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CLINICAL STUDY

The Comparison of Cardiac Biomarkers Positivities in Hemodialysis Patients without Acute Coronary Syndrome

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Abstract

Aim: We aimed to compare heart-type fatty acid-binding proteins (H-FAB) and other cardiac biomarkers to determine the most reliable cardiac marker in hemodialysis (HD) patients without acute coronary syndrome (ACS). *Materials and methods*: Sixty HD patients without ACS were included the study. Blood samples were taken before HD session for measurement of H-FAB, troponin I, troponin T, creatine kinase-MB (CK-MB) isoforms. *Results*: Mean age of patients was 55 ± 15 years. Males were 55%. Mean serum level of blood urea nitrogen was 75 ± 15 mg/dL, mean serum level of creatinine was 8.3 ± 2.5 mg/dL, mean serum level of hematocrit was 33 ± 5%, mean ejection fraction was 54 ± 9%, and mean left ventricular mass index (LVMI) was 136 ± 54 g/m^2. H-FAB was positive in 32%, troponin T in 20%, troponin I in 12%, and CK-MB in 5% of all patients. Three or four of all parameters were not positive together in any patient. While 5% of patients had positive troponin T with H-FAB, 3% of patients had positive troponin T with troponin I and 2% of patients had positive troponin I with H-FAB. *Conclusion*: Our study found that CK-MB had the lowest positivity in the HD patients without ACS. H-FAB had the highest rate of positivity in all markers. If only one marker is assessed it should be CK-MB. But using two parameters in HD patients in ACS diagnosis increases the reliability of diagnosis. If we use two biomarkers it should be CK-MB and troponin I.

Keywords: Hemodialysis, troponin T, troponin I, CK-MB, H-FAB

INTRODUCTION

Clinical evaluation, electrocardiography (ECG), and cardiac markers are considered together to diagnose acute coronary syndrome (ACS). However, typical chest pain and ECG changes indicating ischemia may not be seen every time in patients with suspected ACS.[1] Inaccuracies in the diagnosis of this condition can cause serious problems. For this reason, the myocardial markers became more valuable in the diagnosis of ACS with nondiagnostic ECG. The diagnosis of ACS is more difficult in patients with chronic renal failure (CRF).[2] In these patients, symptoms may not be typical and valuation of ECG can be difficult. Myocardial markers are more important to diagnose ACS in patients with CRF. In CRF patients, a false-positive rate of myocardial markers is high and therefore the reliability is low.

The aim of this study is to compare the false-positive rate of cardiac biomarkers including heart-type fatty acid-binding proteins (H-FAB), troponin I, troponin T, and creatine kinase-MB (CK-MB), and to determine the most reliable cardiac marker in patients with CRF without ACS.

METHOD

A total of 60 patients undergoing hemodialysis (HD) treatment for at least 6 months in our HD center were included in this cross-sectional study. The local ethics

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committee approved the study, and informed consent was obtained for each patient. Patients' demographic variables [age, sex, the duration of CRF, body mass index (BMI)] were recorded and blood samples were taken before HD session for measurement of H-FAB, troponin I, troponin T, CK-MB isoforms, and biochemical parameters [blood urea nitrogen (BUN), serum levels of creatinine, fasting blood glucose, albumin, total protein, hematocrit]. BMI [i.e., ratio of weight (kg) to height squared (m^2)] was calculated.

Exclusion criteria were ACS, stable angina pectoris, history of coronary artery disease, congestive heart failure, cerebrovascular events, sepsis, pulmonary embolism, and acute abdomen in the past month. All patients underwent HD using cellulosynthetic dialyzers with an average blood flow rate of 300–350 mL/min and mean Kt/V maintained at >1.2 at three times/week.

Biochemical Measurement

H-FAB measurements in heparinized blood were based on dual-line positivity by POCT method in CardioDtect med tests (rennesens GmbH, Berlin, Germany). Blood samples were taken into biochemistry gel tube and serum was separated for measurement of CK-MB values. It was measured by photometric assay with Roche P 800 device (Roche Diagnostics, Mannheim, Germany). It was considered positive if CK-MB levels were two times the upper limit of 25 IU/L. Blood samples for troponin T were taken into blood tubes with lithium and heparin. Blood samples for troponin T were measured with Roche kits in Elecsys/e 411 Roche device (Roche Diagnostics, Mannheim, Germany). The values greater than 0.10 μg/L were considered to be positive. Blood samples for troponin I were also taken into blood tubes with lithium and heparin. They were measured by electrochemical assay with Siemens Status CS Dade-Behring device (Glasgow, DE, USA). The values greater than 0.06 μg/L were considered to be positive.

Echocardiography

The transthoracic echocardiography was performed in all patients using a 3.0 MHz probe GE Vivid 3 (GE Healthcare, Milwaukee, WI, USA). All echocardiography results were obtained after HD session. All echocardiographic examinations were performed with the patient lying in the left lateral decubitus position, and two-dimensional images were recorded and measured at the apical four chambers, two chambers, and parasternal long-axis views. Left ventricular systolic diameters, diastolic diameters, and left ventricular wall thickness were measured by M-mode echocardiography. Left ventricular ejection fraction (LVEF) was assessed using the modified biplane Simpson's method. The left ventricular muscle mass (LVM) was calculated with the Devereux formula[3]:

$$\mathrm{LVM} = 1.04\,[(\mathrm{IVST} + \mathrm{LVEDD} + \mathrm{LVPT})^3 - (\mathrm{LVEDD})^3] - 13.6(\mathrm{g})$$

where IVST is the interventricular septum thickness, LVEDD the left ventricular end-diastolic diameter; and LVPT the left ventricular posterior wall thickness. The left ventricular mass index (LVMI) was calculated as LVM divided by body surface area (BSA):

$$\mathrm{LVMI} = \frac{\mathrm{LVM}}{\mathrm{BSA}}(\mathrm{g/m^2})$$

Statistical Analysis

Statistical analysis was performed with SPSS 16.0 (Chicago, IL, USA). Categorical variables were expressed as percentage. Continuous variables were expressed as an average. Differences of between-groups were analyzed using chi-square test and Mann–Whitney *U* test. Correlation between H-FAB and independent variables was analyzed using Spearman correlation test. Results are given as mean ± SD. Statistical significance was assumed if the *p*-value was less than 0.05.

RESULTS

Mean age of patients in the study was 55 ± 15 years with 55% of all patients being male. Mean serum level of BUN was 75 ± 15 mg/dL; mean serum level of creatinine 8.3 ± 2.5 mg/dL; mean serum level of hematocrit 33 ± 5%; mean LVEF 54 ± 9%; and mean LVMI 136 ± 54 g/m^2 (Table 1). H-FAB was found positive in 19 (32%), troponin T in 12 (20%), troponin I in 7 (12%), and CK-MB in 3 (5%) of all patients. Three or four of all parameters were not positive together in any patient. Three patients (5%) had positive troponin T with H-FAB. Two patients (3%) had positive troponin T with troponin I. One patient (2%) had positive troponin

Table 1. The demographic properties and biochemical data of study patients.

Age (years, mean ± SD)	55 ± 15
Gender, male	56%
Duration of dialysis (months, mean ± SD)	64 ± 63
BMI (kg/m^2, mean ± SD)	23 ± 5
LVMI (g/m^2, mean ± SD)	136 ± 54
EF (%, mean ± SD)	54 ± 9
LVEDD (cm, mean ± SD)	4.3 ± 0.8
LVESD (cm, mean ± SD)	3.0 ± 0.9
IVST (cm, mean ± SD)	1.28 ± 0.18
LVPT (cm, mean ± SD)	1.19 ± 0.14
Hemoglobin (g/dL, mean ± SD)	11 ± 2
Hematocrit (%, mean ± SD)	33 ± 5
FBG (mg/dL, mean ± SD)	112 ± 45
BUN (mg/dL, mean ± SD)	75 ± 15
Serum creatinine (mg/dL, mean ± SD)	8.3 ± 2.5
Serum total protein (g/dL, mean ± SD)	6.6 ± 0.6
Serum albumin (g/dL, mean ± SD)	3.9 ± 0.5

Note: SD, standard deviation; BMI, body mass index; BUN, blood urea nitrogen; FBG, fasting blood glucose; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; IVST, interventricular septum thickness; LVPT, left ventricular posterior wall thickness.

I with H-FAB. There were no patients who had positivity in H-FAB and CK-MB, troponin I and CK-MB, and troponin T and CK-MB together.

When we divided the patients into two groups according to the H-FAB positivity, the following were the results:

Group I ($n = 19$): H-FAB positive
Group II ($n = 41$): H-FAB negative

There was no significant difference between the two groups in age, duration of HD, residual renal function, LVMI, LVEF, BMI, BUN, serum levels of creatinine, and hematocrit ($p > 0.05$). No correlation was found between H-FAB and the other parameters including age, duration of HD, residual renal function, LVMI, LVEF, BMI, BUN, serum levels of creatinine, and hematocrit ($p > 0.05$).

DISCUSSION

In patients with CRF, the evaluation of ACS with ECG was difficult because of previously existing left ventricular hypertrophy, electrolyte disturbances, conduction abnormalities, and the drugs used.[2] For this reason, cardiac biomarkers become more important to diagnose ACS in patients with CRF. However, in those, cardiac biomarkers can be found higher in some conditions except ACS.[4,5] These conditions consist of difficulties in the diagnosis of ACS. A study comparing H-FAB and other cardiac biomarkers' positivity in HD patients without ACS was unable to find in the literature. In the diagnosis of ACS, the first choice of the biomarkers is indeterminate for why the studies comparing the cardiac biomarkers positivity in HD patients without ACS and detecting a more reliable biomarker were limited in the literature. In our study, we compared H-FAB and CK-MB, troponin T, and troponin I in HD patients without ACS. It was seen that CK-MB has the lowest rate of positivity, while H-FAB has the highest rate of positivity. Therefore, we think that H-FAB is not a reliable cardiac indicator in HD patients because of its high positivity rate without ACS.

H-FAB is a low-molecular-weight protein present in the cytoplasm of cardiac muscle cells. It increases in circulation in the early period of ischemia and is cleaned as soon as possible due to fast renal excretion of blood.[6–8] Therefore, it is a practical and useful biomarker to diagnose ACS in the early stage.[6–8] Its excretion by the kidneys may be a disadvantage for patients with HD. It might be a reason of higher blood concentration of H-FAB in HD patients. It should be investigated with another study why 32% of HD patients had positive and rest of them had negative H-FAB values without ACS. In our study, H-FAB did not correlate with parameters such as duration of HD, residual renal function, LVMI, and LVEF, which might have a relationship with H-FAB. To the best of our knowledge, there is no study researching the H-FAB's positivity in patients without ACS. Nevertheless, several studies have investigated the reasons of troponin positivity in patients without ACS, which is a sensitive and specific marker of heart muscle damage.[9–11] Some studies suggested that uremic skeletal muscle myopathy could lead to an increase in the level of troponin in HD patients without ACS.[9] But the relationship between troponin T and the patients having skeletal muscle damage after the use of second- and third-generation troponin T antibodies, which only linked with cardiac troponin T, was detected and this hypothesis was weakened. Left ventricular hypertrophy was often seen in patients with CRF. It has been reported that LVH was associated with an increased level of troponin T in patients with CRF.[10] Recurrent, small, and clinically quite infarcts may be one of the reasons of increased troponin T levels. As with heart failure, it is released from cytosolic pool through impaired cell membrane integrity and decreased catabolism. It cannot be said that increased troponin T levels are only resulting from the decrease in renal clearance. Because both free troponin and banded troponin have high molecular weight similar to albumin, it was suggested that excretion of troponin may not be mostly provided by renal clearance. It was also demonstrated that improved renal function after kidney transplantation did not affect troponin level.[11] It was found that there was no difference in the half-times of troponin I during acute myocardial infarction between patients with end-stage renal failure and normal renal function.[12]

A meta-analysis showed similar characteristics between troponin I and troponin T in patients without CRF.[13] However, higher troponin T level was detected more frequently than troponin I in patients with CRF.[14] In our study, higher troponin T level was detected more frequently than troponin I in patients with CRF similar to these studies. CK-MB had the lowest positivity ratio compared with other markers in our study. This was one of the most remarkable results of our study. According to some studies, troponin I was more sensitive and specific than CK-MB and troponin T in the evaluation of acute coronary events in patients with CRF.[15–17] According to some sources, it was seen that the positivity of CK-MB was lower in HD patients than in some prospective studies.[18] It was reported that serum CK-MB levels were elevated in 3–30% of HD patients without signs of myocardial ischemia.[19] The higher rates reported by some studies may be due to the methods used. More recent studies have been reported that lesser than 5% of HD patients had an increased percentage of CK-MB.[19]

There are advantages and disadvantages in the biomarkers used for the diagnosis of ACS. Therefore, multimarker approach has been accepted.[20,21] According to our study, the use of multimarker approach reduced the positivity problem in HD patients without ACS. There was no patient who had positivity in three or four of all parameters together and some

binary parameters together. Especially, the evaluation of CK-MB and troponin I together seems more reliable, because the lowest positivity rates for these parameters were seen in HD patients without ACS separately.

Although our study showed the high ratio of positivity in cardiac markers in HD patients without ACS, it put forward that the diagnosis of ACS in HD patients should be excluded more carefully. In spite of the highest positivity rate seen in H-FAB, we think that the rate was still low. Especially, the HD patients who admitted to the emergency with symptoms, we should not away from to the diagnose of ACS with thinking the high positivity rate of cardiac biomarkers except ACS in these patients. More recent studies have been reported that lesser than 5% of HD patients had an increased percentage of CK-MB. The other cardiac biomarkers that positive detected in HD patients, they might have lesser H-FAB positivity in fact they have not ACS. If two cardiac markers were detected to be positive, it required to be much more careful.

LIMITATIONS OF THIS STUDY

The number of patients in the study is less. It might be larger. The study could not explain the factors associated with the H-FAB positivity. In addition, the study was insufficient in showing the comparison of cardiac markers in peritoneal dialysis and HD patients.

CONCLUSION

In our study, CK-MB has the lowest rate of positivity while H-FAB has the highest rate of positivity in HD patients without ACS. If only one marker was assessed, it should be CK-MB. But using two parameters in HD patients for the diagnosis of ACS increases the reliability. In binary parameters, the use of CK-MB and troponin I seems more convenient.

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