Research Article

Importance of Heart-Type Fatty Acid-Binding Protein Combined with Creatinine Kinase and Homocysteine in Determining the Severity of Acute Poisoning

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ABSTRACT

Background: This study aimed to assess the importance of Heart-type Fatty Acid-Binding Protein (H-FABP), Creatinine Kinase (CK) and Homocysteine (Hcy) in determining the severity of acute poisoning.

Materials and methods: 224 poisoning patients were divided into four observed groups-Carbon monoxide (CO), alcohol, pesticide and drug, 50 health people as control group were included in this study. The patients were diagnosed moderate or severe acute poisoning. Blood samples were collected at the time of admission and the H-FABP, CK and Hcy of serum were tested at the time point.

Results: All the four observed groups of patients, the average H-FABP, CK and Hcy levels were significantly higher than those of the control group. We found H-FABP combined with CK had a statistically correlation between the moderate and severe of acute CO and pesticide poisoning, H-FABP combined with Hcy had a significantly correlation between the moderate and severe of acute alcohol poisoning, H-FABP combined with CK and Hcy had a significantly correlation between the moderate and severe of acute drug poisoning. Receiver Operating Characteristic (ROC) curve showed that the combination of three biomarkers could improve the diagnostic ability of the type and severity of acute poisoning.

Conclusion: H-FABP combined with CK and Hcy in determining the type and the severity of acute poisoning has an important value.

Keywords: Acute poisoning; Heart-type Fatty Acid-Binding Protein (H-FABP); Creatinine Kinase (CK); Homocysteine

INTRODUCTION

Acute poisoning is a common disease in Emergency Medicine (ED) which usually secondary results in destruction of multiple organs and system especially myocardial damage [1]. Although it does not represent the largest group of disease, such as stroke, heart attacks and infections, but in China acute poisoning is responsible for about 10.7% of all causes of death. It mainly includes the following categories: Intoxication with carbon monoxide (CO), intoxication with medical drugs, and intoxication with chemical products and pesticide.

Heart-type Fatty Acid-Binding Protein (H-FABP) is a soluble small molecule protein composed of 133 amino acid residues, mainly distributed in the heart, skeletal muscle, kidney, brain and other tissues [2,3]. It plays a role in intracellular fatty acid transport [4]. This protein has been recently used as a new marker since it released into the blood when myocardial cell destruction. In the acute poisoning patients, an increase in cardiac biochemical indicators like e.g. Creatinine Kinase (CK), Creatinine Kinase MB (CK-MB), myoglobin changes have been reported [5,6]. Homocysteine (Hcy) is an oxidant that causes oxidative stress in the body [7,8]. It has been reported that the

role of oxidative stress as a major pathogenetic factor in some exogenous intoxication [9,10].

In recent years, serum H-FABP is more specific than myoglobin and it can be identified earlier than CK-MB and troponins in acute coronary syndromes [11,12]. Meanwhile, H-FABP combined with other biochemical indicators have been widely used in the detection of myocardial damage caused by different diseases [13]. However, studies specially focused on the significance diagnosis of H-FABP combined with CK and Hcy in the acute poisoning are limited. Herein, we monitor the difference of H-FABP, CK and Hcy in different type of the acute poisoning patients. Our specific objective is to assess the value of the three biomarkers in the diagnosis of moderate and severe acute poisoning.

MATERIALS AND METHODS

The study followed the STROBE guidelines and was approved by the Ethical Committee of the Xi'an Central Hospital (2021-2020). The study was conducted as an observational study. Participating subjects read and signed the informed consent prior to enrolling in the study. This study was conducted on 224 cases of clinically diagnosed acute poisoning including carbon monoxide (CO), alcohol, pesticide and drug in the Department of Occupational Medicine of Xi'an Central Hospital between July 2017 and September 2020. Fifty healthy sex and age matched people were included in the control group. The sample size of our study was calculated after conducting a statistical analysis.

Distribution

• By gender: 102 women and 122 men
• By age: From 18 to 76 years old, the mean age of subjects was 50.4 ± 9.7 years

Blood samples were collected at the time of admission and the H-FABP, CK, Hcy of serum were tested at the time point. Laboratory tests were performed at the Clinical Laboratory of Department of Occupational Medicine of Xi'an Central Hospital.

Statistical analysis

Statistical analysis was performed using SPSS19.0 software (SPSS, Chicago, USA). All data were expressed as mean ± Standard Deviation (SD). All the data were normally distributed. The results of the parameters (H-FABP, CK, Hcy) were compared using the One-Way Analysis of Variance (ANOVA) among the groups. The Receiver Operating Characteristic (ROC)-curve analysis was conducted to evaluate the consequence of the index we established. The P-value<0.05 was considered significant.

RESULTS AND DISCUSSION

Analysis of data from monitoring serum biomarkers traceability showed that in all four observed groups, the average H-FABP, CK and Hcy levels were significantly higher than those of the control group (p<0.05). The H-FABP of CO and drug groups were higher than the other two groups (p<0.05). The CK of CO group was highest and that of drug and alcohol groups were higher than pesticide group (p<0.05). The Hcy of alcohol group was highest and that of CO group was higher than pesticide and drug groups (p<0.05) (Table 1).

To assess the dependence between the type of toxic substance and the severity of poisoning, we used cross tabulation on these categories. We found the expression of H-FABP had a statistically significant correlation between the moderate and severe of all types of poisoning (p ≤ 0.01) (Table 2). The expression of CK had a statistically significant correlation between the moderate and severe of all types of poisoning (p<0.01) expect alcohol group (p=0.318) (Table 3). The expression of Hcy were significant correlation between the moderate and severe of alcohol and drug poisoning (P<0.01) while no difference was found in the CO and pesticide poisoning (Table 4).

Group	Number	H-FABP (ng/ml)	CK (u/l)	Hcy (umol/L)
CO	44	7.29 ± 5.95* #▲	926.18 ± 822.23* # ▲ △	13.89 ± 3.71* #▲ △
Alcohol	46	3.09 ± 1.18*	211.26 ± 60.73* ▲	18.52 ± 7.19*▲ △
Pesticide	60	3.00 ± 1.34*	145.97 ± 104.82*	10.32 ± 2.29*
Drug	74	8.31 ± 3.49* # ▲	279.49 ± 258.86*▲	10.74 ± 2.60*
Control	50	1.51 ± 0.61	88.36 ± 27.81	9.59 ± 1.98
F	-	16.039	40.253	33.012

Note: *: Difference between the group and control group; #: Difference between the group and alcohol group; ▲: Difference between the group and pesticide group; △: Difference between the group and drug group.

Table 1: Serum level of H-FABP, CK and Hcy in the groups.

Group	Severity	Number	Mean ± SD	t	p
CO	Moderate	18	2.48 ± 1.08	34.975	<0.01
	Severe	26	10.64 ± 5.65		

Alcohol	Moderate	30	2.18 ± 1.06	42.619	<0.01
	Severe	16	4.81 ± 1.59		
Pesticide	Moderate	41	2.41 ± 0.99	13.075	<0.01
	Severe	19	4.18 ± 2.70		
Drug	Moderate	50	3.88 ± 3.12	59.817	<0.01
	Severe	24	13.22 ± 2.80		

Note: p value refers to the statistically significant difference between groups in the same period (P<0.05).

Table 2: H-FABP (ng/ml) of toxic substance and severity of acute poisoning.

Group	Severity	Number	Mean ± SD	t	p
CO	Moderate	18	264.06 ± 90.87	34.217	<0.01
	Severe	26	1384.58 ± 790.41		
Alcohol	Moderate	30	217.93 ± 64.42	1.019	0.318
	Severe	16	198.75 ± 50.79		
Pesticide	Moderate	41	107.17 ± 35.25	21.909	<0.01
	Severe	19	223.60 ± 146.43		
Drug	Moderate	50	156.30 ± 81.28	64.313	<0.01
	Severe	24	536.13 ± 308.81		

Note: p value refers to the statistically significant difference between groups in the same period (p<0.05).

Table 3: CK (u/l) of toxic substance and severity of acute poisoning.

Group	Severity	Number	Mean ± SD	t	p
CO	Moderate	18	11.08 ± 2.63	8.317	0.06
	Severe	26	15.14 ± 3.83		
Alcohol	Moderate	30	14.56 ± 2.79	58.293	0.01
	Severe	16	25.95 ± 7.02		
Pesticide	Moderate	41	9.99 ± 1.63	3.302	0.074
	Severe	19	11.06 ± 2.95		
Drug	Moderate	50	10.14 ± 1.77	32.158	<0.01
	Severe	24	13.22 ± 2.80		

Note: p value refers to the statistically significant difference between groups in the same period (p<0.05).

Table 4: Hcy (umol/l) of toxic substance and severity of acute poisoning.

Binary logistic regression was used to evaluate the effect of H-FABP, CK and Hcy on the diagnosis of the severity of acute poisoning. ROC curves depicted the discriminative value of our established evaluating system. The AUC was highest for combination group (H-FABP, CK and Hcy) (0.91) among all biomarkers (H-FABP 0.854, CK 0.833, Hcy 0.735). According to the ROC curves, we found that the optimal cutoff values were 4.08 ng/mL for H-FABP, 294.5 u/l for CK, 14.245 ng/mL for Hcy. Above their cutoffs, combination group had high sensitivities and specificities (81.4% and 90.0%, respectively). Meanwhile, combination group of the cutoff values could improve diagnostic performances of severity of acute poisoning (Table 5).

Variables	AUC	95% CI	Cutoff	Sensitivity (%)	Specificity (%)
H-FABP	0.854	0.804-0.905	4.08	74.40%	86%

CK	0.833	0.78-0.886	294.5	59.30%	89%
Hcy	0.735	0.664-0.805	14.245	59.30%	81%
H-FABP+CK+Hcy	0.91	0.867-0.953	-	81.40%	90%

Table 5: Performance parameters for predictors of severity of acute poisoning.

Acute poisoning is defined as an acute exposure (less than 24 hours) to a toxic substance and characterized by extensive damage to organs, including chemical pulmonary edema, bone damage, heart failure, toxic encephalopathy, liver disease, and even death. It is one of the most frequent causes of visits to the ED. The annual rate of ED visits associated with poisoning varies widely across the world, and ranges from 0.1% to 0.7% [14]. Common symptoms due to intoxication include headaches, nausea, vomiting, slumber, and weakness, which may lead to neurological symptoms varying from confusion to coma. Sometimes the poison is unknown when a patient is found comatose with an unknown history. Thus, early identification of findings of type and severity of poisoning is highly important. In the various types of intoxication, CO poisoning is a type of intoxication with serious mortality particularly during winter months, alcohol poisoning mostly occurs in young adults, pesticide poisoning is the most common in most regions of China, while therapeutic drug poisoning is the main type of intoxication in developed regions or cities, such as Shanghai [15-18]. Therefore, poisoned patients were divided into the following categories in our study: CO, alcohol, pesticide and drug.

Erenler, et al. [19] showed that H-FABP might be a promising biomarker in evaluation of clinical severity in acute CO poisoning. Kim, et al. [20] considered higher CK-MB could be a screening tool for CO poisoning. Tufkova, et al. [21] showed that monitoring the serum level of Hcy could be a reliable marker in alcohol poisoning. But previous researches have been limited to a single biomarker or a single type of poisoning.

In our study, we monitored three biomarkers and H-FABP, CK and Hcy were significantly increased in all four poisoning groups than control group. Furthermore, we assessed the dependence between the type of toxic substance and the severity of poisoning. We found H-FABP and CK was significantly increased in severe patients than moderate patients in CO and pesticide poisoning. H-FABP and Hcy was significantly increased in severe patients than moderate patients in alcohol poisoning, while CK had no difference. H-FABP, CK and Hcy were significantly increased in severe patients than moderate patients in drug poisoning. The reasons of different expression of biomarkers in different types of poisoning maybe as follows: H-FABP is a cytosolic protein found in large amounts in the myocardium and also found in the neuronal cell [22]. It plays a role in intracellular transport of fatty acid and would be released very early from damaged cells into the circulation. So it is the most sensitive biomarker in all types of poisoning patients. The results of previous study showed that serum CK activity was

increased in imazalil and cypermethrin treated groups [23]. It is consistent with our study in pesticide poisoning. Alcohol mainly causes liver damage, while CK is mainly distributed in myocardium and skeletal muscle but the least in liver. Hcy as an oxidant is mainly associated with the systematic alcohol dependence [9,24]. Study on Hcy suggested that there was no difference between moderate and severe medications poisoning [21]. However, the present results showed an increasing Hcy in severe drug poisoning. It maybe because most of the drug poisoning were composed of anti-psychotic and anti-depressant drugs in our study. A number studies on Hcy showed that elevations of serum Hcy was identified as the harmful cause of the cardiovascular and nervous system [25,26].

CONCLUSION

In summary, serum H-FABP, CK, and Hcy are closely related to acute poisoning. H-FABP combined with CK and Hcy in determining the type and the severity of acute poisoning has an important value. This result implies that the expression of Hcy depends on the type of toxic drug. In assessing the kind and degree of acute poisoning, H-FABP has significant usefulness in combination with CK and Hcy. Meanwhile, we established the system to evaluate moderate and severe poisoning, the result showed H-FABP combined with CK and Hcy could improve the severity diagnostic performances.

DECLARATIONS

Author's contributions

Yanli Wang and Xikai Wang conceived and designed the study. Xikai Wang and Jingjing Ma performed the study, collected and assembled the data. Yanli Wang performed the data analysis and interpretation. Xikai Wang and Yanli Wang wrote the manuscript. All authors read and approved the manuscript.

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Competing interests

The authors declare that there are no competing interests in this study.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

REFERENCES

1. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: Walking the tightrope. Emerg Med J. 2005;22(9):612-616.

2. Onal O, Celik D, Aslanlar E, Avci A, Celik JB. Myocardial infarction in a young patient after acute exposure to carbon monoxide. Anesth Pain Med. 2016;6(3):e33154.

3. Gandini C, Castoldi AF, Candura SM, Priori S, Locatelli C, Butera R, et al. Cardiac damage in pediatric carbon monoxide poisoning. J Toxicol Clin Toxicol. 2001;39(1):45-51.

4. Shepardson RP, Bazilevskaya EA, Harvatine KJ. Physical characterization of fatty acid supplements with varying enrichments of palmitic and stearic acid by differential scanning calorimetry. J Dairy Sci. 2020;103(10):8967-8975.

5. Zhang S, Wang Y, Cheng J, Huangfu N, Zhao R, Xu Z, et al. Hyperuricemia and cardiovascular disease. Curr Pharm Des. 2019;25(6):700-709.

6. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-635.

7. Yu YM, Hou FF, Zhang X, Zhou H, Liu ZQ. Hyperhomocysteinemia, oxidative stress and microinflammation in chronic renal failure: Their roles in atherogene. Zhonghua nei ke za zhi. 2004;43(4):292-295.

8. Perna AF, Ingrosso D, Molino D, Galletti P, Montini G, Zacchello G, et al. Hyperhomocysteinemia and protein damage in chronic renal failure and kidney transplant pediatric patients-Italian Initiative on Uremic Hyperhomocysteinemia (IIUH). J Nephrol. 2003;16(4):516-521.

9. Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. Nutr Metab. 2017;14(1):1-2.

10. Aydemir D, Sarayloo E, Nuray UN. Rosiglitazone-induced changes in the oxidative stress metabolism and fatty acid composition in relation with trace element status in the primary adipocytes. J Med Biochem. 2020;39(3):267-275.

11. Suzuki M, Hori S, Noma S, Kobayashi K. Prognostic value of a qualitative test for heart-type fatty acid-binding protein in patients with acute coronary syndrome. Int Heart J. 2005;46(4):601-606.

12. Nakata T, Hashimoto A, Hase M, Tsuchihashi K, Shimamoto K. Human heart-type fatty acid-binding protein as an early diagnostic and prognostic marker in acute coronary syndrome. Cardiology. 2003;99(2):96-104.

13. Alhadi HA, Fox KA. Do we need additional markers of myocyte necrosis: The potential value of heart fatty-acid-binding protein. QJM. 2004;97(4):187-198.

14. Hanssens Y, Deleu D, Taqi A. Etiologic and demographic characteristics of poisoning: A prospective hospital-based study in Oman. J Toxicol Clin Toxicol. 2001;39(4):371-380.

15. Zhang J, Xiang P, Zhuo X, Shen M. Acute poisoning types and prevalence in Shanghai, China, from January 2010 to August 2011. J Forensic Sci. 2014;59(2):441-446.

16. Zhang M, Fang X, Zhou L, Su L, Zheng J, Jin M, et al. Pesticide poisoning in Zhejiang, China: A retrospective analysis of adult cases registration by occupational disease surveillance and reporting systems from 2006 to 2010. BMJ Open. 2013;3(11):e003510.

17. Wang BS, Lin CH, Li XT, Ming XU, Zhu BL, Zhang J. Acute pesticide poisoning in Jiangsu Province, China, from 2006 to 2015. Biomed Environ Sci. 2017;30(9):695-700.

18. Jiang DF, Zhang ZM, Hu DH, Liu QH. Analysis of the characteristics of toxins in 6005 cases of acute poisoning in Guangxi. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013;25(7):429-431.

19. Erenler AK, Yardan T, Baydin A, Gunay M, Amanvermez R. Heart-type fatty acid-binding protein as a potential biomarker of acute carbon monoxide poisoning. Am J Emerg Med. 2013;31(8):1165-1169.

20. Kim JS, Ko BS, Sohn CH, Kim YJ, Kim WY. High-sensitivity troponin I and creatinine kinase-myocardial band in screening for myocardial injury in patients with carbon monoxide poisoning. Diagnostics. 2020;10(4):242.

21. Tufkova S, Paskaleva D, Sandeva M. Acute exogenous intoxications and homocysteine. Folia Med. 2020;62(3):519-524.

22. Liou K, Ho S, Ooi SY. Heart-type fatty acid binding protein in early diagnosis of myocardial infarction in the era of high-sensitivity troponin: A systematic review and meta-analysis. Ann Clin Biochem. 2015;52(3):370-381.

23. Đikić D, Landeka I, Knežević F, Ćuić MA, Benković V, Knežević HA, et al. Carbendazim impends hepatic necrosis when combined with imazalil or cypermethrin. Basic Clin Pharmacol Toxicol. 2012;110(5):433-440.

24. Prior PL, Vaz MJ, Ramos AC, Galduróz JC. Influence of microelement concentration on the intensity of alcohol withdrawal syndrome. Alcohol Alcohol. 2015;50(2):152-156.

25. Zis P, Grünewald RA, Chaudhuri RK, Hadjivassiliou M. Peripheral neuropathy in idiopathic Parkinson's disease: A systematic review. J Neurol Sci. 2017;378:204-209.

26. Djuric D, Jakovljevic V, Zivkovic V, Srejovic I. Homocysteine and homocysteine-related compounds: An overview of the roles in the pathology of the cardiovascular and nervous systems. Can J Physiol Pharmacol. 2018;96(10):991-1003.