Ain Shams Journal of Forensic Medicine and Clinical Toxicology
July 2018, 31: 23-32

A Prospective Comparative Study between Three Chemical Markers for Predicting Delayed Neurological Sequelae in Patients with Acute Carbon Monoxide Poisoning of Poison Control Center in Minia University Hospital

Osama A. Hassan, Shereen Abdelhakim Abdelaleem[1]and Lamiaa Hamdy[2]

[1] Department of Forensic medicine and Toxicology.
[2] Department of Clinical Pathology.

Faculty of Medicine- Minia University, Minia, Egypt.

Abstract Carbon monoxide poisoning (CO) is a major public health problem. Brain is the most sensitive organ to hypoxia induced by CO poisoning. Delayed Neurological Sequelae (DNS) is considered to be a delayed onset of neuropsychiatric symptoms after apparent recovery from acute CO poisoning. Therefore, this study was aimed to make a prospective comparative study between three markers (serum glutathione reductase, S100b protein and serum neurone- specific enolase) to predict the occurrence of DNS. This study was performed on 57 adult patients with acute CO poisoning. The markers were measured after arrival and the patients were divided into two groups: the DNS group (8 patients) & the non –DNS group (49 patients). There was a statistical difference between the two groups in terms of significant increase in loss of consciousness, syncope, dizziness, ECG changes, pneumonia, carboxyhemoglobin level, creatine phosphokinase, creatine phosphokinase-MB, troponin I, S100b protein, neurone-specific enolase in DNS grouped patiens and significant decrease in glasgow coma scale and glutathione reductase in DNS group. The cut off value of glutathione reductase was ≤ 30 U/L with a percentage of accuracy 94. 74. The cut off value of S100b protein was > 18.94 Pg/ L with 98.25 % percentage of accuracy, while, the cut off value of neurone-specific enolase was > 30.49 ng/ml and its accuracy was 96.49 %. All these cut off values predicted the occurrence of DNS. SO, it is concluded that serum S100b protein may represent the most reliable chemical marker for the prediction of DNS after acute CO poisoning by logistic regression analysis.

Keywords | Carbon monoxide, DNS, glutathione reductase, S100b protein, neurone-specific enolase, cut off value.

Introduction

Carbon monoxide (CO) poisoning is a major public health problem worldwide & considered to be one of the most common causes of death in the world. It is the commonest cause of morbidity and mortalilty in the United Kingdom and the United States. CO is a toxic, colorless, odorless, tastless and non irritating gas (Durmaz et al., 1999; Satran et al., 2006).

Carbon Monoxide is formed by incomplete combustion of organic materials due to insufficient oxygen supply to enable complete oxidation to carbon dioxide. The atmospheric concentration of CO is generally below 0.001%, but it may be higher in urban areas or enclosed environments (Weaver, 2009). CO has a significant affinity for all iron or copper containing sites and competes with oxygen at these active sites. The affinity of hemoglobin for CO is 250 times higher than that for oxygen , the result is the formation of carboxy hemoglobin (CO-Hb) which is a molecule incapable of carrying O_2 to tissue sites resulting in tissue hypoxia (Suner and Jay, 2008).

Brain is the most sensitive organ to hypoxia induced by CO poisoning. The major neurological manifestation of CO toxicity is delayed neurological syndrome (DNS) which includes many symptoms and signs as mental deterioration, amnesia, gait disturbances, psychosis, depression, parkinsonism (Pang et al., 2013). There are many prognostic factors that were suggested in previous studies to be associated with DNS in CO-poisoned patients e.g. older age, prolonged coma, headache upon hospital admission , metabolic acidosis,

high lactate levels and globus pallidus or white matter lesions on early brain computed tomography or magnatic resonance image (Hu et al., 2011 ; Moon et al., 2011).

Many studies were done to detect reliable plasma biomarkers that could be of a great value in the prediction of the development of DNS such as Plasma copeptin, nitrix oxide, serum s100b protein, serum Tau protein, carboxy hemoglobin level (Co-Hb), white blood cells (WBC) count, creatine phosphokinase (CPK), creatine kinase- MB (CK-MB) and others (Pang et al., 2013). Therefore, this present study was aimed to assess the usefulness of serum 100b protein, neuron specific enolase (NSE) and glutathione reductase (GSH) as biomarkers for the prediction of DNS in CO poisoned patients and compare the accuracy, sensitivity and specificity of them to detect the best one by logistic regression analysis.

Subjects & methods

This prospective comparative study was conducted on 57 patients (aged from 20- 45 years old) with acute CO poisoning, admitted to the Poison Control Center in Minia University hospital (tertiary- care hospital) in the period from November, 2016 to March 2017. Diagnosis of CO poisoning was made according to medical history, clinical manifestations at the time of admission, CO-Hb level > 5% in non smokers (> 10 % in smokers) and improvement on 100% high flow oxygen therapy through a face mask and hyperbaric oxygen if indicated (if CO-Hb > 25%, or the prescence of syncope, seizures, evidence of focal neurological deficits or acute myocardial infacrction (Brvar et al., 2004).

Exclusion criteria

1) A previous history of neuropsychatric disease.
2) Pregnancy
3) Concurrent head trauma or toxicity with another poison.
4) Refusal to participate in this study
5) Administration of any medications or presence of any systemic diseases that can affect CO-HB level as hemolytic anemia, hemolytic jaundice, severe sepsis and pneumonia.
6) Exclusion of any cause that can elevate S100b protein or NSE as status epilepticus, permanent neurological injury, current head trauma, dementia, parkinsonism, or failure to follow up after discharge and presentation more than 24 h after acute CO poisoning because the half life of serum NSE is 24h (Rasmussen et al., 2004).

The Protocol of this study was approved by the Medical Ethical Committee of Minia- University hospital and also it was done according to the ethical guidelines of Declaration of Helsinki. A written consent was taken from all patients or from their relatives in cases of unconscious patients including their agreement to participate in this study. Finally, patients were informed the symptoms of DNS (delayed symptoms of gait disturbances, mental deterioration, urinary incontinence, psychosis, depression and Parkinsonism (Hu et al., 2011) at the time of hospital discharge and were encouraged to return to the hospital if they experienced one of these symptoms. Follow up of discharged patients were for at least 2 months based on Choi's (1983) observation who was indicated that the lucid interval for the development of DNS is generally from 2- 40 days. Data, symptoms and signs of the development of DNS were investigated by reviewing the medical records of the patients or by completing a questionnaire containing simple yes / no questions. Patients' confidentiality was considered and ascertained in reviewing their records and questionnaires.

Clinical Assessment

Demographic data of patients were collected (age, sex, occupation, residence, special habits as smoking). Clinical assessment of patients recruited for the study was performed at the time of their admission. This assessment included symptoms, signs and investigations. Symptoms included headache, dizziness, nausea, vomiting, dyspnea, muscle weakness, blurred vision, confusion, palpitations, agitations and syncope. Clinical evaluation of patients was carried out regarding vital signs (temperature, pulse, blood pressure, and respiratory rate), conscious level, and Glasgow coma scale (GCS) scoring symptoms for coma. Assessment of complications during admission such as cardiac complications e.g. myocardial infarction, rhabdomyolysis and renal problems.

Electrocardiography (ECG) and Laboratory investigations included CO-Hb level, liver function tests including serum aspartate aminotransferase (AST), Serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), renal function tests including blood urea and serum creatinine, random blood sugar (RBS), serum electrolytes (Na and K), pH, creatine phosphokinase (CPK), creatine kinase-MB (CK-MB), Troponin I were done. Also, serum GSH, S100b protein and NSE were also assessed. Kits of GSH, S100b protein and NSE were obtained from Bio-diagnostic company-Egypt. GSH was measured according to Goldberg and Spooner, 1983, while serum S100b protein was measured as described by Goncalves et al., 2008. NSE was measured according to Kirino et al., 1983. The previous 3 parameters was measured using ELISA (Humareader plus, Germany).

Statistical analysis

The collected data were statistically analyzed using SPSS program version 20. Descriptive statistics were done as follow, continuous (quantitative) data were presented as median and IQR (inter quartile range), while categorical data were presented as number and percentage. Comparison between groups was done using Mann Whitney test for quantitative data, while, Fisher Exact test was used for categorical data. Pearson's correlation was used. Logistic regression analysis was used to determine the predictors of DNS. Receiver Operating Characteristics Curve (ROC curve) was done to determine sensitivity, specificity and accuracy of the predictors. Comparison between Predictors and

determination of the best one to predict DNS was done by Z-statistics test. Significance difference was taken at P value < 0.05.

Results

This study was conducted on 57 patients aged from (20-45 years old) with acute CO poisoning. Acute CO poisoning was diagnosed according to medical history, physical examination, laboratory investigations including CO-Hb level > 5 % in non smokers (> 10% in smokers). The studied patients were classified according to the development of DNS into 8 patients with DNS (DNS group) and 49 patients without DNS (Non-DNS group). The mortality rate within this study was zero. DNS developed in cases with CO-Hb level > 40 % and not received hyperbaric oxygen.

Acute CO poisoning was increased in married, non- smoking males. Also, it was frequently found in students and in subjects living in urban areas (table **1**). As regards, table (**2**) revealed that there was significant increase of respiratory rate, dizziness, syncope, loss of consciousness, pneumonia and cardiac affection in the form of inverted T-wave in DNS grouped patients. Also, there was significant decrease in GCS in the same group.

There was significant increase in CO-Hb level, CPK, CK-MB, troponin I, S100b protein NSE and significant decrease in pH and GSH in cases with DNS (table **3).** There was a significant correlation between serum GSH, S100b protein and NSE and certain significant numerical parameters (GCS, CO-Hb level, CK-MB, CPK, Troponine I, pH and respiratory rate) and there was insignificant correlation between NSE level and CK-MB level (table **4)**.

Simple logistic regression analysis of serum GSH, S100b protein and NSE levels showed that Odds ratio (OR) of GSH is less than one (0.81) and this means that increased level of GSH in CO intoxicated patients has a protective effect (increased GSH level led to decrease the incidence of occurrence of DNS). While, Odds ratio of S100b protein and NSE is more than one (1.51 & 2.3) respectively and this indicated that if their levels increased, the incidence of occurrence of DNS is increased (table **5).**

Table (**6)** showed multiple logistic regression analysis of GSH, S100b protein and NSE. The use of combination of the previous parameters in prediction of DNS revealed insignificant changes in Odds ratio. Table (**7)** indicated that there was one significant model to predict DNS by multiple stepwise logistic regression analysis which was the use of S100b protein (Odds ratio = 1.51). Increased the level of S100b protein increased the incidence of occurrence of DNS by one and half time. ROC curve analysis of the previous parameters revealed that the most accurate one in prediction of DNS was S100b protein; its sensitivity and specificity were 87.5 & 100 respectively. Also, if the cut off value of S100b protein is > 18.94 Pg/L, DNS will be occurred. While, if the cut off value of GSH is ≤ 30 U/L & NSE is > 30.49 ng/ml, DNS will be occurred (table **8) (**Fig **1, 2 &3).**

The results of comparison between GSH, S100b protein and NSE by Z- statistics test to determine the best predictable value for the occurrence of DNS in table (**9)** revealed that there was not a significant clear difference in AUC between them which means that there is no superiority of one to the others. Finally, if we need to depend on one of them to predict DNS, we will use multiple stepwise logistic regression analysis test that showed that the use of only one model which was S100b protein model.

Table (1): Distribution of Sociodemograghic data of patients of acute carbon monoxide poisoning.

Sociodemographic data	Number of acute CO intoxicated Cases (n=57)	percent
Sex		
Male	29	50.9%
Female	28	49.1%
Residence		
Urban	30	52.6%
Rural	27	47.4%
Marital state		
Single	28	49.1%
Married	29	50.9%
Occupation		
Student	32	56.1%
Worker	18	31.6%
Non worker	7	12.3%
Smoking		
Absent	51	89.5%
Present	6	10.5%

Table (2): Mann Whitney & Fisher exact statistical analysis of some clinical parameters affecting the development of DNS.

Mann Whitney test for numerical data			
Clinical parameters	**DNS**		**P value**
	Non DNS group (n=49)	**DNS group (n=8)**	
Heart rate	90 (80-115)	109.5 (82-114)	0.490
Respiratory rate	20 (18-22)	25 (23.5- 25.8)	**< 0.001***
Temperature (C°)	37.1 (36.9-37.3)	36.9 (36.8- 37.1)	0.200
Blood pressure (mmHg)	115 (110-130)	115 (110-140)	0.486
GCS	15 (13-15)	11 (11-12)	**< 0.001***
Fisher exact test for non-numerical data			
Headache	34(69.4%)	6 (75%)	1
Dizziness	1(2%)	2(25%)	**0.049***
Nausea and vomiting	23(46.9%)	4(50%)	1
Tinnitus	15(30.6%)	2(25%)	1
Weakness	38(77.6%)	4(50%)	0.188
Dyspnea	14(28.6%)	2(25%)	1
Blurred vision	15(30.6%)	2(25%)	1
Palpitations	6(12.2%)	0(0%)	0.580
Confusion	21(42.9%)	2(25%)	0.453
Syncope	12(24.5%)	6(75%)	**0.009***
Agitations	10(20.4%)	0(0%)	0.327
Conscious Transient loss Unconscious	21(42.9%) 14(28.6%) 14(28.6%)	0(0%) 3(37.5%) 5(62.5%)	**0.029***
Cardiac affection (inverted T wave)	9(18.4%)	8(100%)	**<0.001***
Pneumonia	3(6.1%)	4(50%)	**0.005***

DNS: delayed neurological sequelae, GCS: Glasgow coma scale, Continuous data presented as median and IQR while categorical data presented as number and percentage, Mann Whitney test for quantitative data between the two groups Fisher exact test for qualitative data between the two groups,: Significant difference at p value < 0.05*

Table (3): Mann Whitney test statistical analysis of laboratory parameters affecting the development of DNS

Laboratory data	**Delayed neurological sequelae**		**P value**
	Non DNS group (n=49)	**DNS group (n=8)**	
CO-Hb level	22.5 (20.5-28.6)	40.5 (35.7-43.3)	**<0.001***
Urea (mg/dl)	30 (25-31)	25 (24.3-33.3)	0.333
Creatinine (mg/dl)	0.8 (0.6-1.1)	0.8 (0.6-1.3)	0.889
ALT (U/L)	24 (18-29)	20 (17-35.3)	0.427
AST (U/L)	24 (19-30)	22 (22-37)	0.872
ALP (U/L)	68.26(64.1-70.1)	63.23(62-71.1)	0.077
RBS (mg/dl)	107.41(103-112.2)	101.59(98.7-105)	0.286
Na^+ (mEq/L)	140.02(135.1-145)	139.9(134.3-143)	0.741
K^+ (mEq/L)	4.42(3.4-6.2)	5.04(4.89-8.2)	0.813
CPK (IU/L)	204(200-208)	238.5(226-253)	**< 0.001***
CK_MB (IU/L)	28(26-29.5)	39(33.5- 44.5)	**0.001***
pH	7.3 (7.1-7.3)	7.2 (7.2-7.3)	**<0.001***
Troponin I (ng/ml)	0.09 (0.06-0.12)	1.04 (0.6-1.35)	**<0.001***
GSH (U/L)	63 (48.5-79.5)	26.5(24.3-29.5)	**<0.001***
S100b protein (Pg/L)	7.6 (6-8.4)	28.3 (24.9-31.4)	**<0.001***
NSE (ng/ml)	18.8 (14.4-25.6)	31.3 (28.5-33.2)	**<0.001***

*DNS: delayed neurological sequelae, ALT: alanine aminotransferase, AST: aspartate amino transferase, ALP: alkaline phosphatase, RBS: random blood sugar, CPK: creatine phosphokinase, CK-MB: creatine kinas-MB, GSH: glutathione reductase, NSE: neurone specific enolase, Continuous data (quantitative data) presented as median and IQR, *: Significant difference at p value < 0.05*

Table (4): Pearson's Correlation between serum GSH, S100 protein, NSE and some significant quantitative parameters

	Glutathione		S100b protein		NSE	
	r	P value	r	P value	r	P value
GCS	0.821	**<0.001***	-0.797	**<0.001***	-0.844	**<0.001***
CO-Hb level	-0.380	**0.004***	0.483	**<0.001***	0.390	**0.003***
CPK	-0.373	**0.004***	0.795	**<0.001***	0.418	**0.001***
CK-MB	-0.310	**0.019***	0.343	**0.009***	0.250	0.061
Troponine	-0.490	**<0.001***	0.721	**<0.001***	0.489	**<0.001***
Respiratory rate	-0.299	**0.024***	0.452	**<0.001***	0.362	**0.006***
pH	0.439	**0.001***	-0.758	**<0.001***	-0.447	**<0.001***

*GSH: glutathione reductase, NSE: neuron specific enolase, r: correlation coefficient "weak (r = 0-0.24), fair (r = 0.25-0.49) , moderate (r = 0.5-0.74), strong (r = 0.75-1), *: significant difference at p value < 0.05*

Table (5): Simple logistic regression analysis of GSH, S100 protein and NSE

	OR	95% CI	P value
GSH	0.81	0.71-0.93	**0.003***
S100b protein	1.51	1.15-1.98	**0.003***
NSE	2.3	1.2-4.4	**0.012***

GSH: glutathione reductase, NSE: neuron specific enolase, OR: Odds Ratio, CI: Confidence Interval
**: Significant level at p value < 0.05*

Table (6): Multiple logistic regression analysis of GSH, S100 protein and NSE

	OR	95% CI	P value
GSH	0.87	0.71-1.07	0.195
S100b protein	1.56	0.89-2.73	0.117
NSE	0.66	0.2-2.2	0.502

GSH: glutathione reductase, NSE: neuron specific enolase, OR: Odds Ratio, CI: Confidence Interval
**: Significant level at p value < 0.05*

Table (7): Multiple stepwise logistic regression analysis revealed one model

	OR	95% CI	P value
S100b protein	1.51	1.15-1.98	**0.003***

*OR: Odds Ratio CI: Confidence Interval *: Significant level at p value < 0.05*

Table (8): ROC curve analysis for prediction of DNS

	AUC	Std. error	P value	95% CI
GSH	0.964	0.024	**<0.001***	0.878-0.996
S100b protein	0.990	0.011	**<0.001***	0.918-1
NSE	0.954	0.033	**<0.001***	0.863-0.992

	Optimal Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
GSH	≤30	87.5	95.92	77.8	97.9	94.74
S100b protein	>18.94	87.5	100	100	98	98.25
NSE	>30.49	75	100	100	96.1	96.49

AUC: area under curve PPV: positive predictive value CI: Confidence interval NPV: negative predictive value
GSH: glutathione reductase NSE: neuron- specific enolase

Table (9): Z- statistics test for comparison between AUC of GSH, S100 protein and NSE:

	GSH vs S100	GSH vs NSE	S100b protein vs NSE
AUC	0.026	0.010	0.036
Std. error	0.025	0.038	0.027
95% CI	-0.0234-0.075	-0.065-0.085	-0.018-0.089
Z statistics	1.020	0.266	1.314
P value	0.308	0.790	0.189

GSH: glutathione reductase NSE: neuron-specific enolase CI: Confidence interval

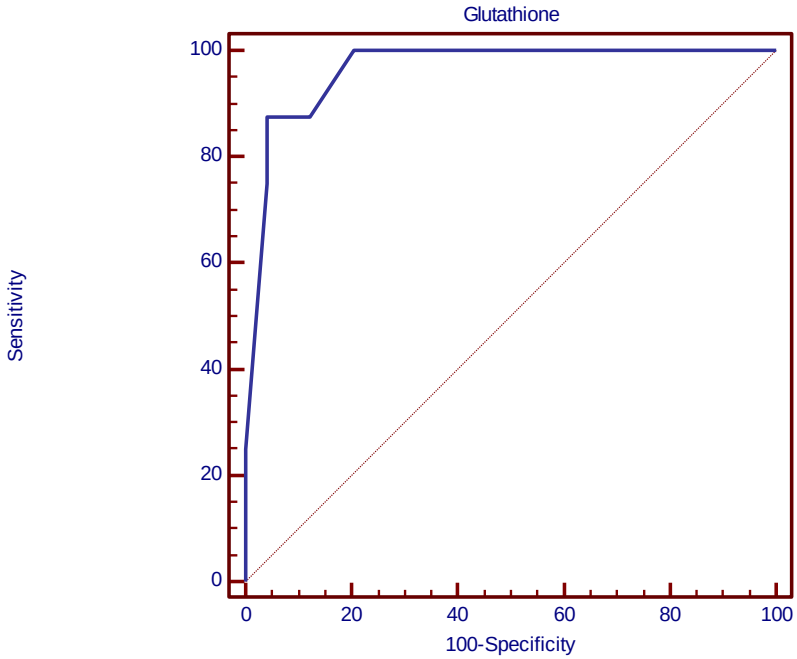

Figure (1): Receiver Operating Characteristics Curve (Roc curve) analysis of GSH for prediction of DNS

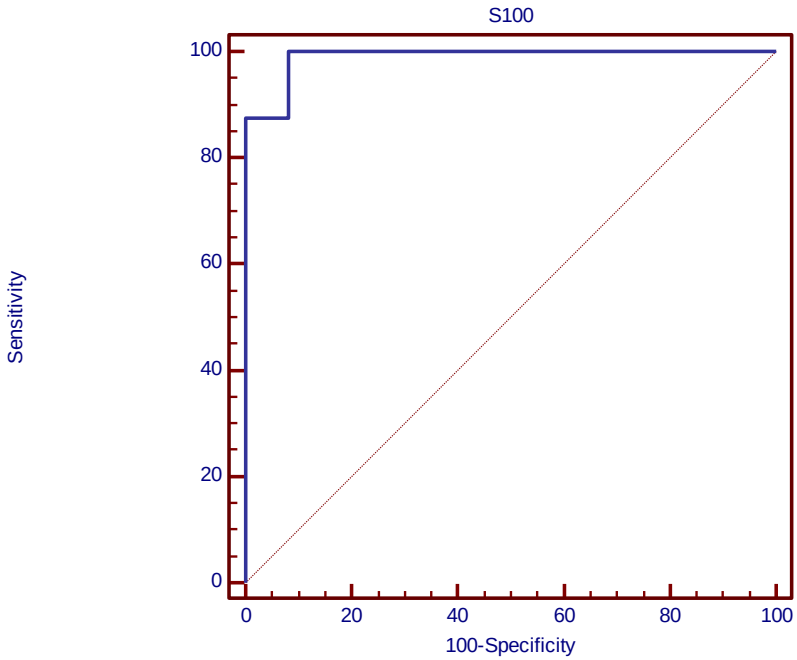

Figure (2): Receiver Operating Characteristics Curve (Roc curve) analysis of S100 protein for prediction of DNS

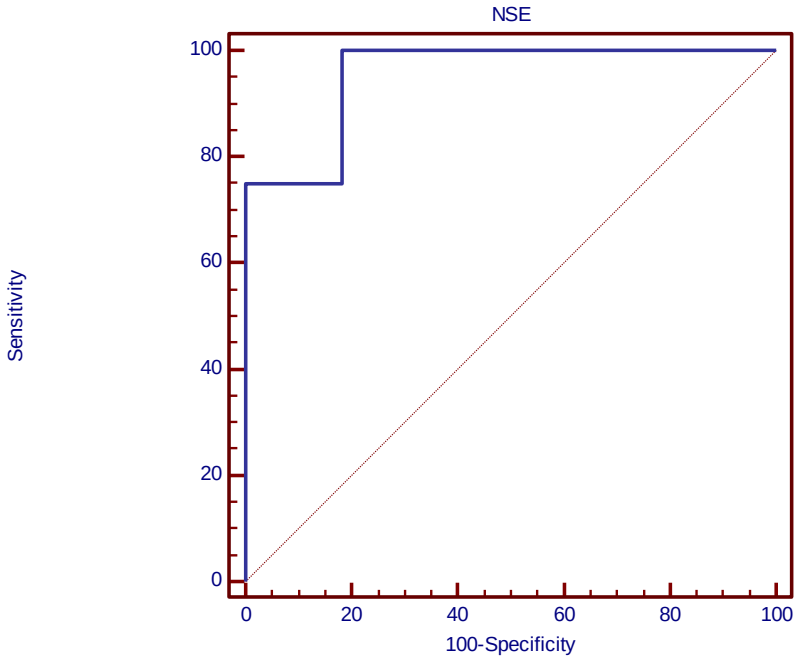

Figure (3): Receiver Operating Characteristics Curve (Roc curve) analysis of NSE for prediction of DNS

Discussion

Carbon monoxide (CO) has been termed "the unnoticed poison of the 21th century as it lacks a unique clinical signature. CO poisoning is difficult to be detedcted and can mimic other common disorders such as food poisoning. CO competes with oxygen for hemoglobin binding leading to reduction of the delivery of oxygen to tissues and the occurence of cellular hypoxia (Won and Jae, 2010)

The severity of CO poisoning depends on several factors as CO concentration, duration of exposure, individual susceptibility to CO effects, general health status of the exposed individual. The brain and heart are the most susceptible organs to CO toxicity because of their high metabolic rate (Weaver, 2009). CO poisoning increased the release of nitric oxide and other reactive O_2 free radicals, the end result is lipid peroxidation and a variety of lesions in myelin base protein (MBP) which constitutes about 30 % of myelin protein of CNS with the influx of macrophages and CD-4 lymphocytes. This mechanism can explain the delayed CO neurological sequale (Yu et al., 2012).

Many studies were done to detect reliable biomarkers for the prediction of the possibility of development of DNS as nitric oxide, serum TAU protein, serum GSH, S100b protein and NSE (Pang et al., 2013). NSE is one of the five isoenzymes of the glycolytic enzyme "enolase". This enzyme is released into CSF when neural tissue is injured. It is released from the neuronal and glial tissue to the blood only when the axons are damaged. It can be used as a marker indicating neuronal cell damage in patients with certain tumors e.g. neuroblastoma, medullary thyroid cancer, endocrine tumors of pancreas and melanoma. Also, it is increased in traumatic and hypoxic brain damage, status epilepticus and cardiac arrest (Akelma et al., 2013).

The biomarker S100b protein is a calcium-binding protein that·s produced mainly by glial cells of brain. Its secretion is increased in response to ischemic or oxidative stress injury e.g. traumatic head injury, stroke, subarachnoid hemorrhage, cardiac arrest (Yang & Rosenberg, 2011). This present study was aimed to assess the usefulness of serum S100b protein, NSE and GSH biomarkers to predict DNS and determination of the most accurate one by logistic regression analysis.

The results of this study revealed significant increase in some symptoms , signs and laboratory parameters in DNS grouped patients as respiratory rate, dizziness, syncope, loss of consciousness, inverted T wave, pneumonia, CO-Hb level, CPK, CK-MB, troponin I, S100b protein and NSE. Also, there was significant decrease in GCS, pH and GSH. The results of these study agree with the results of YS et al., 2017. Their study

revealed significant increase in loss of consciousness, CPK, troponin I, CO-Hb level, NSE, cardiac affection and pneumonia in DNS grouped patients.

On the contrary of these findings, YS et al., 2017 concluded that there is no significant difference in respiratory rate between DNS and non-DNS grouped patients. Also, the study of Chou et al., 2000 showed that low teperature is highly associated with CO poisoned patients (DNS grouped patients) and this finding does not agree with the results of the present study that revealed that no signifficant difference in temperature between DNS and non- DNS groups . Eunjung et al., 2012 conducted a study indicated the usefulness of S100b protein for predicting DNS in acute CO poisoning. Their study revealed significant increase in CO-Hb level, AST, creatinine, blood urea nitrogen (BUN), CPK and serum S100b protein.

The study of Giuseppe et al., 2011 and Chan et al., 2016 found that GCS score of 3 and loss of consciousness were possible prognostic factors for the development of DNS, their results agree with the results of this study. The currect study revealed that there was a significant correlation between serum GSH, NSE, S100b protein and some parameters (e.g. GCS, CPK, CK-MB, troponin I, pH). These findings disagree with the results of YS et al., 2017. Their results revealed that there was no variables showing significant correlation with the level of serum NSE.

Serum GSH, S100b protein and NSE were analyzed in this study by logistic regression analysis to identify predictors releated to the development of DNS. Multiple stepwise logistic regression analysis revealed one significant model which is the use of S100b protein (OR= 1.51, 95% CI was 1.15-1.98). These results disagreed with the results of YS et al., 2017 who reported that there were only 2 significant predictors by multivariate logistic regression analysis which were GCS (OR=3.336, 95% CI was 0.130-0.867) and serum NSE (OR= 1.105, 95% CI was 1.019-1.199).

The results of ROC curve analysis of GSH for predicting DNS in this study were (AUC: 0.964, optimal cut off value ≤ 30 U/L , sensitivity =87.5 , specificity = 95.95 and its accuracy was 94.74%). While, the values of S100b protein were (AUC: 0.990, cut off value > 18.94 pg/L, sensitivity= 87.5, specificity= 100 and its accuracy was 98.25%). NSE values were (AUC: 0.954, cut off value > 30 ng/ml, specificity : 100 , sensitivity : 75 and its accuracy in prediction of DNS was 96.49%). These results were in contrast to those reported by Eunjung et al., 2012, in which their results revealed that the cut off point of S100b protein was 0.165 and this value predicted the development of DNS after CO poisoning with 90% sensitivity and 87% specificity. Also the results of this present study disagreed with the results of YS et al., 2017. Their study showed that NSE is a good predictor of DNS (OR= 1.105, 95% CI was 1.019- 1.199 and AUC = 0.836).

This current study revealed that there was no significant differences between areas under the ROC curve by Z- statistics when we compared GSH vs S100b protein (AUC = 0.062), GSH vs NSE (AUC = 0.010) and S100b protein vs NSE (AUC= 0.036) which means that there is no superiority of one to the others, and if we need to choose one predictor of DNS we use the only one model of multiple stepwise logistic regression analysis which was S100b protein. These results were not in accordance with that of YS et al., 2017 whose study indicated that combination of initial GCS and NSE was better than the use of GCS or NSE alone.

Yang and Rosenberg, 2011 clarified that acute CO poisoning is associated with hypoxia and ischemia which can activate two substances which are gelatinase A (MMP-2) & gelatinase B (MMP-9) with subsequent degradation of tight junctions of endothelial cells and basal lamina and finally compromising the blood brain barrier and so the passage of elevated S100b protein or NSE from CSF to blood. The explanation of decreased GSH, increased NSE & S100b protein in DNS grouped patients in CO poisoning may be due to neuronal cell injury, hypoxia, oxygen radical- mediated lipid peroxidation and nitric oxide liberation from platelets (Weaver, 2009).

Conclusions & recommendations

Basing on the results of the current study , there are some significant clinical manifestations and laboratory parameters affecting the development of DNS as respiratory rate, GCS, syncope, dizziness, loss of consciousness, CO-Hb level, CPK, CK-MB, pH, troponin I, GSH, NSE, S100b protein. Also, these results indicated that if the cut off value of serum GSH is ≤ 30 U/L, S100b protein is > 18.94 pg/L and NSE > 30.49 ng/ml predicte the development of DNS after acute CO poisoning. Finally, it is concluded that serum S100b protein may represent a novel biomarker for predicting DNS after CO poisoning by multiple stepwise logistic regression analysis (its accuracy was 98.25%).

It is advised to make further studies with large sample sizes of acute CO poisoned patients with severe neurological injury to validate the results of the present study. The observation period for the development of DNS was relatively short (2 months), so there is a possibility that the DNS incidence rate was

underestimated, and so it is advised to prolong the period of observation. It is recommended that an out patient clinic to be initiated to assess all possible delayed neurological manifestations of acute CO poisoning and this clinic should be related and linked to the poison control center. Finally, it is recommended to find new predictors for DNS and other complications of CO poisoning.

References

Akelma AZ, Celik A, Ozdemir et al., (2013): Neuron-specific enolase levels in carbon monoxide poisoning: children are not just small adults. Am J Emerg Med. 31: pp. 524-528.

Brvar M, Mozina H, Osredkar J et al., (2004): S100B protein in carbon monoxide poisoning: a pilot study. Resuscitation. 61: pp. 357-60.

Chan MY, Au TT, Leung KS, et al., (2016): Acute carbon monoxide poisoning in a regional hospital in Hong Kong, historical Cohort study. Hong Kong Med J. 22: PP. 46-55.

Choi S (1983): Delayed neurological sequelae in carbon monoxide intoxication. Arch Neurol. 40: pp. 433-435.

Chou K, Fisher J, Silver E (2000): Characteristics and outcome of children with carbon monoxide poisoning with and without smoke exposure referred for hyperbaric oxygen therapy. Pediatr Emerg Care. 16: pp. 151-1.

Durmaz E, Laurence S, Carruthers S (1999): Carbon monoxide poisoning and hyperbaric oxygen therapy. Brjunurse. 8: pp.1067-1072.

Eunjung P, Junghwan AHN, Young-GI MIN, et al., (2012): The usefulness of the serum s100b protein for predicting delayed neurological sequelae in acute carbon monoxide poisoning. Clinical Toxicology. 50: pp.183-188.

Giuseppe P, Matteo C, Peiman N, et al., (2011): Delayed neurological sequelae after carbon monoxide poisoning, predictive risk factors in the emergency department. A retrosepective study . Scand. J Trauma Resusc Emerg Med . 19: pp.16.

Goldberg DM and Spooner RJ (1983): Methods of Enzymatic Analysis (Bergmeyen HV, ed.), 3rd edn., Vol 3, Verlog Chemie Deerfield Beach, pp. 258- 265.

Goncalves CA, Leite MC, Nardin P (2008): Biological and Methodological features of the measurements of S100b, a putative marker of brain injury. Clin Biochem Cell Biol. 41: pp. 755-63.

Hu H, Pan X, Wan Y, et al., (2011): Factors affecting the prognosis of patients with delayed encephalopathy after acute carbon monoxide poisoning. Am J Emerg Med . 29: pp.261-264.

Kirino T, Brightman MW, Oertel WH, et al., (1983): Neuron-specific enolase as an index of neuronal regeneration & reinnervation. J Neurosci. 3: 915-23.

Moon JM, Shin MH, Chun BJ (2011): The value of initial lactate in patients with carbon monoxide intoxication: in the emergency department. Hum EXP Toxicol. 30: pp.836-843.

Pang L, Bian M, Zang XX, et al., (2013): Neuroprotective effects of erythropoietin in patients with carbon monoxide poisoning. J Biochem Mol Toxicol. 27: pp.266-71.

Rasmussen L, Poulsen M, Christinansen M, et al., (2004): Biochemical markers for brain damage after carbon monoxide poisoning . Acta Anaesthesiol Scand. 48: 469-473.

Satran D, Henry C, Adkinson C (2006): Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. J Am Coll Cardiol. 45: 1513.

Suner S and Jay G (2008): Carbon monoxide has direct toxicity on the myocardium distinct from effects of hypoxia in an ex vivo rat heart model. Acad Emerg Med. 15: 59-65.

Weaver LK (2009): Clinical practice. Carbon monoxide poisoning. N Engl J Med. 360: 1217-25.

Won J and Jae H (2010): Transient left ventricular systolic dysfunction associated with carbon monoxide toxicity. J Cardiovasc Ultrasound. 18 : 12-15.

Yang Y and Rosenberg GA (2011): Blood- brain barrier breakdown in acute and chronic cerebrovascular disease. Stroke. 42: pp. 3323-3328.

Ys Cha, Kim H, Do HH, et al., (2017): Serum neuron-specific enolase as an early predictor of the delayed neurosychiatric sequelae in patients with acute carbon monoxide poisoning. Human and experimental toxicology. 37: pp.240-246.

Yu GF, Huang Q, Dai WM, et al., (2012): Prognostic value of copeptin: one-year outcome in patients with traumatic brain injury. Peptides. 33: pp. 164-9.

الملخص العربي

دراسة مقارنة مستقبلية بين ثلاث مؤشرات كيميائية للتنبؤ بالمضاعفات العصبية المتأخره في مرضي التسمم بغاز أول أكسيد الكربون في مركز مراقبة السموم في مستشفي المنيا الجامعي

أسامة عبد العزيز حسن و شيرين عبد الحكيم عبد العليم١ و لمياء حمدي٢

يعتبر التسمم بغاز أول أكسيد الكربون مشكلة رئيسية من مشاكل الصحة العامة في العالم ويعتبر المخ أكثر عضو حساس لنقص الأكسجين المسبب بواسطة تسمم أول أكسيد الكربون. و يمكن تعريف المضاعفات العصبية المتأخرة بأنها تأخر بداية ظهور الأعراض العصبية النفسية بعد الشفاء الظاهر من تسمم اول اوكسيد الكربون .

ولهذا كان الهدف من هذه الدراسة عمل مقارنة مستقبلية بين ثلاث مؤشرات (سيريم جلوتاثيون ريداكتيز , سيريم اس-١٠٠ بروتين , ونيورن اسبيسفيك اينوليز) للتنبؤ بحدوث المضاعفات العصبية المتأخره للتسمم. وقد أجريت هذه الدراسة علي ٥٧ مريضا بالغا مصابين بالتسسم الحاد لغاز أول أكسيد الكربون وقد تم قياس هذه المؤشرات السابقة عند وصول المرضي المستشفي وتشخيصهم وقد تم تقسيم المرضي الي مجموعتين : مجموعة ظهرت بها المضاعفات وتضم ثمانية مرضي ومجموعة خالية من هذه الأعراض وتضم ٤٩مريض.

وقد أظهرت الدراسه عن وجود اختلاف ذو دلالة احصائية حيث زادت نسبة فقدان الوعي , الدوخة , الاغماء وتغيرات رسم القلب والالتهاب الرئوي ونسبة الهيموجلوبين المحمل بأول اوكسيد الكربون وانزيم الكيرياتين فوسفوكينيز و انزيم الكيرياتين كيناز- MB ونسبة التربونين ١و نسبة سيريم اس-١٠٠ بروتين وسيرم ونيورن اسبيسفيك اينوليز ونقصت مقياس غلاسكو للغيبوبة ونسبة سيريم جلوتاثيون ريداكتيز في المجموعة المصابة بالمضاعفات العصبية المتأخره .كما أوضحت هذه الدراسة أن الحد القاطع لنسبة جلوتاثيون ريداكتيز أصغر من أو يساوي ٣٠ وحده /لتر ونسبة الدقة والصحه له هي ٩٤,٧٤% و الحد القاطع لسيريم اس-١٠٠ بروتين أكبر من ١٨,٩٤بيكو جرام /لتر ونسبة الدقة هي ٩٨,٢٥% وأخيرا الحد القاطع لنيورن اسبيسفيك اينوليز أكبر من ٣٠,٤٩ نانو جرام /مل و نسبة الدقة ٩٦,٤٩% و عند هذه الحدود القاطعة يمكننا التنبؤ بحدوث المضاعفات العصبية المتأخره و نخلص من هذه الدراسه أن نسبة سيريم اس-١٠٠ بروتين يعتبر أكثر مؤشر كيميائي موثوقاً به في التنبؤ بالمضاعفات العصبية المتأخره التي تحدث بعد التسمم الحاد لأول أوكسيد الكربون بواسطة تحليل الانحدار اللوجستي.

١ قسم الطب الشرعي و السموم الإكلينيكية- كلية الطب - جامعة المنيا

٢ قسم الباثولوجية الاكلينيكية - كلية الطب - جامعة المنيا