A STUDY TO ASSESS THE USEFULNESS OF BRAIN NATRIURETIC PEPTIDE (BNP) AND OTHER PLASMA PARAMETERS AS BIOMARKERS TO CLASSIFY ISCHAEMIC STROKE SUBTYPES, ESPECIALLY CARDIOEMBOLIC

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ABSTRACT

BACKGROUND

Globally, stroke is a major public health problem and as per the Global Burden of Diseases (GBD) study in 1990 stroke was the second leading cause of death worldwide. Subsequent efforts to update the GBD study reported nearly 5.87 million stroke deaths globally in 2010 as compared to 4.66 million in 1990.

Objectives- To assess the usefulness of brain natriuretic peptide (BNP) and other plasma parameters as biomarkers to classify ischaemic stroke subtypes, especially cardioembolic.

MATERIALS AND METHODS

This prospective observational study was conducted in Department of Internal Medicine and Department of Neurology, LLR (Lala Lajpat Rai) Hospital and Associated Hospitals, GSVM Medical College, Kanpur (India), from October 2015 to September 2017. Random patients admitted to general ward of Medicine and Neurology Department willing to give informed consent and fulfilling requisite criterion for the study were included.

RESULTS

One hundred and eighty one patients of Acute Ischaemic Stroke had been screened during the study and finally 122 patients were included for analysis. There were 64 males (52.5%) and 58 (45.9%) females. The mean age of study subject was 60.73 ± 13.36 years with a male-to-female ratio of 1.10: 1. The most common acute ischaemic stroke subtypes was large artery atherosclerosis (65.5%) followed by small vessel disease (17.2%). The mean BNP level (pcg/mL) was highest in cardioembolic subtype. The mean level of GCS was highest in small vessel disease and lowest in other aetiology. The mean level of NIHSS was highest in cardioembolic subtype and lowest in undermined aetiology group.

CONCLUSION

The present study highlighted that Atherosclerotic AIS was the most prevalent type of AIS and Mean BNP levels were highest in Cardioembolic AIS and Cardioembolic stroke had the highest mean NIHSS and lowest mean GCS (excluding "other" aetiology).

KEYWORDS

Brain Natriuretic Peptide, Stroke, Ischaemic, Cardioembolic.

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BACKGROUND

Globally, stroke is a major public health problem and as per the Global Burden of Diseases (GBD) study in 1990, stroke was the second leading cause of death worldwide.[1] Subsequent efforts to update the GBD study reported nearly 5.87 million stroke deaths globally in 2010 as compared to 4.66 million in 1990.[2,3] This indicated a 26 percent increase in global stroke deaths during the past two decades. With the rising proportion of mortality, stroke still remains the second leading cause of death worldwide.[2,3]

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India has been experiencing significant demographic, economic and epidemiological transition during the past two decades. These have resulted in an increase in life expectancy and consequently an increase in ageing population.[4] Reliable morbidity and mortality estimates for stroke in India are very limited.[5-9]

There are two main types of stroke, ischaemic and haemorrhagic. In ischaemic stroke, blood supply to the part of brain is reduced and it causes dysfunction of the brain tissue in that area. The main causes of cerebral infarction are Thrombosis (obstruction of a blood vessel by a blood clot forming locally), Embolism (obstruction due to an embolus from elsewhere in the body), Systemic hypoperfusion and Cerebral venous sinus thrombosis.[10]

In thrombotic stroke, a thrombus (originates from large vessel and small vessel), usually forms around atherosclerotic plaques. In embolic stroke emboli most commonly arise from the heart (mainly in atrial fibrillation), but may also originate from elsewhere in arterial tree.[11]

Brain natriuretic peptide (BNP) is a 32-amino-acid cardiac natriuretic peptide neurohormone with a 17-amino-

acid ring structure and the proteolytic enzymes corin and furin split the prohormone into its two equimolar subsections of the active BNP-32 (amino acid 77-108) and the remaining part of the prohormone, biologically inactive NT-pro BNP (amino acid 1-76) which can also be measured by immunoassay.[12] Brain natriuretic peptide (BNP) is synthesised by cardiomyocytes in a short time and in large quantities and released after the stimulation of cardiomyocytes in response to volume or pressure overload.[12]

It is also known that BNP is secreted in the brain, primarily the hypothalamus and this release is induced by cerebral ischaemia.[13-15]

Many studies have demonstrated a relationship between elevated levels of brain natriuretic peptide and the acute phase of ischaemic stroke (AIS).[16-18]

Patients with elevated BNP or NT-proBNP levels around the time of their incident stroke are more likely to have a cardioembolic mechanism identified[19] to have a worse outcome from their stroke and to have an increased risk of future events such as recurrent ischaemic stroke and death.[20]

The present study was done to assess the usefulness of brain natriuretic peptide (BNP) and other plasma parameters as biomarkers to classify ischaemic stroke subtypes, especially cardioembolic.

MATERIALS AND METHODS

This prospective, observational study was conducted in Department of Internal Medicine and Department of Neurology, LLR (Lala Lajpat Rai) Hospital and Associated Hospitals, GSVM Medical College, Kanpur (India) from October 2015 to September 2017. Random patients admitted to general ward of Medicine and Neurology Department willing to give informed consent and fulfilling requisite criterion for the study were included.

A total of 181 patients of acute ischaemic stroke had been screened during the study and finally 122 patients were included for analysis.

Inclusion Criteria

- Age 25 - 80 years.
- Clinical features suggestive of CVA diagnosed with Acute Ischaemic Stroke.

Exclusion Criteria

- Renal disease with CKD grade > 2.
- Heart failure with NYHA class > 1 or chronic cor pulmonale.
- Those who were thrombolysed.
- History of heart surgery ever.
- Atrial Fibrillation/ Flutter documented at an earlier date ever.
- Presentation to our Hospital more than 72 hours after stroke onset.
- Patients on Nesiritide therapy.
- Expired before completing OR did not complete all investigations required in the study.

Methodology

Detailed history was taken about age, sex, chief complaints along with onset, duration and progress of symptoms, past history, treatment history and personal history with special emphasis on cardiovascular risk factors. Thorough physical examination followed in the Emergency ward with special emphasis on neurological system; presenting Glasgow Coma Scale (GCS) score was recorded.[21] The National Institutes of Health Stroke Scale or NIH Stroke Scale (NIHSS) were recorded within 3 hours of admission.[22]

Blood sample for BNP measurement were taken from all subjects in the emergency room immediately after admission in chilled EDTA tubes and before treatment started. BNP was measured within 24 hours of admission using Alere Triage Meter-Pro 55070 immunoassay machine that was regularly calibrated and maintained by qualified technicians. Fasting Lipid Profile and Liver Function Tests were sent within 24 hours of admission.

Neuroimaging (Computerised Tomographic Scan of Brain) were done to confirm diagnosis of stroke within 24 hours of admission. All patients with intracranial bleed were excluded. In those patients with isolated middle cerebral artery territory AIS, ASPECTS (Alberta Stroke Program Early CT Score)[19] was determined, supplemented by DWi-ASPECTS (similar score determined from a Magnetic Resonance Imaging of the Brain) in some cases; DWi ASPECTS was preferred wherever available.[23] The score divides the MCA territory into 10 regions of interest and represents the number of regions with no evidence of involvement in the scan.

Transthoracic Echocardiography and Doppler Study of Carotid and Vertebral vessels were performed within first 3 days of admission.

Sub-Classification of AIS

Ischaemic Stroke subtypes were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification widely used in recent literature.[24] TOAST classification system includes five categories-

1. **A:** Large-artery Atherosclerosis,
2. **S:** Small-artery occlusion (lacunar),
3. **C:** Cardioembolism,
4. **U:** Stroke of Undetermined aetiology,
5. **O:** Stroke of Other determined aetiology.

Statistical Analysis

Results were tabulated in Microsoft Office Excel 2007 worksheet and expressed in mean ± standard deviation for continuously distributed variables and in absolute numbers and percentages for discrete variables. Appropriate standard statistical methods were utilised. ANOVA and Pearson's two tailed correlation coefficient was used and p-value was computed; p value of less than 0.05 was considered significant unless otherwise specified. SPSS version 19 was used for statistical analysis. The results were graphically represented using Microsoft Office Excel 2007.

RESULTS

A total of 122 patients were enrolled in the present study for final analysis. The percentage of male and female patients were 52.5% and 45.9% respectively. The male-to-female ratio was 1.10: 1. The mean age of the study population was 60.73 ± 13.36 years. In present study, there were 80 patients in the Atherosclerotic subtype constituting the maximum number of patients (65.5%) followed by small vessel disease (17.2%), cardioembolic (12.3%), undetermined aetiology

(4.91%) and dissection of artery (0.8%). The mean age in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 64.3 ± 10.68, 60.62 ± 14.32, 53.53 ± 13.1, 37.17 ± 5.46 and 30 years respectively. The mean serum cholesterol levels (mg/dL), in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 189.18 ± 49.89, 186.43 ± 41.03, 175.8 ± 44.62, 148.17 ± 31.23 and 168 respectively. The mean Serum Triglyceride (mg/dL) in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 129.91 ± 49.81 133.93 ± 48.98, 129.53 ± 75.39, 100.63 ± 45.19 and 89.9 respectively. The mean Serum HDL (mg/dl) in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 49 ± 7.56, 46.36 ± 7.77, 52.19 ± 8.33, 46.98 ± 8.97 and 61.1 respectively. The mean Serum LDL (mg/dL) in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 106.74 ± 39.90, 107 ± 39.51, 92.93 ± 41.53, 78.70 ± 23.74 and 79 respectively. The mean, HbA1c % in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 6.52 ± 2.10, 6.72 ± 1.92, 5.58 ± 0.64, 5.30 ± 0.33 and 5.50 respectively. The mean BNP level (pcg/mL) in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 515.22 ± 330.90, 247.51 ± 39.21, 801.30 ± 381, 358.82 ± 144.32 and 467 respectively. The other details are given in Table Number 1.

The mean level of GCS in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 11.44 ± 2.90, 14.05 ± 1.36, 10.93 ± 2.71, 13.33 ± 2.66 and 10 respectively. The mean level of NIHSS in atherosclerotic subtype, small vessel disease, cardioembolic, undetermined aetiology and dissection of artery were 12.77 ± 9.92, 4.10 ± 2.93, 13.93 ± 10.87, 4.33 ± 4.54 and 8 respectively. The other details are given in table number 2. The statistical analyses of BNP with other parameters are given in Table Number 3.

Aspect Score was calculated in a subgroup of 85 patients with isolated Middle Cerebral Artery Territory AIS and subgroup analysis was done. BNP levels showed no correlation with ASPECTS (-0.085). ASPECTS also did not show significant correlation with GCS (+0.150) and NIHSS (+0.041). GCS levels showed very strong negative correlation with NIHSS -0.829. The detailed statistical analysis is given in Table Number 4.

	Investigations	Atherosclerotic (N=80)	Small Vessel Disease (N=21)	Cardioembolic (N=15)	Undetermined Aetiology (N=6)	Other Aetiology (N=01)
1	Haemoglobin	11.33 ± 1.72	11.77 ± 1.79	11.81 ± 2.09	11.05 ± 3.33	10.30
2	Total Leucocyte Count	12547 ± 3696	10748 ± 3131	12433 ± 3854	15733 ± 1644	10000
3	Serum Bilirubin (mg/dL)	0.94 ± 0.42	0.83 ± 0.26	1.12 ± 0.46	0.95 ± 0.33	1.10
4	Serum AST/SGOT (IU/dL)	34.24 ± 16.23	35.71 ± 12.93	50.53 ± 37.17	64.50 ± 37.20	29
5	Serum ALT/SGPT (IU/dL)	29.16 ± 12.29	31.38 ± 15.26	51.93 ± 40.43	60.17 ± 40.15	15
6	Serum Albumin (mEq/dL)	4.16 ± 0.52	4.33 ± 0.46	4.19 ± 0.44	4.28 ± 0.71	4.20
7	Serum Creatinine (mg/dL)	0.99 ± 0.02	0.92 ± 0.14	1.01 ± 0.16	0.93 ± 0.08	0.90
8	Serum Cholesterol (mg/dL)	189.18 ± 49.89	186.43 ± 41.03	175.8 ± 44.62	148.17 ± 31.23	168
9	Serum Triglyceride (mg/dL)	129.91 ± 49.81	133.93 ± 48.98	129.53 ± 75.39	100.63 ± 45.19	89.9
10	Serum HDL (mg/dL)	49 ± 7.56	46.36 ± 7.77	52.19 ± 8.33	46.98 ± 8.97	61.1
11	Serum LDL (mg/dL)	106.74 ± 39.90	107 ± 39.51	92.93 ± 41.53	78.70 ± 23.74	79
12	Serum BNP	515.22 ± 330.90	247.51 ± 39.21	801.30 ± 381	358.82 ± 144.32	467

Table 1

Mean Levels	Mean GCS	Mean NIHSS	Heart Rate (from ECG)	Mean Arterial Pressure (MAP)
A: Atherosclerotic	11.44 ± 2.90	12.77 ± 9.92	77.04 ± 14.89	90.37 ± 8.63
S: Small vessel disease	14.05 ± 1.36	4.10 ± 2.93	78.48 ± 12.72	97.14 ± 9.07
C: Cardioembolic	10.93 ± 2.71	13.93 ± 10.87	77.13 ± 14.81	80.33 ± 5.69
U: Undetermined Aetiology	13.33 ± 2.66	4.33 ± 4.54	77.00 ± 14.95	85.67 ± 3.27
O: Other Aetiology	10.0 ± 0.0	8.0 ± 0.0	64.0 0 ± 0.00	84.00 ± 0.00

Table 2

Variable Name	Pearson's Correlation Coefficient to BNP Level	Significance Level (Two Tailed)
Age	-0.073	<0.05
S. HDL	+0.102	<0.05
S. LDL	+0.180	<0.05
S. Cholesterol	+0.177	<0.05
S. Triglyceride	+0.163	<0.05
HbA1c %	-0.004	<0.05
Haemoglobin	+0.086	<0.05
Total Leucocyte Count (TLC)	-0.180	<0.05
S. Creatinine	**+0.259**	<0.01
S. SGPT	+0.063	<0.05
S. SGOT	+0.098	<0.05
S. Bilirubin	**+0.202**	<0.05
S. Albumin	-0.111	<0.05
S. Sodium	-0.123	<0.05
S. Potassium	-0.057	<0.05
S. Calcium	-0.026	<0.05
Heart Rate	-0.189	<0.05
Mean Arterial Pressure (MAP)	+0.215	<0.05
GCS	-0.625	<0.01
NIHSS	+0.659	<0.01

Table 3. Statistical Analysis of Correlation of BNP with Other Parameters

		BNP Level	Glasgow Coma Scale	NIHS Score	Score Aspect
BNP Level	Pearson Correlation	1	-.812**	-.727**	-.633
	Sig. (2-tailed)		0.00	0.00	0.00
	N	85	85	85	85
Glasgow Coma Scale	Pearson Correlation	-.812**	1	-.778**	0.150
	Sig. (2-tailed)	0.001		0.001	.098
	N	85	85	85	85
NIHS score	Pearson Correlation	0.727**	-.778**	1	0.659
	Sig. (2-tailed)	0.00	0.00		0.00
	N	85	85	85	85
Score ASPECT	Pearson Correlation	-.633	.676	.659	1
	Sig. (2-tailed)	0.00	0.00	0.00	
	N	85	85	85	85
**Correlation is Significant at the 0.01 Level (2-Tailed)					

Table 4. Intercorrelation of BNP, Clinical Stroke Scores and ASPECT Score Correlations

DISCUSSION

Stroke is an acute and rapidly progressive neurological disorder and constituting about 50% of neurological emergencies and responsible for significant morbidity also.[25]

Various imaging methods play an important role in the immediate diagnosis of stroke and the determination of stroke subtypes, but they might also become significant after a delay.[26] The time restrictions associated with imaging have led researchers to consider other possible methods of rapid diagnosis such as using biomarkers.

Brain natriuretic peptide (BNP) is a neurohormone and which is produced in response to such cardiovascular alterations from ventricular myocytes (due to stretching from pressure or volume overload), and atrial myocytes[27-30] cardioembolic stroke and post-stroke mortality[17,31-34] have been proved in many studies.[32,35]

In present study, there were 80 patients in the large artery atherosclerotic subtype constituting the maximum number of patients (65.5%) followed by small vessel disease (17.2%), cardioembolic (12.3%), undetermined aetiology (4.91%) and dissection of artery (0.8%).

Some authors in their studies highlighted that most common aetiology of stroke subtypes was cardioembolic,[36,37-40,41] while some other authors have been reported large artery type as most common stroke subtype.[42,43,44]

In present study, mean of Mean Arterial Blood Pressure (MAP) was highest in the Small Vessel AIS subtype (97.14 ± 9.07 mmHg) followed by Atherosclerotic Subtype (90.37 ± 8.63 mmHg) and lowest in Cardioembolic AIS (80.33 14 ± 5.69 mmHg). In the studies of Estrada et al and Eguchi et al, it was found that BNP levels increased in the acute phase of stroke and that there was a positive correlation between blood pressure levels and BNP levels.

In present study, the mean BNP level (pcg/mL) measurements was highest among cardioembolic AIS types and our results were found similar to others studies.[45,37,38,39,41,46,44] In present study, next highest values were for Atherosclerotic subgroup (515.22 ± 330.90 pg/mL), presumably due to large volumes of infarction.[21] Small vessel disease had a low mean BNP level (247.51 ± 39.21 pg/mL) again presumably related to the small volume of infarcted tissue.

Extensive search of literature revealed that various authors have been finalised cut-off value of BNP as 55.5 pg/mL, 76 pg/mL, 77 pg/mL, 90 pg/mL, 140 pg/mL, 265 pg/mL, 342 pg/mL and 360 pg/mL in order to determine cardioembolic nature of AIS.[47-53] In present study, we have not determined cut-off value of BNP in between cardioembolic stroke and other stroke subtypes.

The present study showed weak positive correlation of serum total bilirubin levels with BNP level (Pearson's 2-tailed correlation coefficient +0.202; $p < 0.05$) and serum SGPT (+0.098, $p < 0.05$) and serum SGPT (+0.063, $p < 0.05$) were also weakly correlated to BNP level. Serum albumin showed a weak negative correlation (Pearson's 2-tailed correlation coefficient -0.111, $p < 0.05$) with BNP level. The lower values of serum albumin and higher values of serum total bilirubin were similar to those reported by Cojocaru.[48]

In present study, Mean Glasgow Coma Scale scores were highest in Small Vessel Disease AIS (14.05 ± 1.36), likely due to their small infarct core size and subcortical nature and this was followed by AIS of undetermined aetiology (13.33 ± 2.66), and large artery atherosclerotic (11.44 ± 2.90) and cardioembolic (10.93 ± 2.71) and other determined aetiology (10.0 ± 0.00). GCS was found to have a strong negative correlation with BNP values (Pearson's 2-tailed correlation coefficient -0.625; $p < 0.01$). Our results are found to be similar to the other studies by Cakir Z et al[25] and Makikallio et al.[20]

In present study, mean NIHS score was the highest in Cardioembolic subtype as well (13.93 ± 10.87) reflecting their clinically severe nature followed by atherosclerotic AIS (12.77 ± 9.92), possibly due to large infarct size. NIHS score was found to be strongly correlated to BNP levels (Pearson's 2-tailed correlation coefficient +0.659; $p < 0.01$). Several other studies also have shown a significant correlation between plasma BNP levels and NIHS score.[21,26,27,28,29]

In present study, we also have done correlations between ASPECT score, GCS, NIHSS score and also BNP level. Subgroup analysis revealed that ASPECT score was strongly positively correlated with GCS AND ASPECT score was strongly negatively correlated to NIHSS score and ASPECT score was not significantly correlated with BNP level.

CONCLUSION

In present study, Atherosclerotic AIS was the most prevalent type of AIS followed by Small Vessel Disease AIS and was slightly more common in males. Mean BNP levels were highest in Cardioembolic AIS and Cardioembolic stroke had the highest mean NIHSS and lowest mean GCS (excluding "other" aetiology).

The data suggests that BNP levels can help to point out cardioembolic origin of an embolus whose workup would take time or whose workup suggested cryptogenic origin. Their incorporation into AIS management protocol might help to identify candidates who will do better with immediate anticoagulation rather than performing invasive TEE or continual Holter monitoring waiting weeks to months to detect an episode of evanescent AF, while sustaining excess risk by being on the suboptimal antiplatelet therapy.

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