Original Article

Role of brain natriuretic peptide as a novel prognostic biomarker in acute ischemic stroke

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Abstract

Aim: We investigated to study the prognostic importance of brain natriuretic peptide (BNP) in ischemic stroke. **Materials and Methods:** We prospectively enrolled 100 patients with acute ischemic stroke and measured plasma BNP levels and compared with age- and sex-matched healthy controls. Risk factors, biochemical parameters, lipid profile, carotid and vertebral Doppler, imaging, and cardiac evaluation were done. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score on admission and functional disability by Barthel Index (BI) at 3 months. Ischemic stroke subtype was classified according to the Oxfordshire Community Stroke Project (OCSP). Data were entered in MS Excel, and appropriate statistical analysis was done using the SPSS software version 21.0. A $P = 0.05$ was considered as significant. **Results:** Mean age of patients was 55.17 ± 11.37 years with a male:female ratio 3:1. OCSP showed total anterior circulation infarct (TACI) 35, partial anterior circulation infarct 9, lacunar infarct 12, and posterior circulation infarct 44. NIHSS on admission was average 10 ± 7 and BI was 57 ± 30. BNP in patients (435 ng/ml) was very high as compared to controls (<60 ng/ml) ($P < 0.001$). There was a positive correlation between age and BNP ($R^2 = 0.34$; $P < 0.00$); NIHSS and BNP ($R^2 = 0.255$; $P < 0.01$), negative correlation between BI and BNP ($R^2 = -0.064$; $P < 0.01$). Mean BNP levels across the OCSP showed higher values in TACI ($F = 4.609$ $P = 0.005$). Regression analysis showed that BNP can predict BI which was statistically significant. **Conclusion:** Plasma BNP levels was significantly elevated in patients with ischemic stroke. Our study concludes that high BNP levels are seen in large anterior circulation stroke and is a predictor for the poor functional outcome at 3 months. Determination of BNP levels as a biomarker could be helpful in predicting the outcome in stroke patients.

Key Words

Brain natriuretic peptide, prognosis, stroke

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Introduction

Stroke is a leading cause of morbidity and mortality. Ischemic stroke shares similarities between coronary disease in terms of mechanism and risk factors of disease.[1] B-type natriuretic peptide is synthesized as a high molecular weight precursor pro-brain natriuretic peptide (BNP) which is cleaved to release BNP and the amino-terminal fragment, N-terminal pro (NT-pro) BNP. Both peptides are released from the cardiac ventricles in response to the increased wall stress and hence its levels may indicate ventricular strain, but evidence also suggests its cerebral origin.[2,3] BNP levels have been seen to be elevated in several cardiac events and has found its role in the prognosis of cardiac ailments in various clinical settings.[4,5] This use has improved the cardiac outcome after heart failure.[6] Thrombolytic therapy has revolutionized stroke treatment; however, there is a paucity of an accurate tool which can predict the outcome and prognosis. We undertook a prospective study to assess the prognostic importance of BNP as a biomarker in ischemic stroke.

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Materials and Methods

We undertook a prospective study in the Department of Neurology over a period of 1-year. All patients with ischemic stroke were evaluated with detailed demographic and clinical examination. A history of stroke and risk factors such as hypertension, diabetes, coronary artery disease, smoking, and alcoholism were enquired. Patients with a history of stroke, age > 80 years, cardioembolic stroke, head injury, intracerebral bleed, renal impairment, seizures, pregnant females, and cor pulmonale were excluded from the study. Patients with any evidence of ischemic heart disease on admission were excluded. Stroke deficit on admission was categorized according to the National Institutes of Health Stroke Scale (NIHSS). All patients were followed up at the hospital monthly, and the stroke disability was measured by Barthel Index (BI) at the end of 3 months. All patients underwent magnetic resonance imaging brain and carotid and vertebral Doppler, the site and size of infarct was classified according to the Oxfordshire Community Stroke Project (OCSP) classification as total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (POCI).[7] An equal number of age- and sex-matched healthy participants were enrolled in the study as controls. Controls were relatives or bystanders who were nonhypertensive, nondiabetic, and with no cardiac ailment.

Blood sample collection and statistical analysis

Seven milliliters of venous blood was collected in fasting condition from the study patients, 2 ml transferred to EDTA-coated vacutainer for hematological analysis, 3 ml of blood transferred to clot activators-coated vacutainer for biochemical analysis, and 2 ml of blood transferred to heparin coated vacutainer for BNP analysis.

Hematological parameters such as hemogram, erythrocyte sedimentation rate, plasma glucose, renal and liver function tests, and lipid profile were done. Plasma BNP was measured on the day of admission by quantitative immune chromatography method using cardiac marker reader instrument from Roche Diagnostics, and values are expressed in ng/ml. Values above 60 ng/ml are high.

The data were entered in MS Excel and analyzed with the Statistical Package for the Social Sciences (SPSS) software version 21.0 for Windows. Descriptive analyses are expressed as mean ± standard deviation (SD). Independent sample *t*-tests were performed between patients and controls for the biochemical parameters and Chi-square test for various risk factors which were categorical. Pearson's rank test was used for the correlation analysis when necessary. One-way analysis of variance (ANOVA) was used to compare the mean BNP levels across the OCSP. Regression analysis was done to know the predictors for BNP. $P < 0.05$ was considered significant.

The study was approved by the Institutional Ethics Committee.

Results

A total of 182 patients were evaluated during the study. Eighty-two patients were excluded from the study as per exclusion criteria. The demographic and biochemical parameters are presented in Table 1. The mean ± SD age of the patients and controls were 55.17 ± 11.37 and 54.11 ± 12.35 years. The male:female ratio of patients and controls was 3:1. Duration of symptoms prior to admission was 1–3 days. None of the patients came in the window period. The average duration of stay in hospital was 12 days. Average blood pressure of patients ranged from 110/70 to 180/110. Risk factors of stroke in patients were hypertension (70%), diabetes mellitus (31%), smoking (44%), and alcohol (29%). The biochemical parameters are shown in Table 1. OCSP showed TACI 35, PACI 9, LACI 12, and POCI 44. NIHSS on admission was 10 ± 7 and BI after 3 months was 57 ± 30. Doppler was normal (33), atheromatous disease (45), <70% stenosis (20), and ICA occlusion in two patients. One patient died during hospitalization. There was no mortality at 3 months.

Biochemical parameters are given in Table 1. BNP on admission was average 435 ± 613. BNP in controls was < 60. Univariate analysis showed a significant difference only in BNP levels between cases and controls ($P < 0.001$) [Table 1]. There was a positive correlation between age and BNP ($R^2 = 0.34$; $P < 0.00$); between NIHSS and BNP ($R^2 = 0.255$; $P < 0.01$) [Figure 1]. There was a negative correlation between BI and BNP ($R^2 = -0.064$; $P < 0.01$) [Figure 2].

Mean BNP levels across the OCSP showed higher values in TACI, and the difference was statistically significant ($F = 4.609$

Table 1: Baseline characteristics in patients and controls

Variables	Patients	Controls	*P*
Age	55.17±11.37	54.11±12.35	NS
Gender			
Male:female	3:1	3:1	NS
HTN	70	-	NS
Diabetes	31	-	NS
Smoking	44	10	NS
Alcohol	29	5	NS
HB (g/dl)	12.90±2.11	13.65±1.21	NS
TLC (cumm)	9495±3346	8100±916	NS
ESR	27±23	14±4	NS
Platelets (lakhs)	2.7±0.98	3.1±0.51	NS
Total cholesterol (mg/dl)	167±46	158±23	NS
Triglycerides (mg/dl)	145±64	139±21	NS
LDL (mg/dl)	98±32	84±18	NS
VLDL (mg/dl)	28±11.8	21±8	NS
HDL (mg/dl)	41±11	45±8	NS
FBS (mg/dl)	105±43	81±11	NS
PPBS (mg/dl)	139±63	89±6	NS
Creatinine (mg/dl)	1.22±0.36	0.81±0.09	NS
Na (mmol/L)	136±5	140±4	NS
K (mmol/L)	3.91±0.51	3.8±0.3	NS
NIHSS	10±7	-	-
BI	57±30	-	-
NT Pro-BNP (ng/ml)	435±613	55±5	S (*P*=0.001)

HTN = Hypertension, NS = Not significant, S = Significant, NIHSS = National Institutes of Health Stroke Scale, BI = Barthel Index, NT Pro-BNP = N-terminal pro-brain natriuretic peptide, PPBS = Postprandial blood sugar, FBS = Fasting blood sugar, LDL = Low-density lipoprotein, HDL = High-density lipoprotein, VLDL = Very low-density lipoprotein, HB = Hemoglobin, ESR = Erythrocyte sedimentation rate, TLC = Total leukocyte count

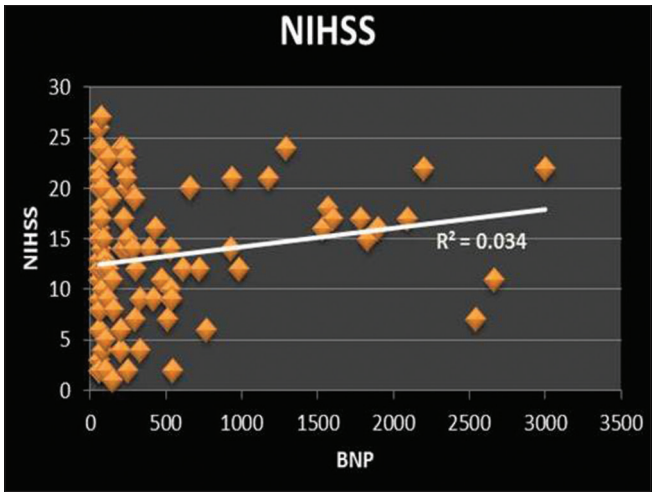

Figure 1: Scatter diagram showing positive correlation between brain natriuretic peptide and National Institutes of Health Stroke Scale

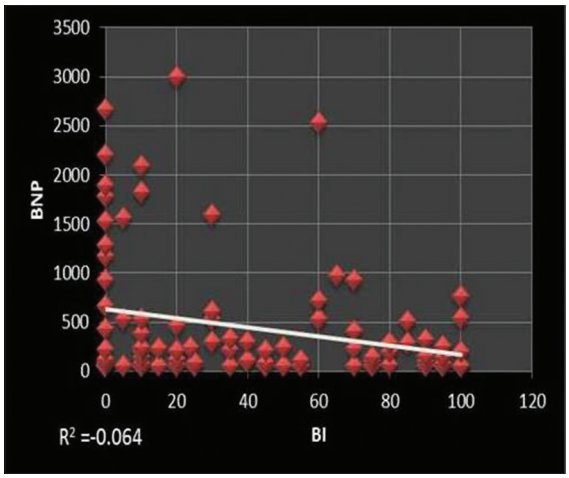

Figure 2: Scatter diagram showing negative correlation between brain natriuretic peptide and Barthel Index

P = 0.005) [Table 2]. Regression analysis showed that BI can be predicted with BNP, and this was statistically significant. R^2 = 0.227 tells that 22.7% of the variation in BI is due to the variation in BNP. The F = 1.921 (ANOVA) with a low P = 0.039 implies that there is a significant functional relationship between BI and BNP [Table 3]. In the coefficients table, a P = 0.010 implies that BNP is a significant explanatory variable to predict BI.

Table: 2: Mean brain natriuretic peptide levels in the different stroke subtypes

OCSP	Frequency	Mean±SD
TACI	28	810.78±915.25
PACI	30	312.43±433.97
LACI	33	307.79±476.94
POCI	09	269.66±260.26

ANOVA test. F=4.609; P=0.005. OCSP = Oxfordshire Community Stroke Project, TACI = Total anterior circulation infarct, PACI = Partial anterior circulation infarct, LACI = Lacunar infarct, POCI = Posterior circulation infarct, SD = Standard deviation, ANOVA = Analysis of variance

Discussion

The present study examined plasma BNP levels in patients after ischemic stroke and to evaluate its prognostic importance. We found that BNP levels were significantly increased in acute stroke patients as compared to control patients. BNP is a natriuretic peptide that is synthesized in cardiac ventricles. It is released in response to increased wall tension, volume, or pressure overload.[2,3] High BNP levels have been observed in heart failure and was seen to have a significant correlation with New York Heart Association classification predicting the extent of cardiac failure.[8] A recent study found that the use of a BNP as a biomarker-based diagnostic approach has proven extremely useful in acute coronary syndromes.[6]

There is evidence that BNP is also released from hypothalamus[9] and in response to cerebral ischemia.[10,11] Our study showed that BNP in patients was significantly higher than in controls (P < 0.001) which is in agreement with studies in the past.[12,13] One of the reasons postulated for raised BNP levels in stroke patients is cardiac dysfunction.[14] In our study, we excluded patients with past or present cardiac aliment, and hence ruled out a possible cardiac cause. Ischemic stroke is an acute stress reaction associated with neurohormonal and systemic inflammatory response which can lead to raised BNP levels.[15-18]

Thrombolytic therapy in stroke is based on the therapeutic time window of 4½ h. However, in a typical stroke neurons die at a rate of about 2 million/min.[19] Hence, clinical tools like NIHHS on admission may fall short for prediction of prognosis. Indeed, a recent study concluded that NIHHS needs to be used in the acute stage of recovery of stroke and has a limited ability to determine the chronic outcome.[20] Our study also failed to find an association between NIHSS and functional outcome. Hence, there is a need of a biomarker to predict prognosis and a stroke triage policy needs to be designed for prioritization of patients. In fact, a study showed that elevated BNP was associated with no early recanalization after intravenous tissue plasminogen activator therapy.[21]

Our study found increased BNP levels in patients with a strong positive correlation with the NIHSS suggesting that high BNP is associated with increasing stroke severity in the acute stage. However, on multivariate regression analysis, after adjusting for other confounders such as age, gender, risk factors, NIHSS, BI, and OCSP; we found that high BNP predicted a large anterior circulation stroke and were functionally dependent at 3 months. However, we report a lack of association of NIHHS with BNP. While NIHSS scale assesses the stroke severity; the BI is a scoring technique that measures the patient's performance in ten activities of daily life and assesses the disability or dependence in activities of daily living. The BI is considered a reliable disability scale for stroke patients.[22] However, the BI cannot be used to measure initial stroke severity as most patients are initially bedbound due to medical directive known as the floor effect. Hence, we assessed the BI at 3 months so that we can have the exact disability of the patient. Stroke patients undergo an initial spontaneous or intrinsic neurological recovery followed by

Table 3: Regression analyses for the predictors of brain natriuretic peptide

Model	Coefficients[a]						
	Unstandardized coefficients		Standardized coefficients	*t*	Significant	95.0% CI for *B*	
	B	SE	Beta			Lower bound	Upper bound
Constant	39.816	42.963		0.927	0.357	−45.605	125.237
Age	0.129	0.361	0.041	0.358	0.721	−0.588	0.847
Cholesterol	−0.093	1.500	−0.123	−0.062	0.950	−3.076	2.889
Triglycerides	0.163	0.104	0.298	1.575	0.119	−0.043	0.369
LDL	0.440	1.676	0.402	0.262	0.794	−2.893	3.772
VLDL	−0.611	1.648	−0.204	−0.371	0.712	−3.888	2.666
HDL	−0.746	1.422	−0.243	−0.525	0.601	−3.574	2.082
FBS	−0.013	0.106	−0.016	−0.124	0.901	−0.224	0.197
Creatinine	−3.273	10.118	−0.033	−0.323	0.747	−23.391	16.845
BNP	−0.016	0.006	−0.293	−2.652	0.010	−0.028	−0.004
HTN	19.809	8.109	0.255	2.443	0.017	3.686	35.933
DM	−1.461	9.945	−0.019	−0.147	0.884	−21.234	18.312
Smoking	−18.531	8.944	−0.262	−2.072	0.041	−36.314	−0.747
Alcohol	4.188	9.941	0.054	0.421	0.675	−15.578	23.954

[a]Dependent variable: Barthel Index. BNP = Brain natriuretic peptide, CI = Confidence interval, LDL = Low-density lipoprotein, HDL = High-density lipoprotein, VLDL = Very low-density lipoprotein, FBS = Fasting blood sugar, HTN = Hypertension, DM = Diabetes mellitus

functional or adaptative recovery. Indeed, studies have shown that baseline NIHSS score predicts long-term outcomes rather crudely because early changes in stroke scores may influence the stroke outcomes.[23] Moreover, it was found that the cutoff score of the baseline NIHSS for a favorable chronic outcome was different in anterior and posterior circulation stroke.[24]

An earlier study concluded that high plasma BNP levels measured during the acute phase of stroke are associated both with early neurological worsening. However, the study concluded that BNP added no prognostic value to clinical predictors of outcome.[25] However, the study measured the short outcome at discharge. Our study did a functional outcome analysis at 3 months with BI. Yet, another study found that high BNP has a predictive value in mortality.[26] One patient died during hospitalization in our series, and the BNP was above 3000.

A recent population-based study which evaluated biomarkers and mortality after transient ischemic attack and minor ischemic stroke showed that NT-pro B-type.

The natriuretic peptide was most predictive of vascular death.[27] BNP, a natriuretic peptide, is elevated because of the activation of the hypothalamus-pituitary-adrenal axis in ischemic stroke. High cortisol and natriuretic peptide values predict long-term mortality after ischemic stroke suggesting that this profound neurohumoral disturbance is prognostically unfavorable.[28] A recent study found the elevated BNP level as an independent marker for cardioembolic stroke and poor outcome at 90 days follow-up.[29] This information can be useful for determining the prognosis for patients, especially during thrombolytic therapy.

Assessing stroke severity and predicting morbidity and mortality are essential while taking treatment decisions and family counseling. A biochemical parameter which is fast and inexpensive will add additional valuable and time-sensitive prognostic information during the early evaluation of acute ischemic stroke, especially during the thrombolytic therapy.

As stroke is a disabling long-term condition, functional assessment is the best outcome assessment. The three scales measure the stroke at three levels, NIHSS is an impairment scale, BI is a functional assessment scale, and OCSP is a scale at the pathological level. The aim of our study was whether we could incorporate a biochemical parameter with the clinical scales and to establish its prognostic significance. We conclude that plasma BNP level predicts a large anterior circulation stroke and high BI could be used as a clinically useful marker for prognosis of stroke. However, further studies in larger scale should evaluate the role of BNP as a prognostic tool to be used in clinical practice.

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Conflicts of interest
There are no conflicts of interest.

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