Research Article

Ischemia-modified albumin levels in the prediction of acute neurological findings in patients with carbon monoxide poisoning in Minia Governorate, a prospective clinical study.

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Abstract
Background and Objectives: Carbon monoxide is responsible for more than half of fatal intoxications in many countries. The aim of this prospective study is to determine serum IMA levels in the prediction of acute neurological findings in patients with carbon monoxide exposure, and if there is a correlation between serum IMA levels and COHB levels and other acute neurological findings. **Methods:** We enrolled 80 subjects (60 patients and 20 controls) hospitalized due to CO poisoning. Ischemia-modified albumin and COHb levels were carried out to all the patients on admission and for healthy controls. In addition, IMA was carried out to all patients after 3 and 6 hour of admission. **Results:** The IMA levels of the study group on admission were significantly higher than those of the control group. The IMA levels of patients with ANFs were significantly higher than those of patients without ANFs. **Conclusion:** The optimal cutoff value for IMA levels on admission of > 15.66 ng/ml to predict acute neurological findings with CO intoxication. So, it is believed that IMA levels can be used to predict which patients will develop ANFs due to CO poisoning.
Keywords: Carbon monoxide, carboxhemoglobin, ischemia- modified albumin, CO neurotoxicity.

Introduction
Carbon monoxide poisoning is the most common cause of injury and death due to poisoning worldwide[1]. CO is the main cause of intoxication-related mortality in the developed world and is implicated in more than half of fatal intoxications in many countries[2]. CO is responsible for tissue hypoxia by forming carboxyhaemoglobin and shifting the oxyhamoglobin dissociation curve leftward[3]. CO affinity to haemoglobin is around 210–250 times greater than that of oxygen[4]. In most patients, the central nervous system (CNS) is affected, and the clinical effects of CO poisoning on the CNS can be diverse, such as headache, dizziness, seizure, confusion, and coma[5]. Proper diagnosis can be easily missed as the signs and symptoms associated with carbon monoxide poisoning are vague, nonspecific and variable even if the condition is a life-threatening medical emergency[6]. Because it is unclear whether carboxyhemoglobin (COHB) levels correlate with clinical severity, there is clearly a need for a novel biochemical marker such as ischemia-modified albumin (IMA).

During acute ischemic conditions, the metal-binding capacity of albumin for transition metals, such as Cu, Ni, and Co, is reduced, generating a metabolic variant of the protein, commonly known as ischemia-modified albumin (IMA)[7].

The aim of this prospective study is to determine serum IMA levels in the prediction of acute neurological findings in patients with carbon monoxide exposure, and if there is a correlation between serum IMA levels and COHB levels and other acute neurological findings.

Subjects and methods
This study included 80 subjects (60 patients, 20 healthy controls). The patients were 42 males and 18 females of different

age groups ranging from (15-55) years. The subjects of the study plus controls were selected from the patients admitted to Minia University Hospital Poison Control Center during the period from November, 1st, 2016 to October, 31th, 2017 and were prospectively cross-sectional studied. A written consent was taken from the patients or from their relatives including their agreement to participate in this study.

The selection criteria were as follows: Patients diagnosed as acute carbon monoxide poisoning according to (history, clinical presentation at the time of admission, carboxyhemoglobin level and improvement on oxygen therapy).

The exclusion criteria were: (1) A previous diagnosis of a neuropsychiatric disease; (2) Post cardiac arrest state; (3) Concurrent head trauma; (4) Concurrent toxicity with another poison; (5) Presence of any systemic disease that causes elevated COHb level such as hemolytic anemia, during the progesterone phase of the menstrual cycle and severe sepsis[8]; (6) Pregnancy; (7) Refusal to participate in this study; (8) Patients with coronary artery disease, peripheral arterial disease, acute mesenteric ischemia and acute ischemic cerebrovascular disease[9]; (9) Patients with severe heart or liver failure; (10) Albumin level, <3.5 g/dL & >5.5 g/dL[10].

Physical, neurological examinations and laboratory investigations were carried out to all patients on presentation and for healthy controls. Subjects were classified into 3 groups according to absence or presence of acute neurological findings (ANFs) in the form of seizures, altered state of consciousness, syncope, focal neurological deficit, coma and Glasgow Coma Score (GCS) less than 15 on admission. Group I: control group. Group II: patients without ANFs. Group III: patients with ANFs.

Measurement of IMA levels was conducted using venous blood samples taken from patients on admission, and subsequently during the 3rd hour, and 6th hour after admission. In addition, arterial blood gas analysis, including COHB levels and biochemical values, was performed routinely on every patient on admission. Blood samples were drawn from 20 healthy controls to provide normal levels for the studied parameters. Samples taken for measurements of IMA levels were immediately placed into sterile test tubes and allowed to clot for 30 minutes before centrifugation for 15 minutes at approximately 1000 rpm. Then serum was removed and stored at -80^{o} C until assayed by IMA ELISA kits.

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 24. Descriptive statistics were done for parametric quantitative data by mean, standard deviation and minimum& maximum of the range, and for non-parametric quantitative data by median, while they were done for categorical data by number and percentage. Analyses were done for parametric quantitative data between the three groups using One Way ANOVA test followed by Post Hoc Tukey correction between each two groups, and for non-parametric quantitative data between the three groups using Kruskal Wallis test followed by Mann Whitney test between each two groups. Analyses were done for parametric quantitative data within each groupusing paired sample t test. Analyses were done for qualitative data using Chi square test (if number per cell >5), and Fisher exact test (if number per cell<5). Correlation between two quantitative variables was done by using Pearson's correlation coefficient. Correlation coefficient ranges from (0-1):-weak (r=0-0.24), fair (r=0.25-0.49), moderate (r=0.5-0.74), strong (r=0.75-1). ROC curve was done to determine the cutoff point, AUC, sensitivity, specificity, PPV, NPV and accuracy of IMA prediction ANF in CO intoxicated patients. Simple binary logistic regression analysis of IMA on admission for prediction of ANF in CO intoxicated patients.

Results

The study group included 60 patients, 42 males (70%) and 18 females (30%). There were no deaths among the study group. The

control group comprised 12 males (60%) and 8 females (40%). The age of the studied patients ranged between 15-55 years, and its mean ± SD was 33.7 ± 15.8 years in comparison to 35.3 ± 9.3 years in control group. Smoking was significantly higher in group III compared to group II. All the cases presented in this study were accidentally exposed to CO poisoning.

General examination among the different groups is presented in Table (1), while clinical presentation and some of laboratory investigations among the different groups are presented in Table (2) and Table (3).

The levels of ischemia- modified albumin on admission, after 3 hours and 6 hours, in group II and group III were significantly higher compared with group I as shown in Table (4) and Figure (1). The mean IMA level on admission in group I was 7.1, in group II 15.6, and in group III 20.9.

There was a significant positive correlation between COHB, HB, ALT, AST and Na^+ with IMA levels on admission. Also there was a significant negative correlation between GCS, PH, HCO_3, albumin, k^+, temperature, systolic and diastolic blood pressure with IMA levels on admission.

Simple binary logistic regression analysis revealed that IMA level on admission was a predictor of acute neurological findings. ROC curve analysis revealed that the optimal cutoff point for IMA level on admission was of > 15.66 ng/ml to predict acute neurological findings with CO intoxication with sensitivity 79.17% and specificity 75% as shown in Table (5), Table (6) and Figure (2).

Table (1): General examination among the different groups

General examination¶	**Group I (Control**	**Group II (Without ANFs)**	**Group III (With ANFs)**	**P value**			
				Among 3 groups	***Between each two groups***		
	N=20	**N=36**	**N=24**		***I vs II***	***I vs III***	***II vs III***
Systolic BP	(100-130) 116±10.7	(110-130) 118.6±6.9	(80-140) 105.6±25.8	***0.008****	*0.824*	*0.082*	***0.007****
Diastolic BP	(60-90) 75.5±11.1	(65-90) 79.7±8.5	(40-100) 70.4±22.7	***0.006****	*0.593*	*0.126*	***0.004****
Heart rate	(66-90) 77.8±8.1	(77-120) 93.8±13.3	(105-140) 122.7±12.1	***<0.001****	***<0.001****	***<0.001****	***<0.001****
Respiratory rate	(12-16) 13.7±1.5	(14-24) 19.1±3.2	(15-25) 21.4±3.5	***<0.001****	***<0.001****	***<0.001****	***<0.001****
Temperature	(36.7-37.3) 37±0.2	(36.5-37.4) 36.9±0.3	(36.5-37.2) 36.8±0.3	*0.065*	*0.134*	*0.068*	*0.854*
GCS	(15-15) 15±0	(15-15) 15±0	(8-13) 10.2±1.8	***<0.001****	*1*	***<0.001****	***<0.001****

ANF: Acute Neurological Finding; ¶: quantitative data expressed as range/mean±SD; *: Significant difference at P value < 0.05; quantitative data analysed by one way ANOVA test followed by post Hoc Tukey analysis.

Table (2): clinical presentation among the different groups

Clinical presentation$	Group I (Control	Group II (Without ANFs)	Group III (With ANFs)	P value			
				Among 3 groups	*Between each two groups*		
	N=20	N=36	N=24		*I vs II*	*I vs III*	*II vs III*
Symptoms							
Headache	0(0%)	32(88.9%)	----		***<0.001****		
Tinnitus	0(0%)	22(61.1%)	----		***<0.001****		
Blurred vision	0(0%)	13(36.1%)	----		***0.002****		
Palpitation	0(0%)	4(11.1%)	----		*0.285*		
Nausea	0(0%)	32(88.9%)	----		***<0.001****		
Dyspnea	0(0%)	4(11.1%)	----		*0.285*		
Signs							
Syncope	0(0%)	0(0%)	24(100%)	***<0.001****	---	***<0.001****	***<0.001****
Convulsions	0(0%)	0(0%)	19(79.2%)	***<0.001****	---	***<0.001****	***<0.001****
Agitations	0(0%)	0(0%)	24(100%)	***<0.001****	---	***<0.001****	***<0.001****
Confusion	0(0%)	0(0%)	9(37.5%)	***<0.001****	---	***0.002****	***<0.001****
Arrhythmia	0(0%)	0(0%)	10(41.7%)	***<0.001****	---	***0.001****	***<0.001****
Pulmonary edema	0(0%)	0(0%)	9(37.5%)	***<0.001****	---	***0.002****	***<0.001****
Tachycardia	0(0%)	13(36.1%)	20(83.3%)	***<0.001****	***0.002****	***<0.001****	***<0.001****
Tachypnea	0(0%)	9(25%)	15(62.5%)	***<0.001****	***0.019****	***<0.001****	***0.007****
Vomiting	0(0%)	32(88.9%)	24(100%)	***<0.001****	***<0.001****	***<0.001****	*0.143*

ANF: Acute Neurological Finding; $: qualitative data expressed as n (percentage); *: Significant difference at P value <0.05; qualitative data analysed by Fisher exact test.

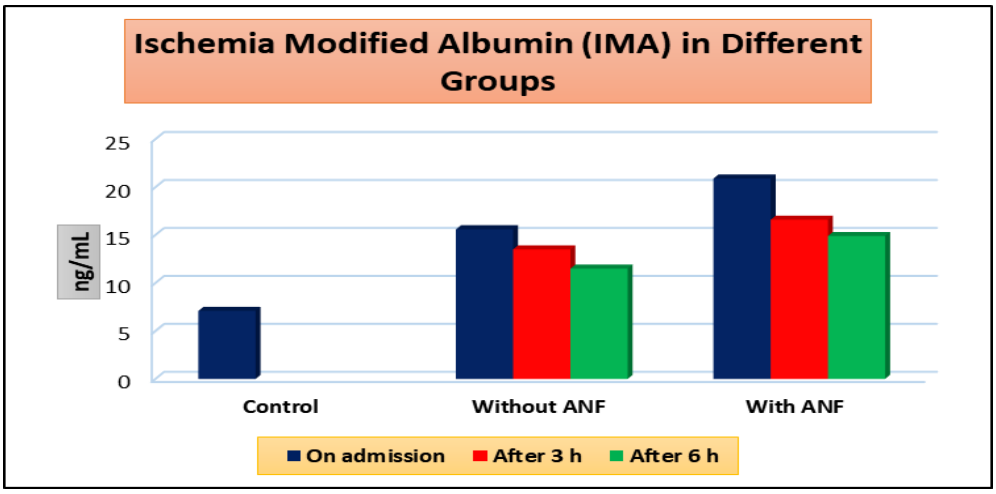

Fig (1): Ischemia Modified Albumin level among the different groups.

Table (3): laboratory investigations among the different groups

Laboratory investigations ¶	Group I (Control	Group II (Without ANFs)	Group III (With ANFs)	P value			
				Among 3 groups	*Between each two groups*		
	N=20	N=36	N=24		*I vs II*	*I vs III*	*II vs III*
pH	(7.35-7.45) 7.42±0.04	(7.28-7.43) 7.37±0.05	(7.24-7.38) 7.31±0.06	***<0.001****	***0.010****	***<0.001****	***<0.001****
HCO_3	(21-25) 23.1±1.2	(18-26) 22.4±2.5	(10-24) 14.8±5.2	***<0.001****	*0.730*	***<0.001****	***<0.001****
SpO_2	(97-99) 98.3±0.8	(95-99) 98.1±1.1	(95-99) 97.9±1.2	*0.424*	*0.747*	*0.391*	*0.740*
COHb	(0.1-2.2) 1±0.7	(12-29) 20.2±5.7	(25-48) 37.8±9.1	***<0.001****	***<0.001****	***<0.001****	***<0.001****
RBS	(88-126) 106.1±13.4	(80-120) 100.9±12.5	(85-119) 101.7±13.7	*0.348*	*0.332*	*0.512*	*0.969*
ALT	(16-24) 19.9±2	(16-21) 19.1±1.3	(15-24) 19.9±3.5	*0.349*	*0.479*	*1*	*0.423*
AST	(16-31) 21.2±4.8	(15-23) 20.2±2.4	(18-24) 21±2.1	*0.450*	*0.495*	*0.975*	*0.607*
Albumin	(3.8-4.9) 4.2±0.3	(3.8-4.4) 4.1±0.2	(3.2-4.6) 4.2±0.5	*0.267*	*0.260*	*0.827*	*0.580*
Urea	(18-40) 28.9±6.2	(25-38) 31.8±4.8	(15-40) 28.4±9.8	*0.144*	*0.315*	*0.972*	*0.174*
Creatinine	(0.4-1.3) 0.86±0.3	(0.5-1.4) 0.9±0.3	(0.8-1.3) 0.89±0.11	*0.874*	*0.863*	*0.934*	*0.989*
Na^+	(135-145) 139.4±3	(133-144) 139±3.2	(134-157) 140.9±8.6	0.412	*0.962*	*0.641*	*0.390*
K^+	(3.5-4.5) 4±0.3	(3.3-4.4) 3.9±0.3	(3.2-4.6) 3.8±0.5	*0.507*	0.703	*0.480*	*0.878*

ANF: Acute Neurological Finding; ¶: quantitative data expressed as range/mean±SD; *: Significant difference at P value < 0.05; parametric quantitative data analysed by one way ANOVA test followed by post Hoc Tukey analysis; non-parametric quantitative data (COHb) analysed by Kruskal Wallis test among the three groups followed by Mann whitney test between each two groups.

Table (4): IMA levels among the different groups

Ischemia modified albumin (IMA) ¶	Group I (Control	Group II (Without ANF)	Group III (With ANF)	P value			
				Among 3 groups	*Between each two groups*		
	N=20	N=36	N=24		*I vs II*	*I vs III*	*II vs III*
On admission	(5.7-8.3) 7.1±0.9	(11-22.6) 15.6±3.8	(13.9-25.5) 20.9±5.3	***<0.001****	***<0.001****	***<0.001****	***<0.001****
After 3 h	(5.7-8.3) 7.1±0.9	(10.5-19.3) 13.5±3.1	(12-23.1) 16.6±4.1	***<0.001****	***<0.001****	***<0.001****	***0.001****
After 6 h	(5.7-8.3) 7.1±0.9	(7.1-18.6) 11.5±3.5	(9.3-19.9) 14.9±3.9	***<0.001****	***<0.001****	***<0.001****	***<0.001****
P value within each group							
Admission vs 3h		***<0.001****	***<0.001****				
Admission vs 6h		***<0.001****	***<0.001****				
3h vs 6h		***<0.001****	***<0.001****				

ANF: Acute Neurological Finding; ¶: quantitative data expressed as range/mean±SD; *: Significant difference at P value < 0.05; parametric quantitative data analysed by one way ANOVA test followed by post Hoc Tukey analysis; analysis within each group done by paired samples T test

Table (5): Simple binary logistic regression analysis of IMA on admission for prediction of acute neurological findings

	Simple binary logistic regression analysis		
	OR	**95% CI**	**P value**
IMA on admission	1.26	1.12-1.43	***<0.001****
OR: Odds ratio; CI: Confidence interval; *: Significant level at P value < 0.05			

Table (6): ROC curve analysis of IMA on admission for prediction of ANFs

IMA at admission	
Optima cutoff point	>15.66
AUC	0.815
95% CI	0.693-0.903
P value	***<0.001****
Sensitivity	79.17
Specificity	75
mmPPV	60.9
NPV	84.4
Accuracy	76.7

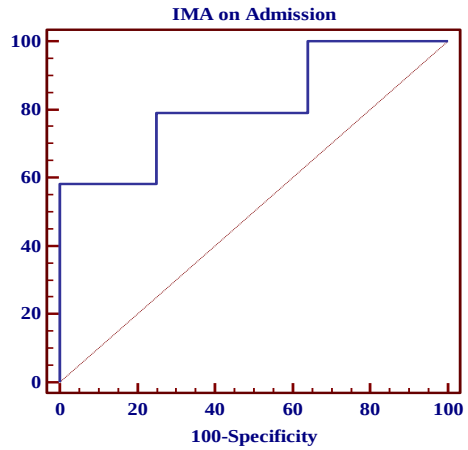

Fig (2): ROC curve analysis of IMA on admission for prediction of acute neurological findings

AUC: area under curve; CI: Confidence interval; PPV: positive predective value; NPV: : negative predective value

Discussion

Carbon monoxide poisoning is the leading cause of poisoning relevant to gas inhalation as a by-product of incomplete combustion of carbon based fuels and substances. It is the most common lethal poison worldwide. Its neurological and cardiological sequelae are the most frequent form of morbidity[11]. CO leads to tissue hypoxia by numerous mechanisms. Indirectly, by connecting with the heme related proteins such as hemoglobin, inhibiting oxygen release[12]. Directly, by binding with the cytochrome C-oxydase and myoglobin causing oxidative stress and destruction of exposed cells and tissues[13].

During acute ischemic conditions, the metal binding capacity of albumin is modified and reduces transition metal binding, generating a metabolic variant of protein. This change is quantifiable and commonly known as IMA[14]. Recently, IMA measurement has been proposed as a sensitive marker for the diagnosis of myocardial ischemia presenting with typical acute chest pain and licensed by the US Food and Drug Administration for diagnostic use in suspected myocardial ischemia[15]. However, high IMA concentrations do not seem to depend purely on myocardial involvement, and other organs seem to be responsible for the increase in IMA levels. Ischemia-modified albumin levels may rise during ischemia-reperfusion, affecting any organ, and cannot be considered together with oxidative stress[16].

To our knowledge, there are three studies that evaluated the relationship of CO poisoning and IMA levels. The first of these studies Turedi et al., 2011[17] compared 33 patients who were admitted for CO poisoning with 44 control individuals in terms of IMA levels. The researchers attempted to determine whether IMA levels

measured in the 3rd hour decreased compared to IMA levels on admission. Turedi et al., 2011[17] found that serum IMA levels were significantly higher in CO-poisoned patients compared with healthy individuals at both time of admission and at the third hour of treatment. That elevation was thought to be in all likelihood related to the hypoxic condition already present in CO-poisoned patients and to increased oxidative stress. There was no significant decrease of IMA levels in the 3rd hour compared to IMA levels on admission. There was no significant correlation between IMA and CO-Hb levels in CO-poisoned patients.

In a second study, conducted by Turedi et al., 2013[18], 18 rats were randomized into three groups. Group 1 served as the control group. Group 2 consisted of rats with low-dose exposure to CO, and Group 3 consisted of rats with high-dose CO exposure. At the end of 30 minutes, laparotomy was performed on all rats under general anesthesia, and blood samples were collected from the abdominal aorta for IMA and COHB measurement. In addition, specimens of brain, heart, kidney, liver, and lung were collected to determine organ damage. Turedi et al., 2013[18] reported that IMA levels are higher in rats exposed to CO and a moderate positve correlation was observed between COHb and IMA levels. However, IMA levels are not a good biochemical marker in terms of determining the severity of poisoning.

In the third study, Das et al., 2016[19] included the first 100 patients who were admitted to the ED because of CO poisoning compared with 50 healthy individuals as control. The aim was to determine whether serum IMA levels in patients with CO poisoning were higher compared with control group. In addition, the study aimed to determine if there was a correlation between serum IMA levels and COHB levels and other critical neurological findings (CNFs).

The results of the current study agreed with Das et al., 2016[19], who found that the IMA levels of the study group on admission and during the 1st hour and 3rd hour, were significantly higher than those of the control group. It was also noted that the IMA levels of patients who had critical neurological findings (CNFs) were significantly higher than those of patients who did not have CNFs. However, it was found that IMA levels in patients with CO poisoning dropped the same value as those of the control group after 6 hours which disagreed with our results.

The results of the present study concerning high IMA levels after 6 hour was in agreement with Gurumurthy et al., 2014[20], who reported that IMA has been shown to rise within minutes after the onset of ischemia, stay elevated for 6 to 12 hours, and return to normal within 24 hours. However, Mertoglu et al., 2018[21] stated that the level of IMA begins to rise in 3 hours in plasma following an ischemic process. It peaks first in 24 hours and reduces gradually in several days to normal levels.

In the current study, Simple binary logistic regression analysis revealed that IMA level on admission was a predictor of acute neurological findings. Also, ROC curve analysis showed that the optimal cutoff point for IMA level on admission of > 15.66 ng/ml to predict acute neurological findings with CO intoxication with sensitivity 79.17% and specificity 75%. This agreed with Das et al., 2016[19], who found that The multivariate analysis results revealed that only IMA level at admittance was an indicator for prediction of CNFs [p=0.002; odds ratio (OR)=1.05; 95% confidence interval (CI), 1.01-1.08].

Based on these results and the results of Das et al., 2016[19], it was believed that especially for selected patients with delayed admission to the ED and who were treated with 100% oxygen, IMA levels may be helpful in diagnosis of CO poisoning as the COHB half-life was about 75 minutes while half-life values of IMA levels were relatively longer than those of COHB about 180 minutes. IMA levels can be used to predict which patients will develop ANFs

due to CO poisoning after exclusion of all other causes of IMA elevation.

Conclusions

This study concluded that serum IMA levels could be helpful in the diagnosis of CO poisoning in selected patients those with delayed admission to the ED and who were treated with 100% oxygen after exclusion of all other causes of IMA elevation. The optimal cutoff value for IMA levels on admission of > 15.66 ng/ml to predict acute neurological findings with CO intoxication. So, it is believed that IMA levels can be used to predict which patients will develop ANFs due to CO poisoning.

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