THE POSSIBLE ROLE OF S100B PROTEIN AS A PROGNOSTIC BIOMARKER FOR BRAIN INJURY IN ACUTE CARBON MONOXIDE POISONING

BY

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ABSTRACT

The current study was carried out on sixty two carbon monoxide (CO) poisoned patients admitted to Poison Control Center Ain Shams University (PCCA), from January 2008 to June 2009. Patients were divided into four groups: Group I: twenty patients (mild CO poisoning). Group II: fifteen patients (moderate CO poisoning). Group III: twenty seven patients (severe CO poisoning). Group IV (control): fifteen healthy non-smokers. Serum S100B protein, blood CO level, random blood sugar (RBS) and arterial blood PH were assessed in all groups. Highly significant increase in serum S100B protein was found in all studied patients in comparison with the control. Patients who developped neurological sequelae had significantly high S100B protein. Blood CO level was significantly high in all tested groups. There was also highly significant increase in RBS in group III only. In addition, there was significant increase in the RBS in patients who died and in those with neurological sequelae. It can be concluded that protein S100B may be used as a useful biomarker of brain damage in acute CO poisoning and is helpful in assessment of its severity and prediction of neurological sequelae and mortality.

Keywords: *Protein S100B, Acute CO Poisoning, Brain Injury.*

INTRODUCTION

The role of protein S-100B is not yet fully understood. It is suggested that it has intracellular and extracellular effects. S100B is released from glial brain cells as what happens during brain damage after head trauma, cerebral hemorrhage and cerebral infarction. It exerts trophic or toxic effects depending on its concentration. At nanomolar levels, S-100B stimulates neurotic outgrowth and enhances survival of neurons during development and after injury. Moreover, it can stimulate glial proliferation in vitro (Koppal et al., 2001). Intracellulary, it regulates a variety of intracellular activities such as protein phosphorylation, enzyme activities, cell proliferation (including neoplastic transformation) and differentiation, the dynamics of cytoskeleton constituents, the structural organization of membranes,

intracellular Ca_{2+} homeostasis and inflammation (Stegert et al., 2004). However, at micro-molar levels it stimulates the expression of inflammatory cytokines and induces apoptosis. It has been shown that high concentrations of S100B exert neurotoxic effects, and that the secretion of S100B during the glial response to metabolic injury is an early and active process (Gerlach et al., 2006). It acts as chemoattractants for leukocytes, modulates cell proliferation and induces nitric oxide release from astrocytes (Liliana et al. 2006). Hence, the current study was conducted to assess the possible role of S100B protein versus other parameters such as carbon monoxide (CO) level, blood PH and random blood sugar level as a biochemical marker for brain injury in CO poisoning.

PATIENTS AND METHODS

(I) PATIENTS :

The present study was conducted in Poison Control Center Ain Shams University (PCCA) Hospital during the period between January 2008 and June 2009. The study included 62 patients of both sexes with different ages diagnosed as acute carbon monoxide poisoning plus 15 healthy non-smoker volunteers (matched for age and sex) and served as a control group. Patients with history of head trauma or evidence of cardiac toxicity and patients who were resuscitated were excluded from the study. The patients were divided as follows according to the clinical grading of carbon monoxide poisoning (Tomaszewski, 2006).

Group I : included 20 patients with mild symptoms and signs i.e. headache, nausea, vomiting, dizziness and blurred vision.

Group II : included 15 patients with moderate symptoms and signs i.e. confusion, syncope, weakness, chest pain, dyspnea, tachycardia and tachypnea.

Group III : included 27 patients with severe symptoms and signs i.e. seizures, coma, arrhythmias, hypotension, myocardial ischemia, cardiac arrest, respiratory arrest and non-cardiogenic pulmonary edema.

Group IV (Control Group): included 15 healthy nonsmoker volunteers.

ETHICAL CONSIDERATION:

Written informed consent was obtained from the volunteers as well as from the patients or from their next kin.

(II) METHODS:

a. SAMPLING

Five cc of venous blood were collected from each patient and control person under aseptic conditions. Blood samples were allowed to clot then centrifuged for 5 minutes with Jouan centrifuge at a rate of

5000c/min. and then supernatants were clotted. The serum for testing S-100B protein was stored at - 78ºC for later analysis (Claus, 2004). One cubic centimeter of arterial blood was collected on heparinized syringe under aseptic precautions for measuring blood PH and carbon monoxide level by ABL 855 machine Semen's Diagnostic. Serum level of glucose was performed immediately after taking the sample by Spectrophotometer.

b. Estimation of S-100B protein using ELISA technique according to Claus (2004):

Principle of the test:

In the BioVendor's Human S100B ELISA, calibrators, quality controls and samples are incubated with polyclonal anti-cow S100B antibody coated in micro titration wells. After 90 minutes of incubation and washing, monoclonal anti-human S100B antibody labeled with horse radish peroxidase (HRP) is added to the wells and incubated with captured S100B. After 90 minutes of incubation and another washing step, the remaining conjugate is allowed to react with the substrate tetramethylbenzidine and H_2O_2. The reaction is stopped by addition of acidic solution and absorbance of the resulting yellow colour product is measured spectrophotometrically at 450 nm. The absorbance is proportional to the concentration of S100B. A standard curve is constructed by plotting absorbance values versus S100B concentrations of calibrators and concentrations of unknown samples are determined using this standard curve (Fig. 1).

Composition: antibody coated micro titer strips (96 wells), coated with polyclonal anti-cow S100B antibody, vacuum sealed S100B Master calibrator.

Quality controls: high and low, lyophilized, the origin volume is 250 µl each (refer to the certificate of analysis for actual quality controls values), conjugate solution (Horseradish peroxidase labeled anti-human S100B antibody), 13ml dilution buffer, 20ml wash solution concentrate (5x concentrated), 100 ml substrate solution and 13 ml Stop Solution (0.2 M H_2SO_4).

Reagent preparation: all reagents need to be brought to room temperature prior to the assay. Assay reagents are supplied ready-to-use, with the exception of S100B Master calibrator, quality controls and wash solution concentrate (4x).

Wash solution: dilute 100 ml of wash solution concentrate with 400 ml of distilled water.

Stability and storage: The diluted wash solution is stable for one month when stored at 2-8°C.

S100B Calibrators: reconstitute S100B

Master calibrator with 100µl of distilled water. Add 900 µl of dilution buffer. Shake gently for 25-30 minutes. The concentration of the S100B in the stock solution is 4000 pg/ml. Prepare calibrator solutions using dilution buffer. Dilute prepared calibrator solutions 1:4 with dilution buffer prior to use in ELISA, e.g. 100 µl calibrator solution + 300 µl dilution buffer for duplicates. Reconstituted and undiluted calibrator solutions should be frozen at -20°C until next use.

Quality Controls: dissolve lyophilized Quality Controls with 250 µl of distilled water to the original volume and shake carefully (not to foam). Let stand for 25-30 minutes. These solutions are prepared for subsequent dilution. Dilute quality controls prior to use 1:4 with dilution buffer, e.g. 60 µl sample + 180 µl dilution buffer when assaying samples in singlet or preferably in duplicates.

Stability and storage: Undiluted quality controls should be frozen at -20°C until next use. Avoid repeated freezing of dissolved quality controls. Do not store the diluted (4x) quality controls.

Preparation of samples: dilute serum prior to use 1:4 with dilution buffer, e.g. 60 µl sample + 180 µl dilution buffer when assaying samples in singlet or preferably in duplicates.

Procedure:

1) Pipette 100 µl of diluted calibrators, quality controls and samples, preferably in duplicates, into the appropriate wells. Pipette 100 µl of dilution buffer as blank in the wells, as shown in Figure (1)

2) Incubate the plate at room temperature (25°C) for 90 minutes, shake at 300 rpm on an orbital micro plate shaker.

3) Wash the wells 3-times with wash solution (0.35 ml per well).

4) Add 100 µl of conjugate solution.

5) Incubatev the plate at room temperature (25°C) for 90 minutes, shaking at 300 rpm on an orbital micro plate shaker.

6) Wash the wells 3-times with wash solution (0.35 ml per well).

7) Add 100 µl of substrate solution. (Avoid exposing the micro titer plate to direct sunlight, cover the plate with aluminum foil).

8) Incubate the plate for 10-15 minutes at room temperature. The incubation time may be extended up to 30 minutes if the reaction temperature is below 20°C.

9) Stop the colour development by adding 100 µl of stop solution.

10) Determine the absorbance by reading the plate at 450 nm. (The absorbance should be read within 5 minutes following step 9).

Calculations:

Most micro titer plate readers perform automatic calculations of analyte concentration. The standard curve is constructed by plotting the absorbance (Y) of calibrators versus log of the known concentration (X) of calibrators, using the four-parameter function. Results are reported as concentration of S100B (pg/ml) in samples.

Statistical Analysis:

It was done using SPSS windows-version 16 software package (SPSS Inc, Chicago, Illinos, USA). The results of the study were recorded as mean and standard deviation for description of quantitative variables for each group. Statistical analysis using student's t-test was done. ANOVA one way statistical analysis was used for comparison between more than two groups. In all tests, the probability (P) was used. $P > 0.05$ (non-significant). $P \leq 0.05$ (significant).

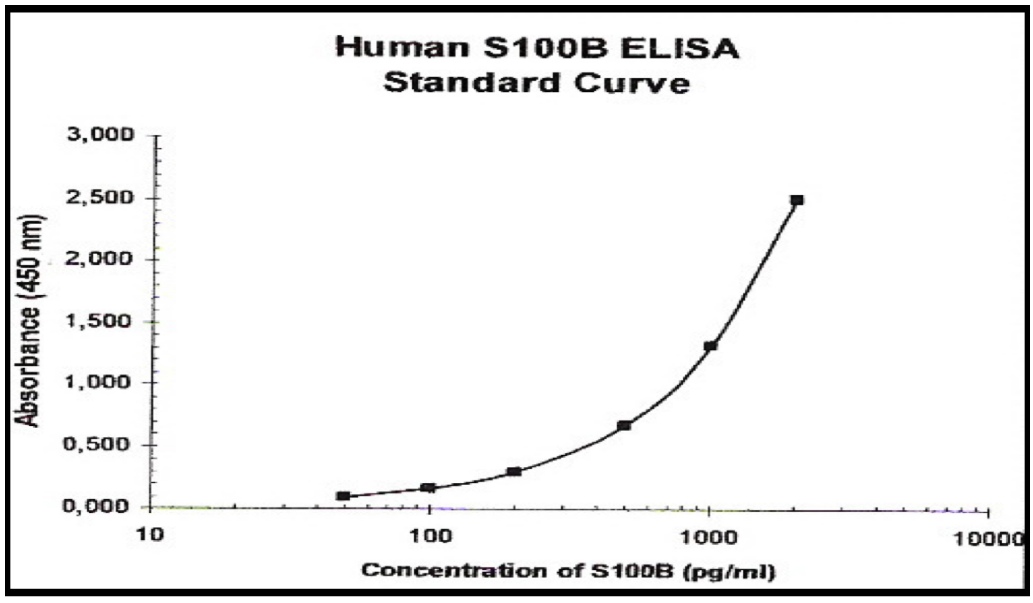


Figure (1) : Standard curve for S100B.

RESULTS

Table (1) & histogram (1) showed highly significant (P≤0.0001) increase in serum concentration of S100B protein in CO-poisoned patients in comparison with control group.

Table (2) showed highly significant (P≤0.0001) increase in S100B protein serum concentration, significant difference in CO level, significant increase in random blood sugar and non significant difference in the blood PH in died patients in comparison with survived patients among group III.

Table (3) showed significant increase in S100B protein in group III when compared with all groups. There was also significant increase in S100B protein in group II when compared with group I. Regarding CO level there was significant increase in all groups when compared with the control and no significant difference between the three groups. Random blood sugar level showed significant increase in group III when compared with all groups, and there was no significant difference in blood sugar in group II when compared with group I. There was significant decrease in blood PH in group III when compared with group I and IV. No significant difference between group III when compared with group II and there was non significant difference between group I when compared with group II.

Table (4) showed highly significant (P ≤0.0001) increase in S100B protein and RBS in patients who developed neurological sequelae when compared with patients without neurological sequelae. The other parameters which include blood PH, CO level, the delay time and the age of intoxicated patients showed non-significant difference.

DISCUSSION

The current study revealed that the six patients who died were from group III and that they had the highest S100B protein values when compared with the survived patients of the same group. Also, the patients who developped neurological sequelae had significant higher S100B protein than those who had no neurological sequelae. These could be attributed to the fact that carbon monoxide poisoning is associated with neurologic injury which leads to release of S100B protein from glial brain cells as what happens during brain damage after head trauma, cerebral hemorrhage and cerebral infarction (Tanaka et al., 2008). So, it could be a biomarker for brain damage and severity in carbon monoxide poisoning. It is possible that elevated S100B protein level could be used to predict the outcome of carbon monoxide poisoning, as it is true for sudden

circulatory arrest and traumatic brain injury (Rainey et al., 2008). All the died patients had S100B protein level above 600 pg/ml so it could be the level that predicts mortality of carbon monoxide-poisoned patients. These results are in agreement with (Brvar et al., 2004a) who studied the level of consciousness and S100B protein in 38 carbon monoxide poisoned patients. They found three comatose patients and six patients with initial transitory unconsciousness. Also, they found significant increase in S100B in comatose patients and two patients with initial transitory unconsciousness. They reported death in the patient with the highest S100B protein. They concluded that carbon monoxide poisoning appears to be associated with elevated S100B levels and can be used as a biochemical marker of brain injury in carbon monoxide poisoning.

The current results showed that the mean values of S100B protein level were significantly higher in group III than in control group and this increase was related to the development of hypoxic-ischemic damage in the cerebral tissue with a carbon monoxide poisoning. This was in agreement with Alain et al. (2007) who investigated the relation of S100B protein levels with the early clinical diagnosis of the hypoxic/ischemic stress and the susceptibility to brain damage. Moreover, Brvar et al. (2004b) exposed rats to a mixture of 3000 ppm CO in air for 60 minutes. Blood samples were taken before and immediately after carbon monoxide poisoning. The level of consciousness was evaluated at the end of the exposure, and the survival rate was monitored for 7 days. They were classified according to level of consciousness into two groups (fully conscious group and disturbed consciousness group). The disturbed consciousness group had significantly higher S100B levels compared with the fully conscious group. The unconscious rats that later died had significantly higher S100B level compared with the unconscious rats that survived. They found that the serum level of S100B below 0.44 ug /L predicted survival of carbon monoxide-poisoned rats. They concluded that S100B is a better predictor of final outcome than the consciousness level, so it could be used as a prognostic parameter for acute carbon monoxide poisoned rats.

On the other hand, Rasmussen et al. (2004) studied 20 carbon monoxide poisoned patients and 20 healthy control individuals. Carbon monoxide poisoned patients were divided into two groups: those in which unconsciousness was found at the scene or during transfer to hospital (11 patients) and those who were conscious (9 patients). Serum levels of S100B protein were measured in all patients on admission and after 12, 24, 36 and 48 hs. They

reported that serum concentrations of S100B protein were not significantly different from the control group in all obtained samples. But, there were few limitations in their study. First, the time profile of S100B protein was difficult to interpret due to insufficient data on duration of exposure and high variability in delay time. Second, the small number of patients in their study.

In the current study, an elevated blood carbon monoxide CO level is a diagnostic of poisoning, but does not predict the mortality or severity of clinical signs and symptoms, particularly those affecting the brain. This could be explained by the fact that carbon monoxide levels and neurologic presentation is related to unmeasured tissue uptake of carbon monoxide. Therefore, blood CO level reflects only the blood levels and does not indicate the degree of tissue involvement (Claude, 2002). Moreover, in clinical practice the precise time measurement is rarely known, making the assessment of CO level insignificant and also once the patient is removed from the CO source, levels fall rapidly with time (Dan Hatlestad, 2005). These results were in agreement with Lam et al., (2006) who performed a study on 148 patients suffering from CO poisoning and Cevik et al. (2006) who evaluated the relationship between the poisoning severity score (PSS) and CO levels in patients with acute carbon monoxide poisoning. They found that the mean CO level among severe group was significantly higher than mild and moderate groups but CO levels according to outcome were not significantly different in severely poisoned patients. Moreover, Claude (2002) reported that although elevated CO level is the primary diagnostic indicator of CO poisoning, it does not predict the severity of clinical signs and symptoms, particularly those affecting the brain. Dan Hatlestad (2005) found that measurement of CO concentration is indicated to confirm the diagnosis, but the percentage of CO in the blood is not always a good indicator of severity.

The present study revealed that there was significant increase in random blood sugar in the patients with neurological sequelae when compared with the patients without neurological sequelae. So, the blood sugar can predict severe cases, brain damage and mortality of CO poisoning. This may be attributed to the increased availability of glucose induced by stress presumably increases cerebral glycolytic flux, and elevation of intracellular and interstitial lactate level, which in turn induces acidosis and edema, resulting in brain damage (Penney et al., 2008). These results were in agreement with Suzanne (2007), who found that elevated blood sugar on admission was associated with

worse neurologic outcome after carbon monoxide poisoning. She found that neurologic outcome in diabetics poisoned with CO is generally worse than in non diabetics. She concluded that acute severe carbon monoxide poisoning characterized by hyperglycemia and this elevation has been linked to increased severity of brain dysfunction. In addition, Penney et al. (2008) studied unanaesthetized rats exposed to carbon monoxide for 90 min to examine the effect of acute CO poisoning on plasma glucose and neurologic dysfunction. Glucose level was increased during CO exposure and after room air recovery. Neurologic deficit, behaviorally-assessed 4 h after recovery, was strongly correlated with the increased glucose. They concluded that elevated blood glucose was associated with poor outcome in the carbon-monoxide-poisoned rats.

Regarding the blood PH, the current study revealed no significant difference between died and survived severely poisoned patients and also between patients with or without neurological sequelae. The presence of metabolic acidosis may be attributed to the combination of hypoxia, inhibition of cellular respiration and increased metabolic demand (Louise and Kristine, 2004). So, metabolic acidosis can predict the severity of toxicity but not the mortality. These results were in agreement with Lam et al. (2006) who studied 148 patients suffering from CO poisoning. They found 25 unconscious patients (16.9%) on arrival. Initial blood results showed that acidosis were associated with likelihood of unconsciousness on arrival (P = 0.007). Also, Cevik et al. (2006) found that acidosis and high glucose levels were significantly associated with poisoning severity score and adverse outcome. The present study revealed that 14 patients out of the 62 patients (22.5%) poisoned with carbon monoxide had neuropsychological sequelae on admission. Statistical analysis revealed highly significant increase in S100B protein and RBS in patients who developed neurological sequelae when compared with patients without neurological sequelae. This might be attributed to the association of CO poisoning with neurologic injury which leads to release of S100B protein from glial brain cells. Moreover, severe acute carbon monoxide poisoning is characterized by hyperglycemia and this elevation has been linked to increased severity of brain dysfunction (Suzanne, 2007 and Tanaka et al., 2008).

CONCLUSION

Protein S100B could be considered as a useful biomarker of brain damage in acute CO poisoning and is helpful in assessment of its severity and prediction of its neurological sequelae and mortality. Elevated carbon monoxide level is diagnostic of CO

poisoning, but does not predict the mortality or severity of clinical signs and symptoms, particularly those affecting the brain. The blood sugar can be considered as a biomarker which predicts severity of toxicity, neurological sequelae and mortality of acute CO poisoning. The presence of metabolic acidosis can predict the severity of acute CO toxicity but cannot predict its mortality or neurological sequelae.

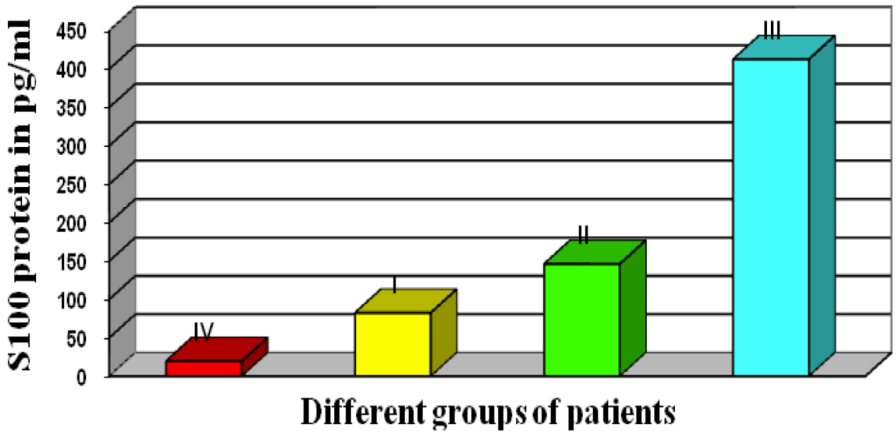
RECOMMENDATIONS

Protein S100B is recommended to be used as a diagnostic and prognostic tool to assess severity of neurological damage in acute CO poisoning. Further studies are needed to evaluate the pattern of S100B protein rise, decline and response to regular treatment and hyperbaric oxygen therapy.

Table (1): Statistical comparison of S100B protein concentration (pg/ml) between carbon monoxide poisoned patients and control group.

Parameter	Groups			
S100B protein (pg/ml) Mean±SD	**I (mild poisoning) n= 20**	**II (moderate poisoning) n= 15**	**III (severe poisoning) n= 27**	**IV (control group) n= 15**
	82.5±28.8	146.1±57.5	412.8±164.1	19.5±6.8
t	8.2	8.4	9.2	
P	**0.0001	**0.0001	**0.0001	

SD: standard deviation ** P≤0.0001 (highly significant)



Histogram (1): Serum concentration of S100B protein in CO poisoned patients (I, II, III) and control group (IV).

Table (2) : Statistical comparison of S100B protein, CO level, random blood sugar level and blood PH between survived and died patients of group III (severe CO poisoning)

Group III (severe CO poisoning)	S100Bprotein (pg/ml)	CO level (%)	RBS (mg/dl)	PH
Survived patients (n = 21)	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
	339.6±95.1	26.3±9.7	142 ±36.8	7.32±0.09
Died patients (n = 6)	668.8±51.7	28.4±14.3	196.5 ±90.5	7.32±0.11
t	8.0	0.4	2.2	0.02
P	**0.0001	0.6	0.03	0.9

SD: standard deviation, **P ≤ 0.0001 (highly significant), P > 0.05 (non-significant).

Table (3): ANOVA one-way statistical analysis of S100B protein, CO level, RBS, and blood PH in studied groups.

Groups / Studied parameters	Group IV (control) n= 15	Group I (mild CO poisoning) n= 20	Group II (moderate CO poisoning) n= 15	Group III (severe CO poisoning) n= 27	Fc value	CL
S100B(pg/ml)	19.5 ± 6.8	82.5±28.8	146.1±57.5	412.8±164.1	64.78	62.8
CO level (%)	0.9 ± 0.2	24.4±9.2	22.9±9	26.8± 0.6	31.03	5.84
RBS(mg/dl)	104.2±9.42	106.6±21.9	103.5±14	154.1±56.1	10.88	43.7
PH	7.39 ± 0.03	7.39±0.05	7.35±0.07	7.31±0.09	7.02	0.04

SD = Standard Deviation. Fc = variance ratio calculated by ANOVA one-way statistical analysis.
CL = confidence limit, Ft = tabulated variance ratio at P 0.05=3.23. Fc > Ft =significant,
Fc < Ft = non-significant. If difference between two groups > CL= significant.
If this difference < CL = insignificant.

Table (4): Statistical comparison between patients who developed neurological sequelae and those without neurological sequelae regarding S100B protein, RBS , PH, CO, delay time and age.

Studied parameters	Patients with neurological sequalae n=14	Patients without neurological sequalae no=48	t	p
S100 B protein Pg/ml	**mean± SD**	**Mean SD**	6.5	**0.0001
	391.9±171.3	154.6± 96.4		
RBS (mg/dl)	152.6±49.2	111.6± 21.9	4.3	**0.0001
PH	7.34± 0.1	7.36± 0.06	0.95	0.3
CO level (%)	21.5± 12.8	25.2± 8.1	1.2	0.2
Delay time/hours	3.6± 2.9	2.9± 2.2	0.9	0.3
Age (Years)	25.4± 11.5	26.7± 14.1	0.2	0.7

SD: standard deviation **P ≤0.0001: highly significant, P > 0.05 = non significant

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الدور المحتمل لبروتين أس١٠٠ ب كدلالة حيوية منبأة بإصابة المخ في حالات التسمم الحاد بغاز أول أكسيد الكربون

المشتركون فى البحث

أ.د. نائلة أحمد النيال أ.د. حنان فتحى عبد العزيز

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قسم الطب الشرعي و السموم الإكلينيكية -كلية الطب- جامعة عين شمس و مركز علاج التسمم- مستشفيات جامعة عين شمس

أجريت هذه الدراسة المستقبلية على إثنين و ستين مريضا يعانون من تسمم حاد بغاز أول أكسيد الكربون تم إدخالهم في مركز السموم الإكلينيكية بمستشفيات جامعة عين شمس في الفترة من يناير ٢٠٠٨ حتي يونيه ٢٠٠٩. تم تقسيم المرضي إلي أربع مجموعات: المجموعة الأولي و تشمل عشرون مريضا تعرضوا لتسمم بسيط بغاز أول أكسيد الكربون والمجموعة الثانية و تشمل خمسة عشر مريضا أصيبوا بتسمم متوسط بغاز أول أكسيد الكربون والمجموعة الثالثة وتشمل سبعة و عشرون مريضا مصابين بتسمم شديد بغاز أول أكسيد الكربون و المجموعة الرابعة وتشمل خمسة عشر شخصا تم اختيارهم من الأصحاء المتطوعين من غير المدخنين كمجموعة ضابطة. وقد تم قياس نسبة بروتين (أس ١٠٠ ب)، مستوي غاز أول أكسيد الكربون ، مستوي السكرالعشوائي بالدم و درجة حموضة الدم لكل المجموعات .

وقد اثبتت الدراسة وجود زيادة ذات دلالة إحصائية عالية في مستوي البروتين (أس ١٠٠ ب) في كل المجموعات المختبرة عند مقارنتها بالمجموعة الضابطة، وإن المجموعة الثالثة كان لديها أعلي نسبة من هذا البروتين. كماوجدت زيادة ذات دلالة أحصائية في المرضي المتوفيين وعددهم ستة مرضي عند مقارنتهم بالمرضي الأحياء من نفس المجموعة كما أن المرضي الذين عانوا من مضاعفات عصبية اظهروا زيادة ذات دلالة احصائية عالية في مستوي بروتين (أس ١٠٠ ب) عند مقارنتهم بالمرضي الذين ليس لديهم مضاعفات عصبية.وبينت الدراسة الحالية ايضا ان هناك ارتفاع ذو دلالة إحصائية لمستوي غاز أول أكسيد الكربون بالدم في كل المجموعات المختبرة عند مقارنتها بالمجموعة الضابطة، ولايوجد إختلاف ذو دلالة إحصائية بين المجموعات الثلاثة و بين المرضي المتوفين والمرضي الأحياء وبين المرضي الذين أصيبوا و الذين لم يصابوا بمضاعفات عصبية. بالإضافة إلى وجود زيادة ذات دلالة احصائية عالية في مستوي السكر العشوائي بالدم في المجموعة الثالثة .كما يوجد زيادة ذات دلالة احصائية في مستوي السكر العشوائي بالدم في المرضى المتوفين مقارنة بالمرضي الاحياء وفي المرضى المصابين بمضاعفات عصبية بمقارنتهم بالمرضي الذين ليس لديهم مضاعفات عصبية من نفس المجموعة. وقد اثبتت هذه الدراسة وجود نقص ذو دلالة إحصائية في درجة الحموضة بالدم فى المجموعة الثالثة فقط .

ونستنتج من هذا البحث أن لبروتين (أس١٠٠ ب) أهمية قصوى ويمكن إستخدامه كدلالة حيوية منذرة للآثار السلبية التى قد تصيب خلايا المخ فى المرضي المتعرضين للتسمم الحاد بغاز أول أكسيد الكربون وللتنبؤ بمدي جسامة المضاعفات العصبية المزمنة وحالات الوفاة التى يمكن أن تحدث فى هؤلاء المرضى.