International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

BNP in Combination with CK-MB and Troponin I is Better Marker than BNP, CK-MB or Troponin I as Independent Isolated Markers

Rasika D. Yadav[1*], Mangesh P. Bankar[2], Abdulrahaman A. Momin[3], Laxmikant J.Borse[4], Vitthal S. Shinde[1], Vijay P. More[5]

[1]Department of Biochemistry, Dr Ulhas Patil Medical College, Jalgaon, Maharashtra
[2]Department of Biochemistry, B J Medical College, Pune
[3]Department of Biochemistry, Institute of Medical Sciences and Research, Mayani, Maharashtra. India
[4]Department of Physiology, Seth G S Medical College and KEM Hospital, Parel, Mumbai
[5]Department of Community Medicine, Dr Ulhas Patil Medical College, Jalgaon, Maharashtra.

[*]Correspondence Email: rasika.dyadav@gmail.com

Received: 11/09//2013 *Revised: 12/10/2013* *Accepted: 24/10/2013*

ABSTRACT

In spite of advances in diagnostic modalities, diagnosis of acute myocardial infarction is challenging. During the last decade B-type natriuretic peptide (BNP) has been recognized as a useful marker for the detection of acute and chronic left ventricular dysfunction. BNP is released by the ventricles as a hormonal response to increased wall stress, pressure and volume overload. It correlates very closely with heart failure, as well as clinical response to treatment and prognosis. This study was designed to examine the plasma levels of brain natriuretic peptide as well as CK-MB & troponin I as a diagnostic marker in acute myocardial infarction patients. This study was conducted on 90 consecutive patients who presented in the emergency department within 6 hrs of having acute chest pain and on 90 healthy age and sex matched volunteers who formed the control group. The plasma levels of brain natriuretic peptide using the quantitative immunofluorescence assay and CK-MB was estimated by Immunoinhibition method using an automated analyzer. Troponin I was measured by chemiluminescence immunoassay (CLIA).The sensitivity and specificity of BNP, CK-MB and troponin I for the detection of acute myocardial infarction were analyzed. The results of BNP, CK-MB and troponin I alone and in combination were correlated. The brain natriuretic peptide, CK-MB and troponin I concentration in serum were significantly higher in acute myocardial infarction than in the healthy controls. The sensitivity and specificity of brain natriuretic peptide was 94.94% and 85.15% as compared to 92.94%, 88.42% and 93.98%, 87.63 % respectively for CK-MB and Troponin I. Also the sensitivity and specificity of combination of BNP, CK-MB and troponin I were found to be 94.57% and 96.59% respectively.BNP along with CK-MB and troponin I is found to be a better marker in the diagnosis of AMI, as the sensitivity and specificity of the combination of these markers was better than independent isolated markers. Therefore we suggest the combination of BNP, CK-MB and troponin I should be used in the diagnosis of AMI in patients with chest pain or early clinical signs of myocardial infarction.

Key Words: Acute myocardial infarction, B-type natriuretic peptide, Troponin I and CK-MB.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the major causes of morbidity and mortality in the world.[1] In 1988 de Bold discovered BNP in blood of patients with congestive heart failure.[2] This peptide was named after porcine brain from where it is first isolated. But later on it was realized that heart was its main source.[3] BNP is released from cardiac myocites due to their stretching, volume overload and high filling pressure. All of these actions result in high wall stress, which is initiating release of BNP precursor, or Pre–Pro-BNP. It cleaves first to pro-BNP then to, the biologically active BNP and the inactive amino terminal fragment, N-terminal prohormone of BNP-NT-pro BNP.[4,5] In the failing heart, BNP release is a part of the compensatory action such as activation of renin-angiotensin-aldosteron system (RAAS) and sympathetic nervous system. Besides its role of mechanical pump, the heart has now become new endocrine organ- by releasing BNP the heart expresses it's suffering. In numerous clinical and epidemiological studies [6-8] it was proved direct correlation between reduction of systolic function of the left ventricle and elevation of natriuretic peptides, this enables possible biochemical diagnosis of the heart failure.[9] The purpose of the study was to evaluate the diagnostic role of BNP, CK-MB and TROPONIN I in AMI patients.

MATERIALS AND METHODS

The present observational case-control study was conducted at the Department of Biochemistry, B J Medical College, Pune. Total 90 patients were included in the study group having the chest pain and brought to the intensive care unit after confirmed diagnosis of AMI. The blood samples were collected immediately after confirmation of diagnosis, along with patients, 90 healthy age & sex matched controls were also included. Acute myocardial infarction was diagnosed by physician with prolonged chest pain and confirmed by clinical examination i.e. electrocardiogram (ECG), echocardiography and blood values. The exclusion criteria were the coexistence of any other serious illness like thyroid dysfunction, diabetes, hypertension and liver or kidney disease. The study was approved by Institutional ethical committee. The study group had the mean age of 58.58 ± 8.55 years Plasma BNP was analyzed within 24 hrs on the same EDTA-anti-coagulated blood sample collected on admission for CKMB and troponin-I, using the quantitative immunofluorescence assay[10] Plasma CKMB was measured by Immunoinhibition method.[11] Plasma troponin-I was measured by chemiluminescence immunoassay CLIA.[12]

RESULT

The mean age limit was 58.58±8.55 years in AMI patients and 59.0 ± 10.11years in control subjects. In the present study patients presenting AMI were evaluated with the following results. The Systolic blood pressure & Diastolic blood pressure value is higher in AMI patients (136.20 ± 1.74, 94.08 ±0.78) than in controls (108.86±2.16, 83.48±1.06) among90 AMI patients 42 patients under the hypertension and about smoking status 17 were smokers in AMI & 23 were in control subjects& 73 were non-smokers in AMI patients &67were in controls. Demographic data of control and AMI group are shown in Table 1.

As shown in table no. 2 The BNP Levels were increased significantly ($P<0.001$) in the MI (199.18±49.40) as compared in controls (57.2±14.07). The mean values of serum CK.MB and troponin I were significantly ($P<0.001$) higher in the MI (72.06±54.97, 2.835±1.380) as

compared to those in the healthy controls (21.71 ± 3.250, 0.442 ± 0.357) respectively.

Table 1: Demographic characteristics of control and AMI patients.

Parameter	Control Subjects	AMI Patients
Age (Mean ±S.D) years	59.0 ± 10.11	58.58±8.55
Systolic blood pressure (mm of Hg)	108.86 ± 2.16	136.20 ±1.74
Diastolic blood pressure (mm of Hg)	83.48 ±1.06	94.08 ± 0.78
Hypertension	00	42
Smoking Status:		
smoker	23	17
Non-smoker	67	73

Table no 2.Values of cardiac parameters in AMI patients.

Parameters	Control Subjects	AMI Patients	P Value
BNP (pg/ml)	57.2 ± 14.07	199.18 ± 49.40	<0.0001
CK-MB (IU/L)	21.71 ± 3.250	72.06 ± 54.97	<0.0001
TROPONIN I (ng/ml)	0.442 ± 0.357	2.835 ±1.380	<0.0001

Table No. 3 Shows the sensitivity, specificity, positive predictive value & the negative predictive values of BNP, CK-MB, troponin I and the combination of (BNP + CK-MB + troponin I). The BNP had sensitivity of 94.94% and specificity of 85.15 %, CKMB and Troponin-I had the sensitivity of 92.94% & 93.98% respectively, while specificity of 88.42% & 87.63% respectively. The positive predictive and negative predictive values of BNP, CK.MB and troponin I were 83.33% & 95.56%, 87.78% & 93.33%, 86.67% &94.44% respectively. We also calculated the effectiveness of combination of BNP, CK-MB & Troponin I the sensitivity, specificity Positive predictive value and negative predictive values are 94.57 %, 96.59 %, 96.69& 94.44% respectively.

Table no 3 Comparative diagnostic accuracy of BNP, CKMB and Troponin-I

Variables	BNP	CK-MB	TROPONIN- I	BNP,CK-MB & TROPONIN I
Sensitivity	94.94%	92.94%	93.98%	94.57%
Specificity	85.15%	88.42%	87.63%	96.59%
Positive predictive value	83.33%	87.78%	86.67%	96.69%
Negative predictive value	95.56%	93.33%	94.44%	94.44%

DISCUSSION

Patients with acute chest pain in the emergency department frequently constitute a clinical diagnostic dilemma to physicians, particularly when the ECG is non-diagnostic. Although 60–70% of these patients are usually admitted to the hospital for investigation, less than one-third of them receive the final diagnosis of acute coronary syndrome.[13, 14]

In the acute ischemic cascade, myocardial cell death (and the release of its necrosis markers) is a final event.[15] One of the first steps in this process is systolic and diastolic dysfunction. BNP is produced by myocardial cells when submitted to wall stress or overload, especially if systolic dysfunction is present.[16-18] previous studies have demonstrated plasma BNP elevation in patients with AMI, reflecting biphasic behavior in those with large infarct and/or significant systolic dysfunction.[19]

Recent studies in patients with ST-segment elevation AMI and non ST-elevation acute coronary syndrome have demonstrated BNP as a potent predictor of early and late cardiac events.[20–26] In these studies, BNP levels were measured hours to days after hospital admission. Jernberget al.[27] collected blood samples of 775 acute chest pain patients to their coronary care unit and demonstrated a significant trend in the rate of AMI diagnosis across BNP levels. Patients with AMI had significantly higher median BNP levels than patients with unstable angina or non-cardiac chest pain. BNP level on admission also provided significant prognostic information in this study.

The present study demonstrates that plasma BNP measured in patients on arrival at the emergency department with chest pain is significantly higher in those with non-ST elevation AMI compared with unstable angina and non-acute coronary syndrome patients. When compared with CKMB and troponin-I on admission, BNP was more sensitive for the diagnosis with a similar high negative predictive value. More importantly, when measured in association with these necrosis markers on admission, BNP levels added significantly to their diagnostic performance, increasing the sensitivity and negative predictive value.

The concept , that ischemia may be an important stimulus for BNP release is supported by several observations In experimental models of infarction, BNP gene transcription is increased in both infracted tissue and surrounding viable myocytes, which exhibit increased wall stress.[28] In patients referred for stress testing, it has been shown that BNP rises after exercise in proportion to the size of the ischemic territory as assessed with nuclear single-photon emission computed tomographic imaging.[29] Finally, after percutaneous transluminal coronary angioplasty, BNP transiently increases, even when intracardiac filling pressures remain unchanged.[30]

The findings of this study confirm previous ones. The biological continuum of myocardial hypoxia is acute coronary syndrome, where AMI represents a greater ischemic burden than unstable angina, the progressive increase in BNP levels is seen. Then, immediate BNP elevation seems not to be directly related to myocardial necrosis or to the amount of cell death as measured by initial troponin blood level as no linear correlation between them was found Rather, BNP seems to be a marker of the ischemic burden that results in ventricular dysfunction. Therefore BNP is a strong predictor as well as a diagnostic tool for AMI, particularly in patients with chest pain and non-diagnostic ECG and CKMB/troponin blood levels.

CONCLUSION

The present findings with combined use of BNP, CK-MB & Troponin I significantly improved the sensitivity, specificity Positive predictive value and negative predictive value, which suggests that diagnostic efficiency of combination of these markers for the diagnosis of AMI than using any single marker. It is concluded that plasma BNP is an early marker of AMI in patients with chest pain and non-diagnostic ECG; its use should be considered in patients with suspicion of Cardiac ischemia in the emergency department in association with serial CKMB and troponin measurements.

REFERENCES

1. Ojha, S.K., Nandave,M., Arora, S., Narang, R., Dinda, A.K., and Arya, D.S., 2008. "Chronicadministration of *Tribulusterrestris* Linn. Extract improves cardiac function and attenuates myocardial infarction in rats". *Int. J. Pharmacol.*, 4: 1-10.
2. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. Life Sci1981; 28:89-94.
3. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988; 332:78-81.
4. Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, etal. Recommendations for the use of natriuretic peptides in acute cardiac care, A position statement from the Study Group on Biomarkersin Cardiology of the ESC Working Group on Acute Cardiac Care. Eur Heart J 2011; doi: 10.1093/eurheartj/ehq509

5. Sudoh T, Maekawa K, Kojima M, Minamino M, Kangawa N, MatsuoH. Cloning and sequence analysis of cDNA encoding a precursor rfor human brain natriuretic peptide in plasma. ClinChimActa 2002; 316:129-35.
6. Sagnella GA. Measurement and importance of plasma brain natriuretic peptide and related peptides. Ann ClinBiochem2001; 38:83-93.
7. Groenning BA, Nilsson JC, Sondergaard L, Kjaer A, Larsson HB, Hildebrant PR. Evaluation of impaired left ventricular ejection fraction and increased dimension by multiple neurohumoral plasma concentrations. Eur J Heart Fail 2001; 3:699-708.
8. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, HollanderJE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-167.
9. Maisel A, Mueller C, Adams JrK, Anker DS, Aspromonte N, Cleland JG. et al. Review: State of the art: Using natriuretic peptide levels in clinical practice. Eur J Heart Fail 2008; 10(9): 824–839.
10. Maisel AS, et al., "Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure". N Engl J Med 2002; 347: 161−8.
11. Bremmer F W cardiac disease and hyper tension in 'clinical chemistry theory, analysis and correlation. 'Kaplan L and Pesce A(ed) CV Mosby Company, 1987.
12. Troponin-I Lumax monobind IMC CLIA strip reader model no 4100 chemiluminescence immunoassay.
13. McCarthy BD, Beshansky JR, D'Agostino RB et al. missed diagnosis of acute myocardial infarction in the emergency department results from a multicenter study. Ann Emerg Med 1994; 22:579–582.
14. Graff L, Joseph T, Andelman R et al. American College of Emergency Physicians Information Paper: chest pain units in emergency departments—a report from the short-term observation section. Am JCardiol1995; 76:1036–1039.
15. Arnand IS, Fisher LD, Chiang Y-T et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the valsartan heart failure trial (Val-HeFt). Circulation2003; 107:1278–1283.
16. Maeda K, Tsutamoto T, Wada A et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135:825–832.
17. Nakagawa O, Ogawa Y, Itoh H et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide as an 'emergency 'cardiac hormone against ventricular overload. J Clin Invest1995; 96:1280–1287.
18. Yasue H, Yoshimura M, Sumida H et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994; 90:195–203.
19. Morita E, Yasue H, Yoshimura M et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation1993; 88:82–91.
20. Hall C, Cannon CP, Forman S et al. Prognostic value of N-terminal proatrial natriuretic factor plasma levels measured within the first12 hours after myocardial infarction. Thrombolysis in Myocardial Infarction (TIMI) II Investigators. J Am Coll Cardiol1995; 26:1452–1456.
21. Omland T, Aakvaag A, Bonarjee VV et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Comparison with plasma atrial

natriuretic peptide and N-terminal proatrial natriuretic peptide. Circulation 1996; 93:1963–1969.
22. Arakawa N, Nakamura M, Aoki H et al. Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction. J Am CollCardiol1996; 27:1656–1661.
23. Darbar D, Davidson NC, Gillespie N et al. Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction. Am J Cardiol1996; 78:284–287.
24. Richards AM, Nicholls MG, Yandle TG et al. Plasma N-terminal probrain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998; 97:1921–1929.
25. de Lemos JA, Morrow DA, Bentley JH et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes.N Engl J Med 2001; 345:1014–1021.
26. Morrow DA, de Lemos JA, Sabatine MS et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST elevation myocardial infarction. J Am CollCardiol2003; 41:1264–1272.
27. Jernberg T, Stridsberg M, Venge P et al. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. J Am CollCardiol2002; 40:437–445.
28. Hama N, Itoh H, Shirakami G et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 1995; 92:1558–1564.
29. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischemia induced by dynamic exercise in patients with angina pectoris. ClinSci1995; 88:551–556.
30. Tateishi J, Masutani M, Ohyanagi M et al. Transient increase in plasma brain (b-type) natriuretic peptide after percutaneous transluminal coronary angioplastic. ClinCardiol2000; 23:776–780.

How to cite this article: Yadav RD, Bankar MP, Momin AA et. al. BNP in combination with CK-MB and troponin I is better marker than BNP, CK-MB or troponin I as independent isolated markers. Int J Health Sci Res. 2013;3(11):97-102.

****