An evaluation of B-type Natriuretic Peptide in Addition to Myoglobin, Creatine Kinase-MB, and Troponin I on the Emergency Department Patients with Acute Myocardial Infarction

Kanit Reesukumal, M.D.*, Busadee Pratumvinit, M.D.*, Adisak Maneesai, M.D., Damras Tresukosol, M.D.**, Nisarat Opartkiattikul, M.D., Ph.D.***

**Department of Clinical Pathology, **Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: To assess the accuracy of B-type natriuretic peptide (BNP) in addition to myoglobin, creatine kinase-MB (CK-MB), and troponin I to diagnose patients with non ST-segment elevation myocardial infarction (NSTEMI) at the emergency department.

Methods: During January to July 2007, a total of 100 patients with suspected acute myocardial infarction at the emergency department were included. 50 were classified as NSTEMI and 50 as non-NSTEMI according to the final hospital diagnosis. Blood samples for investigation of myoglobin, CK-MB, troponin I, and BNP analysis were collected in EDTA tubes concomitantly with routine blood specimens from the emergency department and measured by Biosite Triage Cardioprofiler Panel (Biosite Inc., San Diego, CA)

Results: The diagnostic sensitivity of Myoglobin and BNP (cut-off value of 100 pg/mL) for acute myocardial infarction (AMI) was significantly higher than CK-MB and troponin-I at the emergency department (76 and 82 vs. 36 and 24%, respectively, P< 0.001). BNP in addition to myoglobin, CK-MB, and troponin I improved the diagnostic sensitivity from 86% to 100%. The optimum cut-off point levels for myoglobin, CK-MB, troponin-I, and BNP were 150 ng/mL, 3.8 ng/mL, 0.15 ng/mL and 147 pg/mL respectively. Using the optimal cut-off point, the sensitivity was 96% and specificity was 46% in diagnosis for myocardial infarction.

Conclusion: Multiple cardiac markers by use of quantitative point-of-care testing for myoglobin, CK-MB, troponin-I and BNP are useful for ruling out patients presenting to the emergency department with suspected NSTEMI.

Keywords: B-type natriuretic peptide, myocardial infarction, diagnosis

Siriraj Med J 2009;61:126-129

E-journal: http://www.sirirajmedj.com

Non ST-segment Elevation Myocardial Infarction (NSTEMI) was defined as hospital diagnosis from elevation of CK-MB or troponin beyond the cut-off point within 6-12 hours after presentation without evidence of ST-segment elevation on EKG monitoring. Heart failure was defined as hospital diagnosis from clinical symptoms and chest radiographic evidence. Triage of patients with NSTEMI depends on the laboratory measurement of cardiac markers. Most patients who present to the emergency department with possible acute myocardial infarction (AMI) do not have AMI. Since ECGs at presentation have been non-diagnostic for 50% of patients with evidence of AMI by serum markers,[1] serial cardiac markers testing is essential for accurate evaluation.[2]

Current diagnostic protocols for AMI rely upon measurement in cardiac markers, CK-MB or troponin over 6 to 12 hours.[3] However, Creatine Kinase-MB (CK-MB) and cardiac troponin are unsatisfactory for triage the patients in the emergency department because of its poor sensitivity for the early diagnosis.[4,5] Myoglobin has a potential for ruling out strategy in the early diagnosis.[6] The combined use of myoglobin, CK-MB and troponin has shown a negative predictive value nearly 100% within 90 minutes of presentation.[7-10]

B-type Natriuretic Peptide (BNP) is secreted predominantly from the ventricles and its plasma levels

Correspondence to: Nisarat Opartkiattikul
E-mail: sinop@mahidol.ac.th

have been shown to be markedly increased in patients with acute myocardial infarction.[11]

The present study aims to evaluate the sensitivity, specificity, positive and negative predictive values of BNP in addition to myoglobin, CK-MB, and troponin I for the diagnosis of patients with possible AMI at the emergency department in Siriraj Hospital. The procedure is anticipated to shorten the turn around time (TAT) and improve outcome in the management of patients suspected of having NSTEMI.

MATERIALS AND METHODS

Patients

From January to July 2007, 100 patients were retrospectively included by daily patient's chart reviewed by the authors in the emergency department, Siriraj Hospital, Mahidol University, Thailand. Inclusion criteria were age over 30 years with the symptoms of acute coronary syndrome (chest discomfort with or without radiation to the arm[s], back, neck, jaw or epigastrium; shortness of breath; weakness; diaphoresis; nausea; and/or lightheadedness) within 12 hours of symptom onset, and exclusion criteria were ST- segment elevation myocardial infarction (STEMI), previous myocardial infarction within 2 weeks, patients without informed consent and unavailable blood specimen. All subjects provided written informed consent before enrollment for the permission to use their EDTA blood samples that were left in the Department of Clinical Pathology. Among the patients selected, 50 were classified as NSTEMI and 50 as non NSTEMI according to final hospital diagnosis and chart review performed by full time cardiologists in our hospital who were blinded to the investigational biomarker panel results. The study was approved by the academic center's institutional review board. Clinical characteristics of the patients are reported in Table 1.

Myoglobin, CK-MB, troponin-I and BNP measurements

Blood specimens were obtained at the emergency department for measurement of CK-MB and troponin T, the standard markers for myocardial infarction that are currently performed in our hospital by using the Elecsys 2010 assay (Roche Diagnostics GmbH, Manheim, Germany). Blood samples for investigation of troponin I, CK-MB, myoglobin, and BNP analysis were collected in EDTA tubes concomittantly with blood specimens from the emergency department and measured by a Biosite Triage Cardioprofiler Panel (Biosite Inc., San Diego, CA) following the manufacturer's instructions and stored at 4°C for not longer than 12 hours after blood collection.

Statistical analysis

Group comparisons were made by use of the χ^2 test, Wilcoxon rank sum test, or t test as appropriate. A

TABLE 1. Patient characteristics.

	NSTEMI (n=50)	Non- NSTEMI (n=50)	p - value
Age, year	72.1 + 11.3	69.6 + 8.6	0.223
Male	19 (38)	24 (48)	0.313
Renal insufficiency (serum creatinine > 2 mg/dL)	3 (6)	8 (16)	0.110
Cardiac risk factors			
Hypertension	40 (80)	43 (86)	0.424
Diabetes mellitus	27 (54)	20 (40)	0.161
Family history of AMI	4 (8)	7 (14)	0.338
Current smoking	3 (6)	1 (2)	0.307
Hyperlipidemia	35 (70)	41 (82)	0.160
Past cardiac events			
CHF	18 (36)	20 (40)	0.680
AMI	11 (22)	8 (16)	0.444
Previous PTCA/CABG	9 (18)	22 (44)	0.005*
Positive cardiac catheterization	7 (14)	10 (20)	0.424
Medications			
ASA use within last 7 days	22 (44)	39 (78)	0.002*
Beta-blocker	23 (46)	35 (70)	0.015*
Nitrate	19 (38)	34 (68)	0.003*
ACEI/ARB	22 (44)	29 (58)	0.168
Statin	27 (54)	34 (68)	0.151
Chest pain (CP) characteristics			
CP at presentation	43 (86)	45 (90)	0.538
CP > 2 episode in 24 hour	6 (12)	21 (42)	0.001
Duration of symptom (min.)	124 + 122	90 + 143	0.209
Time since CP onset (min.)	225 + 151	246 + 175	0.522
EKG findings			
Normal	5 (10)	15 (30)	0.012*
ST-segment depression	30 (60)	11 (22)	0.001*
T wave inversion	10 (20)	20 (40)	0.029*
Q wave	6 (12)	10 (20)	0.275
Others	11 (22)	10 (20)	0.806
Evidence of CHF	34 (68)	14 (28)	0.001*

2-sided α level of 0.05 was used to determined signific ance. The diagnostic accuracy of each marker was investigated by means of the receiver-operating characteristic curve (ROC), area under the curve (AUC) and 95% confidence intervals (CI). The diagnostic cut-off and the related sensitivity, specificity and 95% CI were determined.

RESULTS

Patient characteristics

Table 1 showed the demographics and medical histories of the study population. The mean age + standard deviation (SD) for NSTEMI and non-NSTEMI patients were 72.1 + 11.3 and 69.6 + 8.6 years respectively. The male sex was found 38% and 48% in NSTEMI and non- NSTEMI patients respectively. In past cardiac events, the previous PTCA/CABG was found in NSTEMI patients and non- NSTEMI patients 18% and 44% respectively (p = 0.005). ASA, Beta-blocker and nitrates use in NSTEMI patients were 44%, 46% and 38% while non- NSTEMI patients were 78%, 70% and 68% (p = 0.002, 0.015 and 0.003 respectively). Chest pain > 2 episodes in 24 hours was found 12 % in NSTEMI patients and 42% in non- NSTEMI patients (p = 0.001). Normal EKG was found 10% in NSTEMI patients and 30% in non- NSTEMI patients (p = 0.012). In abnormal EKG, ST-segment depression and T wave inversion was found 60% vs 22% and 20% vs. 40% in NSTEMI patients and non- NSTEMI patients (p = 0.001 and 0.029) respectively. Evidence of heart failure was found 68% in NSTEMI patients and 28% in non- NSTEMI patients (p = 0.001).

Diagnostic accuracy of point-of care biomarkers combinations

By use of the manufacturer's cut-off point, the sensitivity of admission myoglobin (107 ng/mL) and BNP (100 pg/mL) for NSTEMI from hospital diagnosis

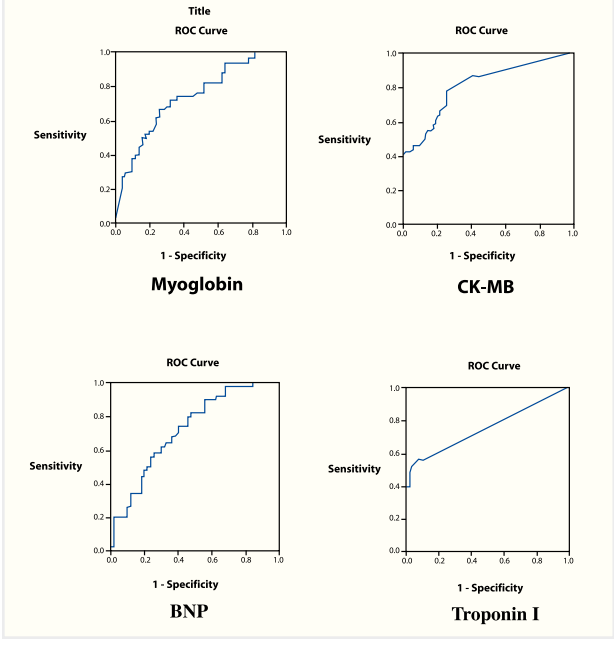

Fig 1. ROC analysis of Myoglobin, CK-MB, Troponin I and BNP for diagnosis of NSTEMI.

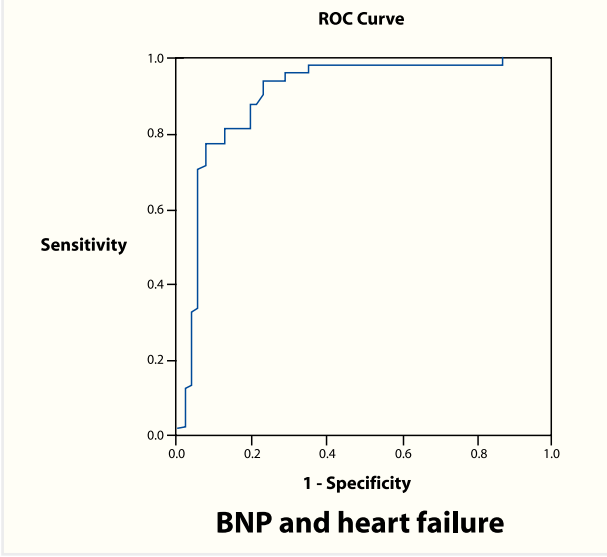

Fig 2. ROC analysis of BNP for diagnosis of heart failure patients.

were 76% and 82% compared with creatine kinase-MB (3.8 ng/mL) and troponin I (0.4 ng/mL) 36% and 24% respectively. The myoglobin, CK-MB and troponin I showed sensitivity 86% and specificity 44%. The combination of all four markers gave a result in sensitivity 100%, specificity 26%, NPV 100% and PPV 57.47%. The Receiver Operating Characteristic (ROC) analysis for point-of-care measurement of myoglobin, CK-MB, troponin I, and BNP was shown (Fig 1) with the areas under the curve were 0.739, 0.808, 0.753, and 0.722 respectively. The calculated optimum cut-off point levels for myoglobin, CK-MB, troponin I, and BNP were 150 ng/mL, 3.8 ng/mL, 0.15 ng/mL and 147 pg/mL, respectively. Using the optimal cut-off point, the sensitivity was 96% and the specificity was 46% in diagnosis for myocardial infarction. BNP and heart failure from this study analyzed by ROC (Fig 2) gave an area under the curve with 0.9 and optimal cut-off point at 150 ng/mL which produced a sensitivity of 96.8% and specificity 76.9% in diagnosis for heart failure.

DISCUSSION

Bassan et al[12] were the first to utilize BNP for diagnosis of acute myocardial infarction by studying in chest pain patients with potential acute coronary syndromes. They chose the cut-off for BNP at 100 pg/mL in combination with only troponin I and CK-MB. This selection resulted in sensitivity and NPV for NSTEMI of 87.3 and 97.3%, respectively.

From the present study results, CK-MB and troponin I were not appropriate screening for NSTEMI at presentation due to their low sensitivity at 36 and 24% respectively. Myoglobin and BNP was statistically significantly higher in sensitivity than the use of CK-MB and troponin I. The combination of all four markers by use of the manufacturer's cut-off point maximized a result in sensitivity of 100% and NPV 100%. However, with the lack of specificity, myoglobin and BNP are not definite tests for NSTEMI. The proper BNP cut-off value in Thai patients was 150 pg/mL. This cutoff value produce a good sensitivity and specificity for the

diagnosis of NSTEMI and heart failure. The BNP cutoff value in the present study was higher than the previous study by Brown et al[13] that used a cut-off point at 51 pg/mL. This result may be from the different age group and the prevalence of the heart failure that was higher in the present study.

A recent study by Khan et al[14] has shown that circulating natriuretic peptide provides prognostic information better than that given by the TIMI risk score in patients with acute myocardial infarction. The addition of BNP in standard blood testing for the patients with acute myocardial infarction may improve diagnostic sensitivity and provide more prognostic information.

The limitations of the present study are selected population and no serial measurement. The selected population was introduced by the inclusion criteria and investigator convenience. The prevalence of NSTEMI in the present study is 50% by selection because of limited resources and has limited application to other situations with lower prevalence of NSTEMI that may produce a negative predictive value lower than the present study. The mean age of this study is high which resulted in the high BNP cut-off point. This study has no serial measurement of the markers because the authors want to use in patients with NSTEMI at presentation, so the cutoff point will be changed if the duration of an onset was different from this study. In order to use in the other situation, this combination of these markers will need to be tested for proper cut-off points before use.

CONCLUSION

BNP 150 ng/mL in addition to myoglobin, CK-MB, and troponin I improves the sensitivity for diagnosis of NSTEMI in the emergency department.

ACKNOWLEDGEMENTS

This study was supported by Biosite Diagnostics, San Diego, California for the Biosite Triage Cardioprofiler Panel kits.

REFERENCES

1. Karlson BW, Herlitz J, Wiklund O, Richter A, Hjalmarson A. Early prediction of acute myocardial infarction from clinical history, examination and electrocardiogram in the emergency room. Am J Cardiol. 1991 Jul 15;68(2):171-5.
2. Gibler WB, Runyon JP, Levy RC, Sayre MR, Kacich R, Hattemer CR, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. Ann Emerg Med. 1995 Jan;25(1):1-8.
3. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). Circulation. 2000 Sep 5;102(10):1193-209.
4. de Winter RJ, Bholasingh R, Nieuwenhuijs AB, Koster RW, Peters RJ, Sanders GT. Ruling out acute myocardial infarction early with two serial creatine kinase-MBmass determinations. Eur Heart J. 1999 Jul;20(13): 967-72.
5. Hamm CW, Goldmann BU, Heeschen C, Kreymann G, Berger J, Meinertz T. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. N Engl J Med. 1997 Dec 4;337(23):1648-53.
6. Brogan GX, Jr., Friedman S, McCuskey C, Cooling DS, Berrutti L, Thode HC, Jr., et al. Evaluation of a new rapid quantitative immunoassay for serum myoglobin versus CK-MB for ruling out acute myocardial infarction in the emergency department. Ann Emerg Med. 1994 Oct;24(4): 665-71.
7. Apple FS, Anderson FP, Collinson P, Jesse RL, Kontos MC, Levitt MA, et al. Clinical evaluation of the first medical whole blood, point-of-care testing device for detection of myocardial infarction. Clin Chem. 2000 Oct;46(10):1604-9.
8. Newby LK, Storrow AB, Gibler WB, Garvey JL, Tucker JF, Kaplan AL, et al. Bedside multimarker testing for risk stratification in chest pain units: The chest pain evaluation by creatine kinase-MB, myoglobin, and troponin I (CHECKMATE) study. Circulation. 2001 Apr 10;103(14): 1832-7.
9. McCord J, Nowak RM, McCullough PA, Foreback C, Borzak S, Tokarski G, et al. Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. Circulation. 2001 Sep 25;104(13):1483-8.
10. Ng SM, Krishnaswamy P, Morissey R, Clopton P, Fitzgerald R, Maisel AS. Ninety-minute accelerated critical pathway for chest pain evaluation. Am J Cardiol. 2001 Sep 15;88(6):611-7.
11. Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsumura T, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation. 1993 Jul;88(1):82-91.
12. Bassan R, Potsch A, Maisel A, Tura B, Villacorta H, Nogueira MV, et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. Eur Heart J. 2005 Feb;26(3):234-40.
13. Brown AM, Sease KL, Robey JL, Shofer FS, Hollander JE. The impact of B-type natriuretic peptide in addition to troponin I, creatine kinase-MB, and myoglobin on the risk stratification of emergency department chest pain patients with potential acute coronary syndrome. Ann Emerg Med. 2007 Feb;49(2):153-63.
14. Khan SQ, Quinn P, Davies JE, Ng LL. N-terminal pro-B-type natriuretic peptide is better than TIMI risk score at predicting death after acute myocardial infarction. Heart. 2008 Jan;94(1):40-3.