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The most sensitive double-marker method of cardiac isoenzymes of creatinine kinase, troponin I, and myoglobin in different time periods for diagnosing acute myocardial infarction

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ABSTRACT

Purpose: Myocardial infarction is among the most common diagnoses in patients admitted to hospitals in western countries, and its rapid diagnosis is of utmost importance. This study was conducted to determine the most sensitive double-marker cardiac isoenzyme of creatinine kinase, troponin I, and myoglobin for diagnosing acute myocardial infarction.

Materials and Methods: This was an observational-analytic research on a diagnostic test conducted on 256 patients who had referred to the emergency department with chest pain from 4 to 24 hours before their referral. They were sorted equally into two groups of 4-14 hours and 15-24 hours from onset of pain, each group including 128 patients.

Results: In the first time period, the combination of troponin and myoglobin had the highest sensitivity (sensitivity = 97.3%, specificity = 98.1%), whereas the combination of double-marker and troponin proved the most sensitive (sensitivity = 100%, specificity = 96.3%).

Conclusion: The double-marker combination of troponin and myoglobin is more appropriate for the first time period (i.e. during the first 24 hours from the onset of chest pain),while it would be more helpful to use the combination of troponin during the second period of time.

Keywords: myocardial infarction; isoenzyme of creatinine kinase; troponin; myoglobin; diagnosis.

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INTRODUCTION

Myocardial infarction is one of the most frequent complications diagnosed in patients admitted to hospitals in western countries. Around 900,000 cases occur annually in the United States, claiming 225,000 lives (mortality rate around 25%).[1] Another study reported 75 million cases of myocardial infarction in the United States with a mortality rate of 30%.[2]

Occlusion of cardiac vessels over a period of longer than 15-20 minutes causes irreversible damage to cardiac muscular tissue; an occlusion of longer than 4-6 hours results in very severe muscle damage. Thus, if acute myocardial infarction is diagnosed within 6 hours of onset of symptoms, it may be possible to re-establish the blood flow and relieve the symptoms through use of thrombolytic agents such as streptokinase and urokinase; however, these agents are contraindicated after 6 hours.[3] Therefore, it is crucial for both the patient and the physician to establish a diagnosis of acute myocardial infarction in a rapid manner.

The diagnostic data for myocardial infarction are obtained from physical examination, electrocardiogram, and routine laboratory tests.[4] Among them, electrocardiography is the simplest and the most universal method. However, it is unable to establish the diagnosis in half of cases and thus it is not sensitive enough, despite being very specific.[5] Routine lab tests such as measuring creatinine kinase (CK), lactate dehydrogenase (LDH) and

serum glutamate oxaloacetate transaminase (SGOT) have long been in use for diagnosing myocardial infarction.

CK measurements used to be the standard method for diagnosis of acute myocardial infarction. Nonetheless, the specificity of these enzymes for diagnosis are questionable nowadays, since they rise in non-cardiac conditions as well. In addition to accuracy and reliability, such a method must be able to confirm diagnosis with little cost and in a short time.[6]

Nowadays, modern indicators such as cardiac isoenzyme of CK, myoglobin and troponin have taken diagnostic roles. D'Costaand colleagues have argued that troponin is most sensitive and specific during the first 24 hours after admission.[6] CK is a dimer, taking the form of three isoenzymes in different tissues: BB (brain type), MM (muscular type), and MB (hybrid type). The isoenzyme of CK-MB is known to be an appropriate indicator for acute myocardial infarction.[7-9] This substance appears in bloodstream after 6 hours of cardiac muscle necrosis and reaches its peak (39-185 ng/mL) in 13-15 hours. The serum level remains elevated for 2-3 days after onset of chest pain.[10,11]

Troponin I is a filament protein of the muscle.[12] It is coded by a different gene. The unique aminoacid sequence of cardiac troponin I renders it ideal for diagnosis of acute myocardial infarction through development of monoclonal antibodies which do not show cross-reaction with troponins of skeletal muscle.[13,14] Both troponin I and CK-MB rise higher than normal in 4-6 hours after heart attack. According to Bucher and colleagues,[15] the reference values for troponin I and CK-MB are 3 and 7 ng/mL, respectively. Troponin I achieves its peak (185-188 ng/mL) 11-15 hours after onset of chest pain and remains elevated for 6-10 hours. Serum level of troponin I is very low in normal people and does not rise on patients with skeletal muscle injury. Thus, troponin I is a specific indicator for acute myocardial infarction.[16] Myoglobin is an intracellular protein involved in oxygen storage and transfer to muscular tissue.[17] In human beings, myoglobin constitutes a major protein of the myocardium and so it is no surprise that cardiac muscle injury releases large quantities of myoglobin into bloodstream.[18,19] The normal measurement of myoglobin in serum is about 60 ng/mL which rises as high as 500 ng/mL in patients with heart attack. Thus, it would be helpful to measure myoglobin to establish a preliminary diagnosis of acute myocardial infarction. Myoglobin levels reportedly begin to rise after 4 hours of pain onset.[20-22]

This study set out to find out which of these cardiac indicators (troponin, myoglobin and CK-MB) have the greatest diagnostic ability and which one proves optimal for diagnosing acute myocardial infarction. Thus, it sought to determine the diagnostic abilities of the cardiac isoenzyme of creatinine kinase, troponin and myoglobin in diagnosis of acute myocardial infarction.

MATERIALS AND METHODS

This was an observational-analytic study by a diagnostic test conducted on patients with cardiac chest pain who had referred to the emergency department of Bessat Hospital, from March 2012 to October 2012. All participants were admitted in the emergency ward and cardiac care unit (CCU) with a diagnosis of acute myocardial infarction. The inclusion criteria were cardiac chest pain initiating 4-24 hours before admission, and having no history of heart attack or cardiac shock. All participants gave their informed consent before participating in this study.

Considering the reported sensitivity for troponin, CK-MB and myoglobin during the first 24 hours after the onset of chest pain, which was about 97%, the sampling volume was determined to be 75 patients with a confidence coefficient of 95% and accuracy of 5%. Using the same confidence coefficient and accuracy and also the reported specificity during the first 24 hours which was about 98%, the number of healthy participants was determined to be 50 people. Thus, a total of 125 people (patients and healthy people) were determined which increased to 129 people with a loss coefficient of 10%. One patient withdrew from the study, and ultimately the study was conducted with 128 people. The calculated sample volume was determined using the reported figures for the above markers during the first 24 hours after the onset of chest pain. However, it was more valuable to determine the diagnostic capabilities of the markers in the early hours. Considering the fact that all three markers were traceable in bloodstream after 4 hours of onset of pain, we divided the time period into two periods of 4-14 and 14-24 hours after onset of pain and applied the sample volume to each period, thus entering a total of 256 people into the study. The data were generated using double combinations of every two factors in the study. If any of the factors were positive, the double-marker test would be deemed positive (parallel method).

The data collection tools included a questionnaire to collect the demographic data, and a form to record the results of the tests. In this study, the diagnosis of acute myocardial infarction was established by a cardiologist using clinical findings, the electrocardiography, and the routine lab tests without knowledge of troponin I,

myoglobin and CK-MB results. In order to prevent any bias, the physician was not informed of the result of CK-MB, myoglobin and troponin during all stages of the study. Data analysis was conducted by the statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 11.5 to yield sensitivity, specificity, positive predictive and negative predictive values for each of the applied methods.

RESULTS

Of patients referring to the emergency department with the mentioned criteria,i.e. increase of CK-MB and myoglobin, 57.8% had acute myocardial infarction (Table 1). During the first period, the isoenzyme CK-MB was positive in 50.8%, troponin I in 54.7%, and myoglobin in 47.7% of patients (Table 2). During the second period, the positivity of markers was 52.7% for isoenzyme CK-MB, 5.76% for troponin I, and 42.2% for myoglobin.

Table 1 contains data regarding the most sensitive, most specific, highest positive predictive, and highest negative predictive values in the double-marker methods of cardiac isoenzyme of CK, myoglobin and troponin I for diagnosing acute myocardial infarction in 4-14 hours after onset of pain. It indicates that the most sensitive method is measuring the double-markers myoglobin-troponin I with a sensitivity of 97.3%. All three methods have equal specificity values of 98.1%.

Table 2 includes the data of cardiac isoenzyme of CK, myoglobin and troponin I for diagnosing acute myocardial infarction in 15-24 hours after onset of pain. Thus, the most sensitive method was measuring double markers of myoglobin-troponin I and cardiac isoenzyme of CK-troponin I with a sensitivity value of 100%. The most specific method was observed with the cardiac isoenzyme of CK-troponin I and myoglobin-cardiac isoenzyme of CK methods with specificity values of 96.3%.

DISCUSSION

Among the old markers used for diagnosing acute myocardial infarction, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH and total CK have fallen out of use due to their lack being specific. Furthermore, the long time it takes for them to reach their peak, as well as the little help they offer for establishing a correct diagnosis, will only result in loss of precious time needed for specialized therapeutic interventions.

According to McCord and colleagues the diagnostic power and specificity of myoglobin and troponin I together during the first 90 minutes of patient's arrival in hospital are 96.9% and 99.6%, respectively. They have not reported the sensitivity for CK-MB in this time period.[4] In addition, troponin I is not normally found in the bloodstream and it is 13 times more concentrated in myocardial tissue compared to CK-MB, thus it is more suitable for detecting subtle necrosis of the heart muscle.[5] Nevertheless, preliminary reports have indicated troponin I and CK-MB to have similar sensitivities and that even troponin I is released more slowly than CK-MB. A survey on seven studies indicates that 12-48 hours after onset of pain, troponin I and CK-MB have similar sensitivities.[6] A similar study conducted on 251 serum samples acquired from 183 patients with chest pain admitted to the emergency department used troponin I, myoglobin and CK-MB found out that troponin I had the highest rank of sensitivity and specificity.[23-25] Table 3

Table 1. Comparison of sensitivity, specificity, positive predictive and negative predictive values of the double-marker method of cardiac isoenzyme of creatinine kinase, myoglobin and troponin for diagnosing acute myocardial infarction in 4-14 hours after onset of pain.

Double-marker Method	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Myoglobin, CK-MB	93.2	98.1	98.6	91.4
Troponin, CK-MB	95.5	98.1	94.7	100
Myoglobin, Troponin	97.3	98.1	98.6	96.4

Keys: CK, creatinine kinase; MB, myoglobin and troponin.

Table 2. Comparison of sensitivity, specificity, positive predictive and negative predictive values of the double-marker method of cardiac isoenzyme of creatinine kinase, myoglobin and troponin for diagnosing acute myocardial infarction in 15-24 hours after onset of pain.

Double-marker Method	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Myoglobin, CK-MB	91.9	96.3	97.1	89.7
Troponin, CK-MB	100	96.3	97.4	100
Myoglobin, Troponin	100	94.4	96.1	100

Keys: CK, creatinine kinase; MB, myoglobin and troponin.

Table 3. Comparison of sensitivity and specificity of cardiac isoenzyme of creatinine kinase, myoglobin and troponin I for diagnosing acute myocardial infarction.

Double-marker Method	CK-MB	Myoglobin	Troponin
Sensitivity	95.8% 69/72	96.7% 89/92	97% 89/92
Specificity	98.9% 177/179	96.8% 154/159	98.9% 182/184

Keys: CK, creatinine kinase; MB, myoglobin.

summarizes the findings of these studies.

Another study by D'Costa and colleagues conducted in an emergency department in USA reported troponin I and myoglobin to have a sensitivity of 97% and specificity of 98% during the first 24 hours. Thus, they suggested to measure troponin I and myoglobin together as an alternative for CK-MB in rapid diagnosis of acute myocardial infarction.[6] Also, McCord and colleagues suggest that using a combination of myoglobin and troponin is a much more rapid method for diagnosing acute myocardial infarction compared to routine tests during the first 90 minutes.[4] Newby and colleagueshave concluded that multiple-marker methods are more rapid in diagnosing ischemia (2.5 hours for multiple-markers, 2.8 hours for double-markers, and 3.4 hours for single marker). Theyhave argued that rapid analysis of multiple markers can diagnose ischemia and warn against acute myocardial infarction more rapidly compared to other methods.[26] The findings of this study are in compliance with lack of troponin I in normal population.[1,2,5] Based on previous studies on the double-marker method, the combination of troponin I and myoglobin has the greatest sensitivity (97.3%) during the first period (i.e. during the first 24 hours from the onset of chest pain) which is probably due to the high sensitivity of troponin I.[23-25] All combinations of the double-marker method have similar specificity values during the first period (98.1%).

Some studies have noted the high sensitivity of troponin I.This high sensitivity observed in the double-marker method may be accounted for by the fact that a small fraction of troponin I is free in the cytoplasm of cardiac myocytes which leaks out readily in case of tissue damage and may be detected in the first time period.[26] Therefore, it is natural to assume the high sensitivity of troponin I combinations during the first period to be due to this marker.

Considering the similarity of specificity of the three combinations and the higher sensitivity of the myoglobin-troponin I combination during the 4-14hourstime period, it is more suitable to measure these two markers after the onset of symptoms.

The findings of this study suggest that with passing time after onset of symptoms, the levels of cardiac isoenzyme of CK and troponin I rise, whereas that of myoglobin falls (Table 2). In the second time period, the troponin I in marker combinations increases the sensitivity.The reasons for this phenomenon have been explained above. It appears that troponin I is the most influential factor in increasing sensitivity which is a result of its non-existence in normal conditions, rapid leakage and its quick peak (within 24 hours).[26]

CONCLUSION

During the second time period, the double-marker combination of CK-MB and troponin I proved the best with a sensitivity of 100% and specificity of 96.3%. The findings of this study indicate that the double-marker combination of troponin I and myoglobin is the most efficient for the first time period, while in the second period, it is more appropriate to use the combination of troponin I and CK-MB.

CONFLICT OF INTEREST

None declared.

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