Original Article

Correlative study of in-hospital clinical outcomes with N terminal – pro B type natriuretic peptide and glycated hemoglobin in acute myocardial infarction

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Abstract

Background and Objectives: Early risk stratification, in cases of acute myocardial infarction(AMI) is essential to treat high risk patients aggressively, to reduce the morbidity and mortality. In this study we assess the short term prognostic value of N terminal pro B type natriuretic peptide (NT pro BNP), Glycated Hemoglobin (HbA1c), measured at admission, in cases of AMI. **Methods**: A total of 100 patients, presenting to R L Jalappa Narayana Hrudayalaya Heart Center, will be included into the study. Patients were evaluated with history, physical, electrocardiogram, cardiac markers, NT pro BNP, HbA1c and Echocardiogram. These patients were observed over a period of 7 days in hospital. Patients were monitored for adverse outcomes like heart failure, arrhythmias, reinfarction, mitral regurgitation and any other complications. NT pro BNP values ranged widely from <20 pg/ml to 2000 pg/ml, a value of 125pg/ml in age < 75y and >450 pg/ml in age >75 y was considered abnormal. HbA1c level of >6.5% was considered abnormal. **Results**: There was a significant negative correlation observed between NT pro BNP and Left ventricular ejection fraction at p – 0.0001. Total of 27 cases developed complications like heart failure, reinfarction, mitral regurgitation which was significantly associated with abnormal NT pro BNP values at p – 0.002. Total 6 patients had died although the NT pro BNP values were elevated in all the cases there was no statistically significant association between NT pro BNP values and mortality. HbA1c was not found to be significantly associated with LVEF, adverse out comes and mortality in short term. **Conclusion**: NT pro BNP is a strong predictor of in hospital adverse cardiac events. HbA1c was not an independent predictor of short-term outcomes.

Key words: N terminal pro B type natriuretic peptide (NTproBNP), Glycated Hemoglobin (HbA1c), acute myocardial infarction (AMI), Prognosis.

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INTRODUCTION

Cardio Vascular Diseases (CVD) are currently the leading cause of death globally, accounting to 21.9 % of total deaths. This number is projected to increase to 26.3% by 2030.[1]With the changing socio-economic landscape in India; there is a rapid and significant transition in the profile of the diseases affecting its people. Chronic non communicable diseases contributed to 53% of deaths and 43% of the disease-adjusted life years (DALYs) lost in 2005.[2] Cardiovascular Diseases (CVD) account for the majority of the chronic non communicable diseases in India. The incidence of CVD has risen from about 7% in 1970 to 32% in 2011.[3] Acute Coronary Syndrome (ACS) is a blanket term for various presentation that result from one common pathology, that of acute myocardial ischemia. A block in coronary arteries due to atherosclerotic plaque rupture or erosion, superimposed with thrombosis is usually the main cause of myocardial

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ischemia.B-type Natriuretic Peptide belongs to a group of three natriuretic peptides including Atrial Natriuretic Peptide (ANP) and C-type Natriuretic Peptide (CNP). ANP and BNP are released by cardiac myocytes and CNP is released predominantly from endothelium. BNP is released mainly due to stretch of the cardiac myocytes, in addition to this hypoxia/ischemia and neurohormonal mechanisms also activate the release of BNP. [4] So the amount of BNP released in AMI, measured at admission, in patients who present within 12 hours of onset of chest pain, can be a useful marker to risk stratify the patients and to predict the in-hospital and long term outcomes. Glycated Hemoglobin (HbA1C) levels have shown to influence the mortality and morbidity in AMI cases in both non diabetics and diabetics.[5]

In this study we tried to study the clinical outcome and in-hospital mortality, morbidity using N terminal B type natriuretic peptide (NT pro BNP), HbA1c and Hb, measured at the time of admission, in patient of AMI presenting within 12 hours.

METHODS

A total of 100 consecutive patients who presented to R L Jalappa Hospital – Narayana Hrudayalaya Heart Center were included in this study. The study period is August 2011 to May 2013. This study is an observational follow up study carried out in R.L. Jalappa Hospital – Narayana Hrudayalaya Heart Center, Tamaka, Kolar. Informed consent from the patient or the relatives was taken prior to the inclusion in the study. The patients were evaluated as per history, physical exam, Electrocardiogram, Complete Blood Count, Blood Urea, Serum Creatinine. NT pro BNP, HbA1c were be measured at admission and thorough Echocardiogram was done within 7 days of admission. The patients who were included were followed for 7 days during their stay in the hospital for various short term complications of acute myocardial infarction. Patients were observed for arrhythmias, heart failure, reinfarction, valvular dysfunction like mitral regurgitation and any other complications.

Sampling for NT pro BNP

Sample volumes of 150 µL of venous blood were collected in heparinised vials and assayed using the VIDAS NT pro BNP quantitiative test manufactured by Biomerieux, France. This test is an Enzyme-Linked Fluorescent assay (ELFA). The assay combines one-step immunoassay sandwich method with a final fluorescent detection. A value of > 125 pg/ml for patients <75y of age and >450 pg/ml for those >75y was considered abnormal.

Estimation of HbA1C

Venous blood EDTA samples were collected and estimation of HbA1c was done by using whole blood mixed with lysing reagent to prepare a hemolysate and was analysed using weakly binding cation exchange resin and by using colorimeter at wavelength (λ)=415nm. A value of >6.5% was considered abnormal.

Echocardiography

All patients were subjected to a detailed echocardiography (Echo) and Doppler evaluation. Qualitative and quantitative assessment of segmental and global LV function was done in all patients with Vivid S5 High Performance Echocardiography machine by GE Medical systems. Modified Simpson's technique was used to determine the end - diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF). EF of <40% was taken as abnormal.

Inclusion Criteria

Those admitted in R L Jalappa Hospital – Narayana Hrudayalaya Heart Center having

1. Typical ischemic symptoms and new onset ST - segment T – wave changes
2. Admitted within 12 hours after onset of symptoms.
3. Patients within the age group of 30- 80 years.

Exclusion Criteria

1. Acute MI patients with previous chronic heart failure.
2. Acute MI patients with previous chronic kidney disease, Valvular Heart Disease, Chronic Obstructive Pulmonary Disease, Atrial Fibrillation
3. Acute MI patients with cardiogenic shock at presentation.
4. Acute MI patients who present 12 hours after the onset of symptoms.
5. Acute MI patients who are taken up for angioplasty within 7 days of study period.
6. Acute MI patient s of age < 30 years or > 80 years.

Statistical Analysis

Data was entered into Microsoft excel after coding and SPSS 11 version software was used to analyze the data. Descriptive statistics like Mean and Standard deviation was computed for Continuous data and Frequencies and proportions for categorical data. Mean difference between two groups was analyzed by student t test. Chi-square test was the test of significance for categorical data. Fisher extract test was used when expected count was less than five in any of the 2x2 cell. Odds ratio was computed to measure the strength of association. $p< 0.05$ was considered as statistically significant.

OBSERVATION AND RESULTS

A total of 100 cases of Myocardial infarctions were included in the study and the mean age of the cases was 56.75 ± 11.14. It was observed that majority of the cases were males i.e. 85% and 15% were females. 51% of cases were found to be diabetics and 46% of patients had high blood pressure. In the study 58% of MI cases were

smokers and 42% were nonsmokers. Majority of cases, i.e. 72% were STEMI(ST Elevation Myocardial Infarction), and the rest were NSTEMI(Non ST Elevation Myocardial Infarction).

In the study it was observed that among 26 cases who had LVEF <40, 100% i.e. all the 26 cases had Raised NT pro BNP and there was highly significant association between NT pro BNP and LVEF among MI cases. Strength of association between NT pro BNP and LVEF was 20.6 i.e. Patients with raised NT pro BNP had 20.6 times higher risk of Left ventricular failure.

Table 1: Showing association between NT pro BNP and LVEF in MI cases

		LVEF		Total	Chi Square test	Odds Ratio
		>40	<40			
NT pro BNP	Normal (<126 in <75yrs and <450 in >75yrs)	21	0	21	χ^2 = 9.34, df = 1, p = 0.002**	20.6
	Increased	53	26	79		
Total		74	26	100		

It was observed that among 14 cases who had Arrhythmia, 92.7% i.e. 13 cases had Raised NT pro BNP and but there was no significant association between NT pro BNP and arrhythmia among MI cases(X^2 = 1.884, df = 1, p = 0.289 Fisher Exact Test). Strength of association between BNP and arrhythmia was 3.93 i.e. Patients with raised NT pro BNP had 3.93 times higher risk of arrhythmia. In the study among 27 cases who had other complications, 100% i.e. all the 27 cases had Raised NT pro BNP and there was highly significant association between NT pro BNP and other complications among MI cases. Strength of association between NT pro BNP and other complications was 21.8 i.e. Patients with raised NT pro BNP had 21.8 times higher risk of other complications.

Table 2: Showing association between NT pro BNP and Other complications in MI cases

		Other Complications		Total	Chi Square	Odds Ratio
		No	Yes			
NT pro BNP	Normal	21	0	21	X^2 = 9.832, df = 1, p = 0.002**	21.8
	Increased	52	27	79		
Total		73	27	100		

Among 26 cases who had LVEF <40, 70% i.e. 18 case had HbA1c >6.5. But there was no significant association between HbA1c and Left ventricular ejection fraction among MI cases (p=0.715). Strength of association between HbA1c and LVEF was 0.83 i.e. HbA1c within normal limits is protective to patients. There was no significant association between elevated HbA1c arrhythmias or other cardiovascular complications (p = 0.82)

DISCUSSION

Mortality in cardiovascular (CV) disease has decreased considerably over the past few decades.[6] Despite this decline, acute coronary syndromes (ACS), and especially acute myocardial infarction (MI), which imposes a great burden on society and the individual patients, is still one of the major causes of death in India[7,8]. ACS represents a spectrum of clinical conditions ranging from unstable angina (UAP) without myocardial necrosis to ST-segment-elevation MI (STEMI) with clear evidence of myocardial damage.[9] The underlying cause of ACS is atherosclerosis, an inflammatory disease that starts early in life as fatty streaks in the coronary arteries and may progress to atherosclerotic plaques, which, if ruptured, may lead to thrombus formation and the impairment of coronary flow.[10]

In 1981, de Bold and coworkers observed that the heart has an endocrine function, which resulted in the detection of the atrial natriuretic peptide (ANP). [11] It has since become apparent that there is a family of natriuretic peptides that play an important role in the control of CV homeostasis and also myocardial and vascular structure and function. [12,13] Three natriuretic peptides have so far been identified and well characterized in humans; in addition to ANP, they also include the B-type natriuretic peptide (BNP) and the C-type natriuretic peptide (CNP). [14]NT pro BNP is released from the stretch of the left ventricle and hence it is used in cases of congestive heart failure to diagnose and also to prognosticate. However, studies have shown that myocardial ischemia also stimulates the release of natriuretic peptides.[4,15,] Studies have suggested that NT pro BNP to be a more sensitively and an effective prognostic tool in all cases of ACS. Glycated Hemoglobin not only is an indicator of long term glycemic state of an individual, it also is a marker of endothelial dysfunction. There has been a conflicting evidence for considering HbA1c as a sensitive prognostic tool in cases of acute myocardial infarction.In this study we evaluated the prognostic significance of NTproBNP

and Hb1Ac, measured at admission, in patients of acute myocardial infarction with respect to outcomes and complications within the first seven days post event.

In the study it was observed that among 26 cases had LVEF <40%, there was highly significant association between NT pro BNP and LVEF among MI cases. (p - 0.002) Strength of association between NT pro BNP and LVEF was 20.6 i.e. Patients with raised NT pro BNP had 20.6 times higher risk of Left ventricular failure. There was highly significant association between raised NT pro BNP and other complications among MI cases (p-0.002). The complications observed were heart failure (20), reinfarction (4) and mitral regurgitation (3).

We observed that 14 patients had arrhythmia; there was no significant association between NT pro BNP and arrhythmia among MI cases. There was no significant association between raised NT pro BNP with deaths. The most exciting part of our results was that NT pro BNP was a significant predictor of risk, even in patients with no signs or symptoms of CHF.Similar results have been presented by others, which support the notion that the release of BNP is more complex than originally thought and that ischemia constitutes a potent stimulus.

There was no significant association between HbA1c and Left ventricular ejection fraction among MI cases. HbA1c was found not to be significantly associated with risk of arrhythmias, all cause morbidity and mortality.

In the present NT-pro BNP(levels > 125pg/dL in <75y and > 450 pg/dL>75y) was found to be a powerful predictor of adverse out comes, especially LV systolic dysfunction, within 1 week in all cases of myocardial infarction. NT pro BNP was also found to be elevated in 92% cases developing arrhythmias and also in all cases of mortality. NT-pro BNP levels varied widely may due to the varying infarct size and the extent of myocardial damage and functional impairment which directly correlates with adverse out comes including mortality. Similar pattern has been observed in other studies too.

A multicentric study by Galvani *et al* done in 2004 at Florence, Italy, included all patients of acute coronary syndrome from 31 coronary care units across the country. It included a total of 1971 patients. The study inferred that NT-pro-BNP levels, measured at admission early after the onset of the ischaemic episode, improve the early risk stratification of patients with acute coronary syndrome and are strongly predictive of short term mortality (p<0.0001) and also heart failure (p=0.0001)[16]

A study was done by Puri *et al* at King George Medical University, Lucknow in 2005; where a total of 120 patients of myocardial infarction both ST elevation and Non ST elevation were admitted and admission levels of NT pro BNP were compared with in-hospital outcomes. NT pro BNP levels above the median (>1403 pg/mL) were associated with low ejection fraction (p<0.05) and adverse out comes at the end of 30 days (p-0.001) [17]

In a study by Kwon *et al* patients with NT- proBNP> 991 pg/mL had lower LVEF (47. 8 ± 11. 8% vs.53.0 ±10.8%, p<0.001), needed longer intensive care (3.7±3.6 days vs. 2.8±2.4 days, *p*<0.001) and had higher in-hospital mortality (1.3% vs. 7.4%, *p*<0.001) than those with NT-proBNP level = 991 pg/mL.[18] The main findings of a study by Mayr and others in Austria were significant correlation of NT-pro BNP measured on day 3 after admission with acute and chronic infarct size, ejection fraction and segmental wall thickening after AMI assessed by cardiac magnetic resonance imaging as well as with biomarkers of myocardial necrosis.(p<0.004)[19]

Ranjith *et al* in their study found that NT- proBNP levels were significantly increased in patients with STEMI (p = 0. 005) and NSTEMI (p = 0. 002) who developed adverse events during their hospital stay, compared with those who did not. NT- proBNP concentrations were superior to those of troponin T as prognostic markers in both STEMI and NSTEMI. [20] In our study elevated HbA1c was found not to be significantly associated with increased risk of adverse out comes. The strength of association of HbA1c with left ventricular systolic dysfunction and other complications was 0.83 and 0.96, respectively; indicating that an HbA1c of within normal limits conferred protection to the patients from these complications. Hence the underlying glycometabolic profile of the patient plays role in the outcome of the patients, although this couldn't be proved beyond doubt in our study. Similar findings were seen in a large scale multi center study done in Beijing, China by Tian *et al*. A total of 608 patients of ST elevation myocardial infarction were included in this study. HbA1c measurement was done at admission and these patients were followed up and observed of adverse outcomes at 7 days and 30 days. After adjusting the baseline characteristics, HbA1c was not an independent predictor of short-term outcomes. (p-0.067).[21]

CONCLUSION

NT- pro BNP is a strong predictor of short term outcome in AMI. NT- pro BNP is a good tool for the risk stratification of acute MI patients so that appropriate treatment strategies could be planned. Further large scale studies are needed to evaluate the usefulness of HbA1C in risk assessment in cases of AMI. Furthermore, NT pro BNP levels correlate with the degree of left ventricular systolic dysfunction and hence an indirect evidence of infarct size, which are amongst the major determinants of long term outcomes in such patients. However, the limitation of this study was that there was small number of adverse cardiovascular events.

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