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Original Research Article

Creatine Kinase-MB measurement using Immunoinhibition methodology. How much is the interference?

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ABSTRACT

Introduction: Creatine kinase-MB (CK-MB) is considered as sensitive and specific indicator for myocardial infarction. Various methods are available for CK-MB measurement but are associated with inherent shortcomings. The routinely used Immunoinhibition method is evaluated for the various interferents and their impact on the estimated CK-MB value.

Materials and Methods: The CK-MB values were analyzed for 500 patient samples whose total CK values were within the normal reference interval. Immunoinhibition method (INH) & N-Acetylcysteine (NAC) methods were used for CK-MB and total CK estimation respectively.

Results: The observed mean ± S.D. for CK was 90.15 ± 48.9 U/L and for CK-MB was 33.29 ± 20.47 U/L. The box and whisker plots were used to represent the data of CK & CK-MB. The CK-MB levels were observed to exceed the total CK under certain circumstances owing to interferents. The CK-MB values were observed to exceed the total CK in 8.6% of the cases.

Conclusion: The utility of CK-MB has ever been questioned. It has been categorized as over-used test. The conventional immunoassay methodology for CK-MB measurement is not free from interferences, awareness about these is important while interpreting the results so as to exclude method related artifactual values.

1. Introduction

Creatine kinase (CK) is an enzyme expressed by various tissues and catalyzes the reversible transfer of high energy phosphate bond from adenosine triphosphate (ATP) to creatine. Therefore, it is also known as creatine phosphokinase.[1,2] CK is found in high concentration in skeletal muscles, heart, urinary bladder, intestinal tract, brain, uterus and in lower concentrations in lung, liver, kidney and prostate.[1,2] It is a dimer consisting of two subunits which is either M (Muscle) or B (Brain). Therefore, the three different cytosolic isoenzymes formed by the various combinations of M (muscle) and B (brain) subunits in the cytosol are- CK-MM, CK-MB and CK-BB.[1–6] The CK-MM is mainly found in all kinds of muscle cells, CK-MB mainly in the myocardial cells and CK-BB exists mainly in the brain cells.[3] The distribution of various isoenzymes in the serum of healthy individuals is:- CK-MM (96-100%), CK-MB (0-6%) and CK-BB is almost undetectable.[6] Apart from these cytosolic enzymes, a mitochondrial isoenzyme of CK (CKm) is found in muscle, brain and cerebrospinal fluid.[2]

The creatine kinase isoenzyme CKMB is cardio-specific and is accepted as the most sensitive and specific indicator of myocardial cell necrosis.[2,5–9] However, the cardio-specificity of this isoenzyme has been questioned due to certain false positive results with diseases contributing to elevated CK-MB values. The reason and the associated conditions are:- Increased cell permeability as seen in pericarditis, myocarditis; abnormal skeletal muscle fibers as in muscular dystrophies, rhabdomyolysis; Atypical CK-MB fractions as in alcoholic cardiomyopathy, traumatic crush injury.[6,7] CK-MB can also be elevated in conditions not involving cardiac or skeletal muscle like septicemia,

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myeloma, head injury, brain diseases, hypothyroidism, hypoparathyroidism, renal failure, patients on hemodialysis, asthma, pulmonary embolism, non-cardiac surgeries and malignancies.[7,10,11]

Various methods have been utilized for assaying the creatine kinase MB isoenzyme. These methods can be broadly categorized as those measuring CKMB activity concentration which are - Electrophoresis, Ion-exchange chromatography, Immunoinhibition (INH) and Immunoprecipitation. The second category consists of those measuring the CKMB mass concentration which includes- Radioimmunoassay and Enzyme Immunoassay.[12,13] In our laboratory set-up the CKMB isoenzyme is analyzed using Immunoinhibition method in which an antibody is directed against the M subunit of CK-MB. Now the activity of only the B subunit is measured which is then multiplied by a factor of 2, to obtain the activity of CK-MB in the serum.[14] None of the above mentioned method is gold standard and is associated with some inherent shortcomings. This study is an attempt to evaluate the extent of interference associated with Immunoinhibition method used for CKMB assay and to assess the possible reasons for erroneous results obtained during the routine investigations.

2. Aims & Objectives

To assess the extent of interference associated with the Immunoinhibition (INH) method for CKMB assay.

3. Materials and Methods

This prospective observational study was conducted over a period of three months from November 2018 to January 2019 in the department of biochemistry, Maulana Azad Medical College & Lok Nayak hospital, New Delhi, India. Standard ethical principles were followed for the study. The sample size was calculated as per convenience (confidence interval 95% and power of study 80%). A total of 500 patient samples were included in the study for which the total CK and CK-MB values were analyzed on Randox Imola autoanalyzers. But, only those samples with normal total CK concentration were included in the study. Routine samples with sufficient serum volume (>2ml) were given a unique lab identification number. Serum was obtained after centrifugation for 8-10 minutes at 3500 rpm after which total CK was measured using CK-NAC (N-acetylcysteine) method and for CK-MB assay Immunoinhibition (INH) method was used. The samples were processed as per manufacturer's instructions and the internal quality control was ensured.

3.1. Statistical analysis

The results obtained were entered in the excel sheet and the data was analyzed using Statistical package for social sciences (SPSS) software. Mean, standard deviation, median & inter-quartile range were calculated. The Box and Whisker plots were used to show the variability and distribution of data.

4. Results

The mean ± standard deviation, median and inter-quartile ranges for both CK & CK-MB in random 500 serum samples whose CK values were within the normal reference intervals (Total CK < 200 U/L) is shown in Table 1.

The box and whisker plot obtained for CK & CK-MB values is represented in Figures 1 and 2 respectively. Despite the problems related to methodology there is a general agreement that if >6% of the total CK is CK-MB, it is indicative of myocardial infarction. A persistently elevated CKMB (>30% of total CK) by immunoinhibition method is less likely to be from continued infarction and should be evaluated for macro-CKs.[4]

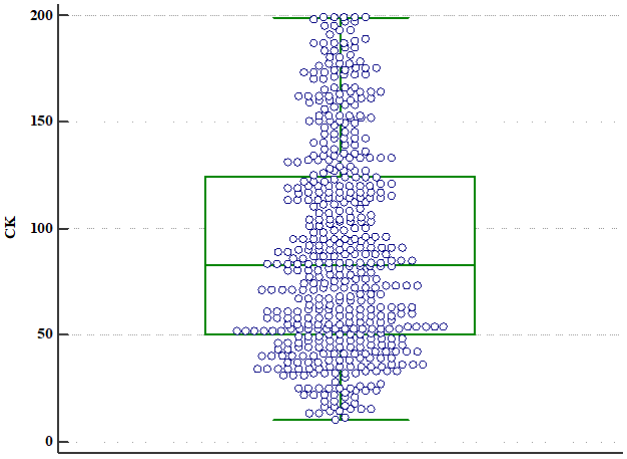

Fig. 1: Box and Whisker plot for totalCK values (n=500)

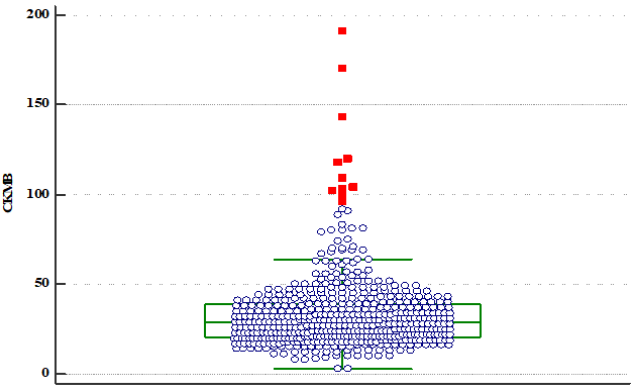

Fig. 2: Box and Whisker plot for CK-MB values (n=500).The red dots represent the outliers

Table 1: Mean±SD levels of CK and CK-MB levels in serum samples (n=500)

	Mean ± S.D.	Median	Inter-quartile range
CK	90.15 ± 48.9 U/L	82.5 U/L	50.5 – 125.5 U/L
CK-MB	33.29 ± 20.47 U/L	29 U/L	21-39 U/L

5. Discussion

Creatine kinase exists as three isoenzymes: MM, MB & BB. The CKMB isoenzyme is considered to originate almost exclusively from the myocardium and its quantification is of considerable value to the physician to know the extent of myocardial damage. But, CKMB values should not be considered the sole diagnostic indicator of acute MI and all positive values must be critically analyzed to exclude other causes of its increase in serum. This study is an approach to emphasize the need for careful clinical and laboratory interpretation of results. Various methods of CKMB measurements and the conditions that can result in apparent increase in CKMB owing to presence of interfering substances/factors have been reviewed in brief. It is important to be aware of the limitations of the individual assays in order to exclude method-related artifactual values & be able to correctly interpret the results obtained.[12]

Based on charge separation, the CK-MB can be assayed by following methods:- CK electrophoresis, Ion exchange chromatography, Immunoinhibition & immunoprecipitation methods. Other methods based on mass conc. are – Radioimmunoassay and Sandwich enzyme immunoassay.[12,13] The role of each method in estimating CK-MB has been discussed in brief.

CK-electrophoresis method separates CK into three bands –CKMM, CKMB & CKBB. Measurement of CK-MB by this method does not give a quantitative estimate of myocardial damage. It requires skilled manipulation so it is technically difficult and time-consuming.[8,13,15] The variation in interpretation can arise from subjective evaluation of CK-MB in addition to considerable error from diffusion and elution. Certain fluorescent compounds (drugs/ bilirubin) may complex with albumin and migrate close to CKMB giving false impression.[16] Despite having highest sensitivity and negative predictive value, this method is not fit for routine use.[8,13,15]

Ion exchange chromatography separates CK into various components. Interference may arise from CK-MM, CK-BB & Macro-CKs but to a lesser extent when using mini-column. It is time-consuming & cumbersome method for evaluation of CK-MB. Hence, it is not a suitable method for processing large number of samples.[8,12,16] Immunoinhibition method is a simple and fast utomated method for assaying CK-MB activity where immunosuppression of CK-M subunit is done using anti-CKMM antibodies. The activity of only the CK-B subunit is measured. The CKMB value is then obtained by doubling the activity of the CK-B subunits present.[8,16,17] We are using this method in our laboratory set-up. Although Immunoinhibition method gives rapid, precise, inexpensive and sensitive results but is not free from interferences. This method cannot differentiate the MB isoenzyme from BB isoenzyme and (or) any variant CK isoenzyme containing BB. It simply measures B-subunit activity and is not MB specific. Therefore, false positive results are obtained due to the presence of CK-BB, free CK-BB, macro-CKBBs, mitochondrial CK, adenylate kinase enzyme to such an extent that the CK-MB results may exceed the total CK values. Therefore, this method lacks specificity and has poor analytical precision and is less sensitive compared to electrophoresis or ion-exchange methods. Despite this, Immunoinhibition method is being used routinely for screening because of its sheer simplicity and rapid turnaround time. It is suggested that all positive results be confirmed by more specific CK-MB assays.[12,16–18]

Immunoprecipitation method is a fast and simple method for MB estimation but is prone to interference by MM, BB & macro-CK1 & other enzymes.[13] A combination of immunoprecipitation and Immunoinhibition method has the advantage of increased specificity but high conc. of MM, BB still interfere.

Radioimmunoassay for CK-MB measurement is the only MB-specific assay, but it requires the use of radioactive label making it an inappropriate method for routine testing. It is also subject to interference to certain extent.[8,12]

Sandwich enzyme immunoassay uses human anti-animal antibody (Ab) like those obtained from Goat or Mouse. This assay uses two different antibodies which act on 2-sites of the MB and form a sandwich. This method was also susceptible to interference by MM & BB which was later overcome by using anti-CKMB tracer Ab-labelled with acridinium ester & immobilizing CKBB on paramagnetic particles providing a chemiluminescent & magnetic separation. This eliminated interference by both MM & BB. Using more specific Abs, paramagnetic solid phase & chemiluminescent label - makes this 2-site CKMB assay superior in performance to previous assay in terms of convenience, reproducibility, faster & efficient separation. Acridinium ester is safe, sensitive and a stable non-isotopic label. The Immunoenzymometric assays requires additional 20-30 minutes of incubation for color development as compared to the chemiluminescent assay which give results much faster.[13]

Apart from these methods, Bioluminescent Immunoinhibition & Dade CARDIOZYME immunoinhibition were also used previously but are only of historical importance now. Bioluminescent assay

used ATP, NAD(P)H or H_2O_2 for light emission. ATP production is monitored using firefly bioluminescence as indicator reaction. The CK-M subunit is inhibited and CK-B subunit is quantified. This assay is more precise than electrophoresis or ELISA making it suitable for urgent measurements, but the coarse temperature requirements have limited its routine use. In Dade CARDIOZYME Immunoinhibition method specific Ab were raised in goats against M subunit of CK and the CK estimation done by Rosalki technique (19). GEMSAEC centrifugal analyzer would rapidly mix reagents and estimate up to 60 samples/hr. This required seven minutes of pre-incubation time before readings in the rotor, thenabsorbance readings at 30 sec interval.[15] These methods are not used today because much better and efficient methods are available now.

5.1. Various interferents in immunoinhibition method for MB

The Immunoinhibition assay for CK-MB gives "false positive or negative" results in more than 5 % of the cases (16), the reasons for which are mentioned below briefly:-

5.1.1. Hemolysis

The activity of CK & CK-MB is significantly increased by hemolysis, although erythrocytes do not contain CK activity. This effect is attributed to lysed erythrocytes which release the enzymes adenylate kinase and glucose-6-phosphate dehydrogenase into the serum. The adenylate kinase mainly effects by increasing ATP (Adenosine triphosphate) which is a sub-product in Immunoinhibition process to such an extent that the CK-MB values might actually exceed the total CK concentration. The CK & CKMB reactions use ATP and glucose-6-phosphate as substrates, so increased levels of substrates in serum ultimately results in increased MB activity as they are not inhibited by the antibodies used against CK. The CK-MB activity measured by Immunoinhibition method is found to correlate positively with the degree of hemolysis. Since CK-MB is present in lower concentration in serum, it can easily be affected by changes in serum. In our laboratory we are using Randox reagents for these assays and are processing samples on Randox Imola autoanalyzers. In order to prevent interference from hemolysis, adenosine monophosphate (AMP) and diadenosine pentaphosphate (Ap5A) are added in the reagent (test kit) which acts as inhibitors of adenylate kinase. Since the complete inhibition is not achieved by these inhibitors, hemolysis continues to positively interfere with the CK-MB results as mentioned in the kit insert and also various other studies.[8,16,17,19–21]

An interesting phenomenon of negative numerical value of CK-MB is also observed at the lower concentration of MB values. The reason behind it is the presence of reduced glutathione (GSH) which is present as an activator in the reagents required for the CK-MB assay. The enzyme glutathione reductase which is normally present inside the erythrocytes is released when they are hemolysed. When such a sample is processed, this enzyme catalyzes the conversion of reduced glutathione present in the reagent to get oxidized consuming NAD(P)H in the process leading to negative absorbance change with time. Therefore, a false negative result and a negative numerical value is obtained in such cases with low CK-MB values.[22]

5.1.2. Macro-CKs

On CK electrophoresis, the bands that exhibit mobilities different from that of CK-MM, CK-BB & CK-MB are known as "atypical" or "macro-CK" iso-enzymes. This phenomenon is commonly encountered in 1-3% of patient samples. Complex between CK and immunoglobulin is called as macro-CK type 1 (molecular weight >200 kDa) and macro-Ck type 2 (mol. Wt >300 kDa) is a polymeric complex of mitochondrial CK. The most commonly formed complex is between CK-BB with IgG and with a lesser frequency with IgA or IgM.[4,23] They interfere with immunoinhibition method by being measured as CK-MB, since atypical CKs remain uninhibited, to an extent that the CK-MB values are found to be similar to the total CK values or might even exceed the later.[8,22] Free CK-BB also increases CK-MB values, CK-B to total CK ratio of (>20%) is almost pathognomonic of presence of macromolecular CK forms.[16,24] Macro-CKs can be found in apparently healthy individuals and in conditions like myopathy, heart diseases, gastro-intestinal disease and auto-immune diseases.[4,23] An elevated CKMB value where cardiac involvement has been rled out or in asymptomatic individuals, these clinically discrepant CK values should raise the suspicion of macro-molecular variants of CK.[4,23,25] Macro-CK type 2 also called as mitochondrial CK is non-immunoglobulin bound is mostly found in malignancies and severely ill patients of all ages. Immunoinhibition assays are positively influenced by the presence of these in serum, because these are not inhibited by antibodies to M-subunit resulting in higher CK-MB values.[8,16,23,25]

5.1.3. Cardiac injuries other than acute myocardial infarction

Any myocardial injury and not just acute myocardial infarction can cause the release of CK-MB e.g. cardiac contusion from trauma. Other insults to cardiac tissue such as cardiothoracic surgery, myocarditis (viral or autoimmune), metastatic involvement of myocardium, coronary arteriography, uncomplicated angioplasty and hemodynamic monitoring can cause increased CK-MB to an extent that it exceeds the normal reference interval.[12,26]

5.1.4. Muscle injury

Non-myocardial CK release in the circulation is most commonly caused by injury to the muscle as occurs in major trauma (including burns, crush injuries, electrical injuries), grand mal seizures, acute alcoholic myopathy, hyperthermia, hypothermia, cardiopulmonary resuscitation, defibrillation and intramuscular injections. Another reason is skeletal muscle regeneration which increases CK-B subunits in the muscle (12). Associated myopathies of diseases like chronic renal failure & sometimes hypothyroidism may also show raised CK-MB values. Other rare causes include placenta as a source of CK-MB and theophylline intoxication (12, 28).

5.1.5. Decreased clearance of CK-MB enzyme from serum

The reticuloendothelial system is responsible for clearance of serum enzymes but changes can be induced in this mechanism by hypothyroidism and hyperthyroidism leading to delayed clearance of CK-MB from serum. This increase persists only till the hypo/hyper-metabolic state is resolved making it easily distinguishable from the picture of acute myocardial infarction.[12]

5.1.6. Organ disorders

Lung tumors, gastro-intestinal disorders, central nervous system, neoplasm, and tumors of colon, kidney, prostate, bladder, testes, breast, uterus & ovaries can all lead to spuriously elevated MB values.[12,20,27]

Although CK-MB assay has served as a useful marker in diagnosing myocardial infarction for a long period but its utility has ever been questioned considering the availability of more specific & sensitive troponin assays, added cost without much information, and misinterpretation of results from immunoassay based CKMB methods.[11] It seems like MB assays have reached the end of their useful life and might just be eliminated in the near future owing to the various associated interferents.[17,28] The initial claims made about absolute specificity of CK-MB have been questioned time & again, yet many clinicians remain unclear as to whether CKMB results adds any extra information to their diagnostic armamentarium or not. The false-positive reports obtained in apparently healthy individuals leads to apprehension or misinterpretation of results in whom there was no need to perform the CK-MB test in the first place itself. It is instead suggested to use CK-MB to total CK ratio. As of now, CK-MB is considered in the category of an over-used test.[2]

Certain guidelines have recommended the discontinuation of CK-MB testing for the diagnosis of myocardial infarction. A new infarction or a suspected extension of infarction in a patient recovering from acute coronary syndrome (ACS) remains the only indication for CK-MB assay. Even this indication for CK-MB testing is disputed and certain institutions have discontinued its use without observing any ill-effects. Just like a lag period seen when a new test is introduced, similar lag is also observed when discontinuing the out-dated & obsolete test. A review of the relevant literature and the local data is required to safely remove a test from laboratory menu.[28] It is important to use the test judicially so as to minimize any apprehension & misinterpretation arising from the elevated results. Need for careful clinical and laboratory interpretation of results, in scenarios of apparently increased CKMB owing to presence of interfering substances. One must be familiar with the limitations of individual assay systems so as to exclude method-related artifactual values.[12]

The analysis based on techniques like microarray and quantitative proteomics have suggested that CK-BB could serve as a potential biomarker for early diagnosis of certain malignancies. In 2015, a study has shown that higher CK-MB to total CK ratio (>1) is associated with various malignancies like colorectal cancer, lung cancers and hepatocellular carcinoma. The association of this ratio with malignancies has found a potential role in primary cancer screening.[6]

6. Conclusion

It must be borne in mind that not all assays measure the same thing, may not necessarily be specific and that even the apparently similar techniques may have different reference ranges. The consumers of tests must consider using methods that are free of these interferences & be aware about the possible causes of interference when interpreting the results. There is less likelihood for harmonization of these assays in the near future. In case of doubt, a different methodology for analysis must be considered to rule out false results. A collaborative effort must be made by the laboratory and the physician to resolve any discrepancy, and avoid mismanagement of the patient. Recently developed newer assays like Aptamer-based fluorescent assay can be considered as potential assay for CKMB measurement but they are still in the initial stages.[29] These might prove to be beneficial to overcome the interferences caused by macro-CKs encountered with the conventional immunoinhibition methodology.

7. Source of Funding

None.

8. Conflict of Interest

None.

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