 25 to 85), were included in the study. Seventy (56.9%) were women. Haemorrhage was found in the CT evaluation of 37 (30.1%) patients. The mean systolic blood pressure (MSBP), the mean diastolic blood pressure (MDBP) and the mean arterial blood pressure (MAP) were found to be 154.3 ± 34.5 mmHg, 93.6 ± 20.1 mmHg and 113.8 ± 23.8 mmHg, respectively. Basic clinical data, such as demographics, GCS and NIHSS of the patients, are shown in Table 1.

The following were found in the medical history of patients: 13% had suffered from stroke, 12% had hyperlipidaemia, 2% had renal insufficiency, 7% had chronic obstructive pulmonary disease (COPD), 10% had diabetes mellitus (DM) and 15% had coronary artery disease (CAD). The mean BNP levels of patients who had a medical history of hyperlipidaemia, COPD, DM and CAD were significantly higher than in patients without these diseases ($P=0.006$, $P=0.01$, $P=0.046$ and $P=0.004$, respectively). Patients who had AF in their ECG had significantly higher BNP levels than patients with sinus rhythm ($P<0.0001$). Median BNP levels in patients with haemorrhagic stroke and with ischaemic stroke were 83.9 pg/mL and 148.0 pg/mL, respectively.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>BNP (pg/mL)</th>
<th>Median (IQR)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/Female</td>
<td>89 (208)/133 (343.9)</td>
<td>NS</td>
</tr>
<tr>
<td>ECG</td>
<td>AF/Sinus</td>
<td>640 (599.5)/72 (183.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>+/-</td>
<td>320 (630.5)/98 (223)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>+/-</td>
<td>549 (680)/94 (211.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>COPD</td>
<td>+/-</td>
<td>624 (555)/94 (224)</td>
<td>0.010</td>
</tr>
<tr>
<td>DM</td>
<td>+/-</td>
<td>455 (915.5)/98 (223)</td>
<td>0.046</td>
</tr>
<tr>
<td>CAD</td>
<td>+/-</td>
<td>501 (656)/89 (214.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>CT</td>
<td>+/-</td>
<td>84 (141.6)/148 (423)</td>
<td>NS</td>
</tr>
<tr>
<td>NIHSS (0-42points)</td>
<td>0-6</td>
<td>57 (158.4)</td>
<td>0.036*</td>
</tr>
<tr>
<td></td>
<td>7-16</td>
<td>84 (213.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17-42</td>
<td>270 (568.5)</td>
<td></td>
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<tr>
<td>Prognosis</td>
<td>Discharged</td>
<td>87 (224.5)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td>154 (273.1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Demographic and Clinical Characteristics of Patients

Table 2. Relationship between Mean BNP levels and Clinical Characteristics

*IQR: interquartile range; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CAD: coronary artery disease; CT: computed tomography; ECG: electrocardiography; NIHSS: National Institutes of Health Stroke Scale; NS: not significant*
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(P = 0.181). The relationship between patients’ characteristics and BNP levels is shown in Table 2. While there were no significant correlations between sex, blood pressure, length of hospital stay and mean plasma BNP levels, a positive correlation was found between plasma BNP levels with age, blood urea nitrogen (BUN) and mean NIHSS (r = 0.3, P < 0.0001; r = 0.4, P < 0.0001; r = 0.3, P < 0.0001) (Fig. 1) and a negative correlation was found between plasma BNP levels and GCS (r = -0.03, P < 0.0001) (Fig. 2). The clinical correlation analysis between mean BNP levels and clinical parameters is shown in Table 3. There was a significant difference between mean BNP levels of NIHSS groups (P < 0.036).

Discussion

The main source of BNP is the cardiac ventricles. It is synthesised by ventricular muscle cells in response to the end diastolic pressure and volume increases. BNP regulates the fluid-electrolyte equilibrium by its effect on the central and peripheral nervous system. It has diuretic, natriuretic and vasodilatory effects. Diuresis and natriuresis is achieved by the effect over renal haemodynamics or by its direct effect on renal tubules. It has been shown that acute ischaemia leads to changes in autonomic functions. For example, stroke increases cardiac arrhythmias and myocardial injury. It is thought that BNP has a special role in the haemodynamic regulation in the acute phase of stroke due to its biological features.

In their study, Suzuki et al found a positive correlation between the plasma BNP levels and age. In another study, however, McLoan et al found the measurements of BNP levels in older female patients to be 3 times greater than the BNP levels in younger male patients in the intensive care unit. We found a significant positive correlation between plasma BNP levels and age in our study as well. The BNP levels in female patients were higher than in males, but the difference was not significant. This result is consistent with those in the literature, supporting that with an increase in age, the mean plasma BNP levels increase in parallel to the decrease of left ventricular compliance.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.314</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.035</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-0.061</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>-0.044</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>0.404</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.039</td>
<td>NS</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>-0.334</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>-0.088</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3. Correlation between BNP levels and Clinical Parameters

BNP: B-type natriuretic peptide; NS: not significant; NIHSS: National Institutes of Health Stroke Scale

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Fig. 1. Positive correlation between BNP and age. (BNP: B-type Natriuretic Peptide)

Fig. 2. Negative correlation between BNP and GCS. (BNP: B-type Natriuretic Peptide, GCS: Glasgow Coma Score)
Studies by Estrada et al.\textsuperscript{20} and Eguchi et al.\textsuperscript{21} showed increased plasma BNP levels in the acute phase of stroke. A positive correlation was found between plasma BNP levels and blood pressure. Nakagawa et al.\textsuperscript{22} reported that the BNP levels in patients with intracranial haemorrhage (ICH) increased to the levels displayed by patients who had ischaemic stroke. Similarly, in this study, there was a positive but weak correlation between the initial BNP levels of ischaemic stroke patients and MAP values. Wei et al.\textsuperscript{23} found a positive correlation between plasma BNP levels and MSBP. We found the mean BNP levels of stroke patients to be high, similar to that in the literature, but there was no significant correlation between BNP levels of stroke patients and patients with ICH. Furthermore, there were no correlations between MSBP, MDBP, MAP and BNP levels.

The prognostic value of natriuretic peptides in patients with cardiac insufficiency and acute coronary syndrome has been shown previously.\textsuperscript{24-31} Makikallio et al.\textsuperscript{25} found that there was a relationship between increased mortality and high BNP levels in the acute phase of stroke. It was also shown that high plasma BNP levels were a better sign than the other risk factors for mortality after stroke. Moreover, it has been reported that patients with high BNP levels have a 4-fold higher mortality risk. However, no significant correlation has been shown between BNP levels and GCS. Also, Makikallio et al.\textsuperscript{25} reported that BNP measurement in stroke patients could be used for risk classification and determining the increased mortality risk. Svi et al.\textsuperscript{32} found that there is a relationship between plasma BNP levels and the development of cerebral ischaemia and neurological deficits. A strong correlation was found between GCS and BNP levels of the patients. BNP measurement in stroke patients can be a prognostic factor. In our study, the mean BNP levels of the patients who died were higher than those who survived, but the difference was not significant. Furthermore, no relationship was found between mean BNP levels of the patients and the length of hospital stay. There was a negative significant correlation between mean plasma BNP levels and GCS.

The NIHSS score, which is ideal for neurological examination, changes between 0 and 42 and is in correlation with the extent of the infarct. The NIHSS score is a diagnostic factor for the evaluation of the seriousness at the beginning of the stroke, in addition to being a predictor of a worse prognosis and mortality risk. An NIHSS score of ≥16 is related with mortality, a bad prognosis and a bad functional capacity. On the other hand, an NIHSS score of ≤6 is related with better prognosis and better functional capacity.\textsuperscript{15} Tomita et al.\textsuperscript{33} reported a positive correlation between plasma BNP levels and NIHSS scores of stroke patients. Giannakoulas et al.\textsuperscript{34} found no correlation between NIHSS and BNP. In our study, there was a significant positive correlation between mean NIHSS scores and mean plasma BNP levels. Furthermore, among the patients with NIHSS scores of ≥16, the BNP levels were significantly different than those of the other 2 groups.

As a result, we consider that mean plasma BNP levels could help us in interpreting the general clinical severity, functional capacity and clinical progress of the stroke patients at the time of admission in the emergency department. In evaluating the high BNP levels in stroke patients, it must be kept in mind that age, AF, BUN and medical history of patients (especially CAD, DM, COPD and hyperlipidaemia) can affect the BNP levels.

REFERENCES


