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Association of Plasma Brain Natriuretic Peptide with Severity of Acute Ischemic Stroke

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Abstract:

Background: *Stroke is responsible for the highest mortality and disability among adult population in Bangladesh. With a death rate of 125.6 per 100,000 populations, Bangladesh ranks 34th globally for stroke related death. This study was aimed to find out association of plasma BNP with acute ischemic stroke severity which may help in management of these patients.* ***Methods:*** *This cross-sectional study was conducted in the Department of Neurology, BSMMU, Dhaka from June 2018 to October 2019. Total 45 subjects with history within 7 days and confirmed by CT scan of head or MRI of brain were selected purposively from the Neurology departments of BSMMU, NINS&H and Internal Medicine department of DMCH, Dhaka, Bangladesh. Venous blood samples were collected from these patients and analyzed at the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka for estimation of plasma BNP.* ***Results:*** *This study found increased plasma BNP of >100 pg/ml in 31.1 % of acute ischemic stroke patients. Mean plasma BNP level was (74.76±52.96 pg/ml) in acute ischemic stroke patient. Significant negative correlation was found between concentration of plasma BNP and time passed in days from first appearance of stroke symptoms (r = - 0.791; p < 0.001).* ***Conclusion:*** *Plasma BNP level was significantly associated with baseline severity of acute ischemic stroke.*

Key words: *Acute Ischemic Stroke, Brain Natriuretic Peptide (BNP), National Institute of Health Stroke Scale (NIHSS)*

Introduction:

Stroke is one of the major global health problems. It found that although stroke incidence, prevalence, mortality and disability-adjusted life-years declined from 1990 to 2013 and the overall stroke burden in terms of absolute number of people affected has increased across the globe in all age[1]. In 2010, stroke was the fifth leading cause of mortality in Bangladesh[2]. It is the third most common cause of death in Bangladesh[3]. However, at present, stroke is the leading cause of death in Bangladesh, followed by ischemic heart disease[4]. So, it is evident that stroke mortality is rising through the years. Stroke prevalence is 0.3% in Bangladesh and it is also the number one cause of disability in Bangladesh[3]. Inflammation and activation of the neuroendocrine systems comprise important aspects of stroke pathophysiology[5]. Activation of the sympathetic nervous system and the hypothalamic pituitary adrenal axis in acute ischemic stroke is associated with elevated levels of neuroendocrine biomarkers[6]. Several of these potential biomarkers has been tested recently to early diagnosis of ischemic stroke, predict severity and assess short- and long-term prognosis.

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Brain natriuretic peptide (BNP) is a 32 amino acid polypeptide containing a 17 amino acid ring structure that was first isolated from porcine brain in 1988[7]. Human BNP gene is located on short arm of Chromosome 1 and encodes the 108 AA pro hormone called pro-BNP[8]. Molecular Weight of glycosylated BNP precursor is 25-36 kDa, whereas, molecular Weight of mature deglycosylated BNP is12 kDa[9]. BNP denotes the biological activity of natriuresis, diuresis, vasodilatation, smooth muscle relaxation[8,11].It is secreted mainly from cardiac ventriclesand various cardiac disorders (e.g., acute coronary syndrome, left ventricular dysfunction, heart failure, atrial fibrillation) leads to increase in plasma BNP[12,13,14].Common non cardiac causes of increased BNP includes increased age, female sex, renal failure and sepsis[14,15].

Studies have shown that plasma BNP level elevated in acute ischemic stroke patients, especially in cardioembolic stroke[16,17]. However, it has been found that plasma BNP is significantly increased in acute ischemic stroke patients even without any evidence of cardiac dysfunction[18].A proposed mechanism of increased plasma BNP is reported by increased catecholamine[19,20]. National institute of Health Stroke Scale (NIHSS), the clinical tool to measure stroke severity has some limitations. Because, it needs training for assessment and inconsistency found in measurement among different clinicians[6]. Again, study have shown, lower NIHSS scores in right hemispheric syndromes than left hemispheric syndromes and less reliable severity scores in posterior circulation syndromes compared to anterior circulation syndromes[6]. Therefore, it is time demanding to identify a biomarker for correct and unbiased assessment of severity in acute ischemic stroke patients, which may substitute or compliment NIHSS. These evidences and justifications led us to formulate hypothesis that plasma BNP may be associated with severity of acute ischemic stroke.

Methods:

This was designed as analytic cross-sectional study. This study was carried out from June, 2018 to October, 2019 from indoor and outdoor services of Bangabandhu Sheikh Mujib Medical University (BSMMU), National Institute of Neurosciences & Hospital (NINS&H) and Dhaka Medical College Hospital (DMCH), Dhaka Bangladesh. The laboratory work (measurement of plasma brain natriuretic peptide) was performed in the department of "Biochemistry and Molecular biology" of BSMMU. Forty-five acute ischemic stroke patients with history within 7 days who were admitted in the Neurology department of BSMMU, NINS&H, Dhaka and Internal Medicine department of DMCH, Dhaka or patients who attended outpatient departments within this period were selected as study population for this study. Subjects were selected by purposive sampling method. After ethical clearance from Institutional Review Board (IRB) of BSMMU, forty-five patients between 18 to 75 years of age of both sexes were selected. Only acute ischemic stroke presented within 7 days of symptom onset and confirmed by CT scan of Head or MRI of Brain were enrolled in this study. Patients having conditions which may affect the plasma BNP level like acute myocardial infarction, heart failure, sepsis, renal failure (s. creatinine >2.5 mg/dl), increased age (>75 years) were excluded from this study. The aims and objectives of the study were explained to the patients and/or attendants in easily understandable local language and then informed written consent was taken.

Blood samples were taken from all selected patients to measure plasma BNP. Their demographic data, examination findings including NIHSS score, laboratory findings and radiological data recorded and copies of investigation reports were preserved. All data collection sheets were filled by the researcher himself. EDTA plasma was used for the ARCHITECT BNP assay. Three milliliters (3 ml) of venous blood samples, preferably from median cubital vein, were collected from each patient in plastic made blood collecting (purple head) tubes by the researcher, because the BNP molecule has been shown to be unstable in glass containers. The ARCHITECT BNP assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of human B type natriuretic peptide (BNP) in human EDTA

plasma on the ARCHITECT iSystem was used for this estimation. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of BNP in the sample and the RLUs detected by the ARCHITECT iSystem optics. Continuous variables were expressed as Mean ± SD. Categorical variable were presented by frequency, percentage and graph. Qualitative data analyzed by chi square test. Quantitative variables were analyzed by student's t test. The correlations between plasma BNP and the other variables were calculated using spearman's correlation test. The cutoff for statistical significance was set at p <0.05 for all data analysis. Data input was done through Microsoft Office Excel version 2016 and Statistical analysis was done by using SPSS (version 22; SPSS Inc., Chicago, IL, USA).

Results:

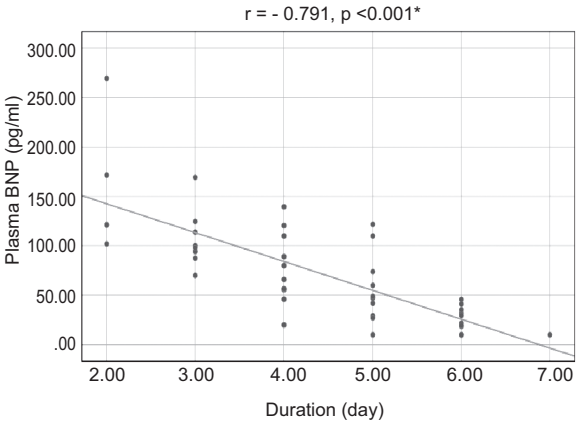
Total 45 patients of acute ischemic stroke were taken in thisstudy. Mean age was 54.04±13.17 years. Most of the subjects were between 41-60 years' age group. Male subjects were larger in proportion (60.0%) with male-female ratio of 1.5: 1.

Table-I

Distribution of plasma BNP among acute ischemic stroke patients (n=45)

BNP level (pg/ml)	Acute ischemic stroke
1-50	19(42.2%)
51-100	12(26.7%)
>100	14(31.1%)
Total	45(100.0%)
Mean±SD	74.76±52.96

Figure-1 showing, a scatter diagram and correlation of plasma BNP (pg/ml), measured from the blood sample taken during the interview, with the approximate time elapsed in days from the first appearance of the stroke symptoms among the subjects as reported by the patients or attendants. Spearman's correlation coefficient test found statistically significant (p value <0.001) negative correlation between these two variables (r = -0.791).



*significant
r= degree of correlation

Fig.-1: *Scatter diagram showing the correlation between plasma BNP and time passed (days) from appearance of first stroke symptoms (n=45)*

Figure-2 showing, frequency of different stroke syndromes according to OCSP classification. Among the acute ischemic stroke patients, Partial anterior circulation stroke and lacunar stroke was comprised 31.1% each. Total anterior circulation stroke was found in 28.9 % of patients. However, least number (8.9%) of subjects were suffering from posterior circulation stroke.

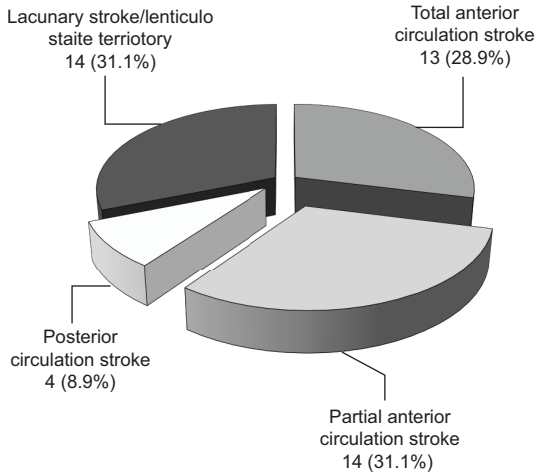
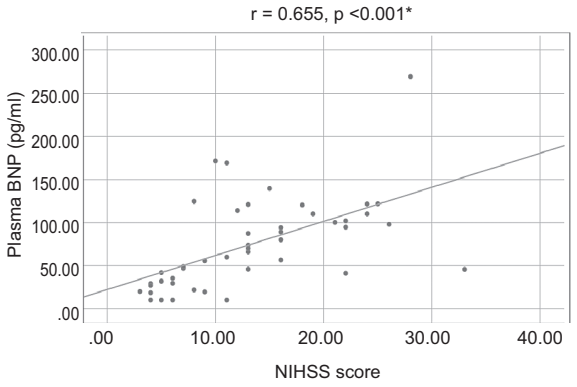


Fig.-2: *Pie chart showing frequency of ischemic stroke subtypes according to Oxfordshire community stroke project (OCSP) classification (n=45)*



*significant , r= degree of correlation

Fig.-3: *Scatter plot showing the correlation of plasma BNP with NIHSS severity score (n=45)*

Table-II

Difference of plasma BNP level inacute ischemic stroke subtypes classified by OCSP (n=45)

Stroke types	Mean±SD	p-value
Total anterior circulation stroke	111.48±54.14	0.003[s]
Partial Anterior Circulation Stroke	72.49±34.47	
Lacunar Stroke	60.04±53.88	
Posterior Circulation Stroke	14.90±5.66	

Data were analyzed by one-way ANOVA test,
s= significant

Table-III

Distribution of severity according to NIHSS score among acute ischemic stroke patients (n=45)

NIHSS	Frequency	Percent
Minor stroke(1-4)	5	11.1
Moderate stroke(5-15)	24	53.3
Moderate to severe stroke(16-20)	6	13.3
Severe stroke(>20)	10	22.2
Total	45	100.0

Table-III

Plasma BNP level in different severity categories among acute ischemic stroke patients (n=45)

Severity category (NIHSS score)	Mean±SD	p-value
Minor stroke (1-4)	20.96±7.60	0.008 [s]
Moderate stroke (5-15)	66.86±49.0	
Moderate to severe stroke (16-20)	91.70±22.54	
Severe stroke (≥21)	110.44±62.42	

Data were analyzed by one-way ANOVA test,
s= significant

Discussion:

This study was conducted with an aim to find out association between plasma BNP andseverity of acute ischemic stroke. In this cross-sectional study, total 45 acute ischemic stroke patients were enrolled. The study subjects were taken from BSMMU, NINS&H, DMCH, Dhaka, Bangladesh. Any relation of plasma BNP with NIHSS score of clinical severity was evaluated through this study, along with the variation of plasma BNP level in different areas of brain involvement according to Oxfordshire Community Stroke Project (OCSP) classification. Study was conducted from June, 2018 to October, 2019. Analysis of age distribution of the study population showed that mean age (±SD) was 54.04(±13.17) years in acute ischemic stroke patients. Male outnumber female in ischemic strokepatients (male: female =1.5:1). Most of the study subjects were middle aged adults of 41-60 years.Increased plasma BNP level above 100pg/ml was found in 31.1% of acute ischemic patients. This finding is consistent with another study which found elevated plasma BNP in 44% subjects of acute ischemic stroke[22]. Significantly increased mean BNP value of (74.76±52.96 pg/ml)was observed in the acute ischemic stroke patients. Similarly, high mean BNP was reported in earlier studies in acute ischemic stroke patients[18,23].The mean BNP was found much higher in earlier studies than found in the current study[18,23]. The higher mean plasma BNP in the above-mentioned studies may be due to early access of patient to health care services in those studies where

sampling of blood was possible without any delay from onset of stroke symptoms[18]. Another possibility of high mean plasma BNP in the above-mentioned studies may be due to inclusion of all subjects irrespective of their cardiac and renal function status.

In this study, a decreasing trendof plasma BNP level observed in ischemic stroke patients as the time increases from onset of stroke symptoms to collection of blood for BNP estimation. Significant negative correlation found between plasma BNP level and time passed in days from stroke ($r = -.791$; $p < 0.001$). Similar dynamic decrease of natriuretic peptide with time from day "0" to day "6" after stroke reported previously[24,25]. This study found statistically significant positive correlation ($r = .655$; $p < 0.001$) between plasma BNP and severity of stroke measured by National institute of health stroke scale, through Spearman's correlation test. This correlation was also observed by in study done on hospital-based stroke patients in Italy[26]. Current study showed that as severity increased, mean plasma BNP rise significantly from 'minor stroke' (20.96 pg/ml) to 'moderate stroke' (66.86 pg/ml). Further increase of plasma BNP also found in 'moderate to severe stroke' (91.70 pg/ml) and 'severe stroke' (110.44 pg/ml). Finding in this study is consistent with previous studies where BNP level was reported independently associated with clinical severity[27]. Although, association between infarct volume (measured in DWI sequence of MRI) and plasma BNP among ischemic stroke patients was found previously, it was not evaluated in this current study[27]. In this study, a statistically significant difference observed in plasma BNP level depending on anatomical variation of infarct as classified by Oxfordshire community stroke project (OCSP). Plasma BNP concentration was found highest (111.48 pg/ml) among 'total anterior circulation infarct' and least (14.90 pg/ml) in 'posterior circulation infarct'. Plasma BNP measurements were in between of the above values for 'partial anterior circulation infarct' (72.49 pg/ml) and 'lacunar infarct' (60.04 pg/ml). These finding accords with earlier studies which have shown highest mean BNP value among the patients of total anterior circulation infarct[23]. The large rise of BNP in anterior circulation infarcts could be due to larger area of involvement through involvement of carotid circulation.

The association, we found, between plasma BNP level with acute ischemic stroke severity could strengthen the potential role of BNP for assessment of severity in acute ischemic stroke both in terms of speed and ease. It may also help to anticipate infarct site.

Conclusion:

This study reveals that high plasma brain natriuretic peptide is associated with clinical severity in acute ischemic stroke. So, plasma brain natriuretic peptide could be a marker for estimation of severity in these patients. Likewise, plasma BNP is associated with anatomical location of ischemic stroke with high level in anterior circulation strokes. This will help to identify infarct site of acute ischemic stroke according to Oxfordshire community stroke project classification. Current study also reveals that Plasma BNP level is significantly higher in acute ischemic stroke and blood level of BNP falls gradually with time after the ischemic stroke.

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