Original Article

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Estimation of Plasma BNP Levels in Rheumatic Heart Disease Patients at a Tertiary Care Teaching Hospital in Eastern India

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Abstract

Background: Brain natriuretic peptide (BNP) is a cardiac hormone secreted from the ventricular myocardium as a response to ventricular volume expansion and pressure overload. Rheumatic heart disease is a major health problem, mostly in developing country like India and particularly in this part of the country. In young age group rheumatic heart disease is the most common cause of cardiac morbidity and mortality. In this study our aim is to measure BNP levels in patients with RHD and to find out whether BNP concentrations correlate with clinical and echocardiographic findings. A total of 88 patients with rheumatic valve disease having different type of single or multivalvular lesions were included in this study. BNP was measured using the chemiluminescence methods (Bayer Centure, Germany) by BNP kit. 2D Echocardiography with colour Doppler was performed in all patients to assess the severity of the valve disease and for the measurement of pulmonary artery pressure. The plasma concentrations of BNP were found significantly higher in patients with aortic stenosis than in control (355.92±204.31pg/ml vs.183.39±93.51pg/ml, $p < 0.001$). The plasma BNP level was significantly higher in NYHA class IV than in class I (921.50±301.93 in class I and 125.85±52.88 pg/ml, $p < 0.001$ in class III). The independent determinants of higher BNP levels were NYHA functional class and systolic pulmonary artery pressure in multivariate analysis. Along with these results we got all other relative output which suggested that increased plasma BNP levels in patients with rheumatic heart disease compared with healthy subjects.

Keywords: Rheumatic heart disease, Aortic stenosis, Systolic pulmonary artery, BNP.

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Introduction

Human brain natriuretic peptide (BNP) is believed to be chiefly delivered from the ventricular myocardium.[1,2] BNP has diuretic, natriuretic, and vasodilator activities.[3] It has been reported that plasma BNP levels are increased in states of left ventricular overload, such as left ventricular failure or left ventricular hypertrophy.[4,5] Rheumatic heart disease (RHD) is still an important cause of heart failure in developing countries. The mortality rate from this disease remain 1-10%. Recent report suggest from the developing world that rheumatic fever rates as high as 206/1 lakh and RHD prevalence rates as high as 18.6/1000.

The insufficiency and stenosis produced in heart valves as a result of RHD puts extra strains to the heart muscles. This leads to increased synthesis of natriuretic peptides specially BNP in the ventricular as well as atrial myocardium and its release in the plasma. So it's expected that plasma BNP levels in rheumatic heart disease patients will be more than normal people.

Prevalence of RHD is very high in our country and most precisely in this part of our country. there has been very less study to show serum BNP levels and its correlation with severity of RHD. Keeping this in to account the present study has been undertaken to estimate the plasma BNP levels in the patients with rheumatic heart disease and see the correlation between BNP levels and disease severity. Also we included the comparison of mean BNP levels in patients with single valvular lesion versus multiple valvular lesion in the study group, Mean BNP levels in NYHA class I to class IV, statistics of multiple comparison between NYHA class, correlation between echocardiographic peak systolic pulmonary artery pressure (sPAP) and plasma BNP levels and statistics of multiple comparison between plasma BNP levels and different groups of peak systolic pulmonary artery pressure.

Subjects and Methods

This was an observational study which included 88 patients with rheumatics heart disease who attended cardiology OPD or were admitted in the cardiology ward of IMS and SUM hospital, Bhubaneswar from January 2018 to May2019. The inclusion criteria was diagnosed RHD of single or

multivalvular lesions, confirmed by patients detail history, laboratory investigations and ecocardiography. Similarly the exclusion criteria were non rheumatic valvular heart disease, advance renal failure, pericardial heart disease and acute coronary syndromes. The control groups consisted of 24 healthy age and gender matched subject (17 female, 7 male: mean age 31.25 ± 12.59 years).

The investigation were included like all standard base line investigations, ECG, X-ray chest PA view, 2D echocardiography with colour doppler etc. Serum brain neutritic levels were found from the blood and the methods of chemiluminescence in measuring of BNP were used.

A total of 88 patients of rheumatics heart disease having different type of single or multivalvular lesions were included in the study. Some patients presents with heart failure, some with other complications like atrial fibrillation, some of them were follow up cases in the cardiology OPD. These all patients were underwent details history, clinical test and laboratory investigation. Serum BNP levels were also measured in these patients along with echocardiography. Finally a correlation was made between the BNP levels of these patients and between their clinical and echocardiographic findings.

Statistical Analysis

All values were expressed as mean ±SD. The statistical analysis included the modified students test, ANOVA, Chi square test, multiple range test, Z test etc. The statistical significance was evaluated by calculating 'p' value. A 'p' Value of ≤ 0.05 was considered significant. The prognostic value of BNP for prediction of any adverse event was defined in terms of statistical parameters. To analyze the data SPSS 10 package was used.

Results

This study was an observational study of 88 patients of rheumatics heart disease having different type of single or multivalvular lesions. Maximum number of patients in this study were in the age of 38 (43.2%), 41.7% in control group were in the age of 20-30 years. 25% study groups and 20.8% subjects in control group were in the age of 31-40 years. Least number of patients i.e. 2.3% and 4.2% in study group and control respectively were above the age of 60 years. the range of year was 16-65. The female number was 76.1% in study and 70.8% in the control groups with insignificant P-value.

61 patients (69.3%) of the study group had CHF at the time of BNP estimation and 27 patients were not in CHF. Similarly 29 patients (33%) in the study group had fibrillation at the time of BNP estimation while 59 patients (67.0%) were in normal sinus rhythm.

Table 1: comparison of mean BNP levels in the study versus control groups

Group	Total No. of cases	BNP (pg/ml) Mean±SD	T-value	P-value
Study group	88	230.44±152.77	6.584	<0.001
Control group	24	24.38±8.07		

2 The study group i.e. the patients with rheumatic heart disease had mean BNP level of 230.44±152.77pg/ml which was higher than in control with a mean BNP of 24.38±8.07pg.ml. The difference was statistically significant with a 'p' value < 0.001[Table-1].

Table 2: comparison of mean BNP levels in patients with pure MS in the study group versus control group

Group	Total No. of cases	BNP (pg/ml) Mean±SD	t-value	p-value
Pure MS	6	114.33±51.12	8.641	<0.111
Control	24	24.37±8.07		

Table 2 shows the mean BNP levels in patients with pure mitral stenosis in the study groups and control. The patients with pure MS had mean BNP levels of 114.33±51.12pg/ml which was higher than in control group with a mean BNP of 24.37±8.07pg/ml. The difference was statistically significant with a 'p' value < 0.001[Table-2].

Table 3: comparison of mean BNP levels in patients with AS versus patient without AS in the study group

Group	Total No. of cases	BNP (pg/ml) Mean±SD	t-value	p-value
AS	24	355.92±204.31	5.438	<0.001
Non-AS	64	183.39±93.51		

The patients with AS had mean BNP levels of 355.92±204.31pg/ml which was higher than in control group with a mean BNP of 183.39±93.51pg/ml. The difference was statistically significant with a 'p' value < 0.001[Table.3].

Table 4: comparison of mean BNP levels in patients with single valvular lesion versus multiple valvular lesion in the study group

Valvular lesions	Total No. of cases	BNP (pg/ml) Mean±SD	t-value	p-value
Single	13	148.15±64.12	2.069	0.042
Multiple	75	240.33±157.78		

[Table- 4] shows the mean BNP levels in patients with single valvular lesion versus multiple valvular lesion in the study group. The patients with multiple valvular lesion had mean BNP levels of 240.33±157.78pg/ml which was higher than the patient with a single valvular lesion had mean BNP of 148.15±64.12 pg/ml. The difference was statistically significant with a 'p' value < 0.042[Table-4].

Table 5: Comparison of mean BNP levels in patients with CHF versus patients without CHF in study group

	Total No. of cases	BNP (pg/ml) Mean±SD	t-value	p-value
Non-CHF	27	125.85±52.88	4.779	<0.0001
CHF	61	276.74±159.78		

The patients with congestive heart failure (CHF) had mean BNP levels of 276.74±159.78pg/ml which was higher than the patient without CHF had mean BNP of 125.85±52.88 pg/ml. The difference was statistically significant with a 'p' value < 0.0001[Table-5].

Table 6: Mean BNP levels in NYHA class I to class IV

NYHA class	BNP (pg/ml) Mean±SD	f-value	p-value
I	125.85±52.88	82.881	<0.0001
II	211.65±66.34		

III	345.89±99.22		
IV	921.50±301.93		

[Table-6] shows the mean BNP levels in patients with NYHA class I to class IV. it was analyzed by the ANOVA test. The plasma BNP level was significantly higher in NYHA class IV than in class I (921.50±301.93 in class I and 125.85±52.88 pg/ml, $p < 0.001$ in class III). This shows that the BNP levels were significantly high in higher functional NYHA class as compared to lower classes with significant p value.

Table 7: Statistics of multiple comparison between NYHA class

Group	Q-value	p-value
I vs II	85.798	<0.001
I vs III	220.04	<0.001
I vs IV	795.64	<0.001
II vs III	134.24	<0.001
II vs IV	709.85	<0.001
III vs IV	575.60	<0.001

[Table-7] shows multiple comparison between NYHA class and found a statistically significant difference in mean BNP levels in higher NYHA functional class than lower classes.

Table 8: Correlation between echocardiographic peak systolic pulmonary artery pressure (sPAP) and plasma BNP levels

sPAP	BNP (pg/ml) Mean±SD	F-value	p-value
A. <35	106.38±33.07	36.824	<0.0001
B. 35-45	179.33±43.21		
C. 46-70	269.31±63.10		
D. >70	449.33±226.37		

[Table-8] shows the mean BNP levels in patients with different group of peak systolic pulmonary artery pressure (sPAP) and plasma BNP levels. The mean BNP levels was higher 449.33±226.37pg/ml in patients with sPAP> 70mm Hg. Mean BNP was minimum 106.38±33.07 in patients with sPAP< 35mm Hg. The BNP levels were significantly raised in patients with higher peak systolic pulmonary artery pressure (sPAP) as compared to patients with lower peak systolic pulmonary artery pressure with significant p value.

Table 9: Statics of multiple comparison between plasma BNP levels and different groups of peak systolic pulmonary artery pressure

Group	q-value	p-value
A vs B	72.952	0.084
A vs C	162.93	<0.001
A vs D	342.95	<0.001
B vs C	89.984	0.014
B vs D	270.00	<0.001
C vs D	180.01	<0.001

The BNP levels were significant in patients with higher peak systolic pulmonary artery pressure (sPAP) as compared to patients with lower peak systolic pulmonary artery pressure. The plasma BNP levels went on increasing in RHD patients in study groups. The mean BNP levels in group B were higher peak systolic pulmonary artery pressure (sPAP) 35-45 than group A (<35) as compared to patients with lower peak systolic pulmonary artery pressure with insignificant p value.

[Table-10] shows grouping of subjects in study group according to mean BNP levels. Maximum patients i.e 74 patients had mean BNP levels between 100-449pg/ml. Only one patients had BNP levels above 1000pg/ml. 10 patients had mean BNP levels <100pg/ml and 3 patients had BNP levels between 500-999pg/ml.

Table 10: Grouping of subjects in study group according to the plasma BNP levels

Group	BNP levels (pg/ml)	No of Cases	Percentage(%)
1	<100	10	11.36
2	100-449	74	84.09
3	500-999	3	3.41
4	>1000	1	1.14

Discussion

The present study was to measure plasma BNP levels in patients with Rheumatic heart disease & to determine whether BNP levels correlate with the clinical & echocardiographic findings" was a cross- sectional study in patients with rheumatic heart disease who attended Cardiology OPD or were admitted in the cardiology ward. The study included 88 patients of Rheumatic Heart Disease, of different single or multivalvular lesions confirmed by detailed history, laboratory investigastions and echocardiography. The control group consisted of consisted of 24 healthy, age –and gender matched subjects.

Maximum number of patients in study group were in the age group of 20-30 years. So in this study, most common age group of presentation of rheumatic heart disease was 20-30 years. The mean age in study group was 30.53±10.83 and in control group was 31.25±12.59 without any statistically significant difference. As regards to sex, the female population dominated over male. 67 out of 88 study subjects were female constituting 76.1% in the study group. So rheumatic heart disease affected females more commonly the males. This showed that patients with rheumatic heart disease did not showed any gender differences in BNP levels.[6]

In our study most of the patients had multiple valvular lesions, while only few patients had single valvular lesion i.e. only mitral valve involvement. Most common valve involved was the mitral valve. Most common valvular lesion was mitral stenosis followed by mitral regurgitation. Tricuspid stenosis was the least common valvular lesion. The plasma concentrations of BNP were significantly higher in patients with rheumatic heart disease then in control subjects. Compared to patients with single valvular lesion i.e. only mitral valve lesion, patients with multi valvular disease had significantly higher plasma BNP levels. Patients with pure mitral stenosis had higher BNP concentrations compared with healthy subjects. This is due to the fact that, although the amount of BNP secreted from the atria is very smallcompared to that from the ventricles in patients with congestive heart failure, BNP is also secreted from the atria. In a study of patients with isolated right ventricular overload, it was demonstrated that plasma BNP levels increased in proportion to the extent of right ventricular dysfunction in pulmonary hypertention. BNP might also be released from atrial and right ventricular tissue in our patients with pure mitral stenosis. The plasma BNP concentration of patients with aortic stenosis was also significantly higher than that in the patients without arotic stenosis. The elevated afterload

(by increasing left ventricular systolic wall stress) seems to be the principle stimulus for BNP secretion in patients with arotic stenosis. There were only two patients who had systolic dysfunction. The mean BNP value of these patients was high.[7]There was no correlation between BNP concentration and ejection fraction in patients with normal ejection fraction. The plasma level of BNP in patients with congestive heart failure was higher than in patients without heart failure and the plasma BNP levels increased in proportion with the degree of left ventricular dysfunction and the severity of symptoms of heart failure .

In our study plasma BNP was increased in NYHA class I patients and continued to increase in more advanced stages. The plasma BNP level was significantly higher in NYHA class III + IV than in class II and in NYHA class II than in class I. However, there was an overlap in BNP levels between than NYHA classification groups. This overlap may be due to subjectivity of the NYHA classification system.[8] The plasma BNP levels of patients with atrial fibrillation were found to be significantly higher than in patients in sinus rhythm. This may be due to left atrial enlargement, hemodynamic impairment, or other hormonal alteration. In our study, patients with atrial fibrillation had greater left atrial diameter and higher NYHA functional class than patients in sinus rhythm. There were statistically significant associations between higher levels of BNP and left atrial dilation ($p < 0.001$), left ventricular dilatation($p<0.001$), right ventricular dilatation ($p<0.001$), right atrial dilation ($p<0.001$), and pulmonary hypertension ($p <0.001$). Positive correlation was observed between severity of systolic pulmonary artery pressure and plasma BNP levels. The independent determinants of higher BNP levels were NYHA functional class and systolic pulmonary artery pressure in multivariate analysis. No correlation was found between plasma BNP levels and severity of regurgitant lesion.[9] There was no statistically significant gender difference of plasma BNP levels in patients with rheumatic heart disease.

Conclusion

In conclusion, plasma BNP levels may be used as a complementary tool to the clinical and echocardiographic evalution of patients with rheumatic heart disease. Further prospective studies are needed to establish the importance of BNP in the follow up and management of patients with rheumatic heart disease.

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