Original Article

Risk factors for the delayed onset of neuropsychologic sequelae following carbon monoxide poisoning

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Aim: Carbon monoxide (CO) poisoning often manifests delayed neuropsychological sequelae. The risks and preventive factors for the development of delayed neuropsychological sequelae are controversial at present. The purpose of this retrospective study was to assess the risk factors for this condition.

Method: We studied 81 patients with CO poisoning admitted to the Critical Care and Emergency Medicine Center at the Kansai Medical University from 2006 to 2012. All patients (64 males and 17 females; average age, 45.9 years) were divided into non-delayed neuropsychological sequelae and delayed neuropsychological sequelae groups and retrospectively studied. Patient data were analyzed by univariate and multivariate analyses.

Results: The results of our study indicated that prolonged CO exposure, elevated serum creatinine phosphokinase levels, head image abnormality in the basal ganglion or white matter region, low Glasgow Coma Scale score, bedsore occurrence, and CO poisoning attributable to burning charcoal were each predictive risk factors for the development of delayed neuropsychological sequelae. Bedsore occurrence and serum creatinine phosphokinase elevation were significant risk factors by multivariate analysis, whereas no significant differences were found for age, gender, mean blood pressure, heart rate, arterial carboxyhemoglobin and lactate concentrations, or base excess.

Conclusion: We identified several predictive risk factors of delayed neuropsychological sequelae. We believe that these factors will contribute to identifying optimum therapeutic methods and follow-up terms for patients with acute CO poisoning at risk of developing delayed neuropsychological sequelae.

Key words: Bedsore, carbon monoxide poisoning, delayed sequelae, risk factor

INTRODUCTION

C ARBON MONOXIDE (CO) poisoning is one of the most common forms of poisoning that manifests not only acute clinical findings but also delayed neuropsychological sequelae (DNS). Several reports have previously described risk factors for the development of DNS,[1–5] although the outcomes of these studies have been uncertain. Therefore, the purpose of this retrospective study was to

assess and clarify the predictive risk factors for the development of DNS.

METHODS AND OBJECTIVES

Patients

A TOTAL OF 88 patients with CO poisoning admitted to the Critical Care and Emergency Medicine Center at the Kansai Medical University (Moriguchi, Japan) from 2006 to 2012 were invited to participate in the study. Of these, seven patients were excluded because of lack of information, disturbance of consciousness without complete recovery, or death. The remaining 81 patients (64 males and 17 females; average age, 45.9 years) included in this retrospective study provided written informed consent. Of the 81

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patients, 69 were categorized as non-DNS type (non-DNS group; average age, 45.8 years) and 12 as DNS type (DNS group; average age, 46.1 years).

We diagnosed CO poisoning based on exposure to CO and clinical manifestations of acute CO poisoning, including headache, nausea, vomiting, dizziness, weakness, palpitation, transient loss of consciousness, coma, confusion, and seizure,[2,6] regardless of arterial carboxyhemoglobin (COHb) concentration because of the effect of the transport time to hospital and oxygen inhalation. In total, 41 patients had CO poisoning following attempted suicide (39 from burning charcoal and 2 from exhaust gas) and 40 patients had been accidently exposed to CO (10 from burning charcoal, 3 from exhaust gas, 13 from subterranean accidents, 12 from fire, 1 from a faulty hot water heater, and 1 from burning coke).

Grouping of patients

Patients who showed no sequelae after recovering from acute CO poisoning were classified as non-DNS. Patients who showed DNS symptoms, such as Parkinson-like syndromes, incontinence, cognitive impairment, personality changes, memory loss, depression, and psychosis[2,3] after completely recovering from acute CO poisoning were classified as DNS. Cognitive impairment was evaluated through patient interview, the use of the minimental state examination, and the Hasegawa dementia scale – revised.

Collection of data

The following information was collected: age, gender, mean blood pressure (BP), heart rate (HR), initial consciousness level (Glasgow Coma Scale [GCS]), CO exposure duration, arterial COHb and lactate concentrations, arterial base excess (BE) and serum creatinine phosphokinase (CK) levels, head image abnormality, bedsore occurrence, and CO poisoning etiology. Of the 81 patients with CO poisoning, 25 (31%) had been transferred from other hospitals because of hyperbaric oxygen therapy; thus, we did not receive some initial data. The COHb, lactate, BE, and serum CK levels were analyzed upon arrival at the emergency department. The head imaging studies were carried out by magnetic resonance imaging and/or computed tomography at our hospital or elsewhere within 3 days of CO exposure to reveal potential abnormality in the basal ganglion or cerebral white matter regions, these being characteristics of CO poisoning.

The approximate duration of CO exposure could be determined if the charcoal was burning when the patient was rescued. However, in cases where charcoal burning had ceased before rescue, it was difficult to determine the time when exposure to CO had ended. In such cases, we estimated the period of CO exposure by assuming exposure to CO had lasted up to the point when the patient was rescued.

Statistics

Statistical analyses of the data was performed using IBM SPSS statistics 19 for Windows (IBM, Chicago, IL, USA). Data were analyzed using the two-tailed unpaired *t*-test for continuous variables and Fisher's exact test for categorical variables. Logistic regression analysis was carried out using the development of DNS as the dependent variable and factors having significant association with DNS as independent variables in each univariate analysis. Their additional contribution to the models was tested with the likelihood ratio test. A *P*-value of <0.05 was determined to be statistically significant.

RESULTS

THE VALUES OF the factors tested for the risk assessment of DNS are shown in Table 1. Age, gender, mean BP, HR, COHb and lactate concentrations, and BE were not significantly different between the DNS and non-DNS groups.

The initial GCS score in the DNS group was significantly lower than that in the non-DNS group. The CO exposure time in the DNS group was significantly longer than in the non-DNS group. The CK level in the DNS group was significantly higher than that in the non-DNS group. The proportion of patients with head image abnormality was significantly higher in the DNS group than in the non-DNS group ($P < 0.001$; odds ratio [OR] = 7.53; 95% confidence interval [CI] = 1.84–30.77). Burning charcoal as the etiology of CO poisoning in the DNS group was significantly higher than that in the non-DNS group ($P < 0.05$; OR = 9.51; CI = 1.16–77.81). In addition, the occurrence of bedsores in the DNS group was significantly higher than that in the non-DNS group ($P < 0.001$; OR = 17.86; CI = 3.79–83.33). The characteristics of the patients in the DNS group are shown in Table 2.

Subsequently, we carried out multiple logistic analysis using GCS, CK, bedsore occurrence, head image abnormality, and burning charcoal as independent variables in the patients with all data ($n = 50$; non-DNS type = 40, DNS type = 10). The duration of CO exposure was excluded because this could not be accurately established in all cases. We confirmed that these independent variables were not

Table 1. Statistical analyses of risk factors for development of delayed neuropsychological sequelae (DNS) following carbon monoxide poisoning

Variables		Non-DNS (*n* = 69)	DNS (*n* = 12)	*P*-value
Sex	Male, *n*	56	8	n.s.
	Female, *n*	13	4	
Age, years		45.9 ± 15.8	46.1 ± 14.0	n.s.
Consciousness level, GCS		12.1 ± 4.0 (*n* = 67)	7.3 ± 3.5 (*n* = 11)	<0.001
Mean blood pressure, mmHg		101.5 ± 17.6 (*n* = 43)	94.9 ± 11.3 (*n* = 7)	n.s.
Heart rate, b.p.m.		104.6 ± 24.8 (*n* = 44)	98.3 ± 24.3 (*n* = 6)	n.s.
Exposure time, h		3.5 ± 0.5 (*n* = 58)	14.6 ± 1.9 (*n* = 7)	<0.001
COHb, %		24.4 ± 1.6 (*n* = 68)	22.1 ± 4.4 (*n* = 10)	n.s.
Lactate, mg/dL		48.3 ± 46.8 (*n* = 64)	29.2 ± 22.4 (*n* = 8)	n.s.
Base excess, mEq/L		−2.6 ± 5.5 (*n* = 65)	−3.7 ± 4.5 (*n* = 7)	n.s.
CK, IU/L		397.1 ± 851.9 (*n* = 58)	5845.9 ± 8722.1 (*n* = 11)	<0.001
Abnormality in head imaging study		10/69	7/11	<0.001
Occurrence of bedsores		3/64	6/12	<0.001
Poisoning from burning charcoal		38/69	11/12	<0.050

Continuous variables are shown as mean value ± SD. COHb, carboxyhemoglobin; CK, creatinine phosphokinase; GCS, Glasgow Come Scale; n.s., not significant.

Table 2. Detailed characteristics of patients who developed delayed neuropsychological sequelae (DNS) following carbon monoxide (CO) poisoning

Case		Exposure time, h	Time interval of CO exposure and DNS, days	GCS score	COHb, %	CK, IU/L	Abnormality in head image
Sex	Age, years						
F	36	18	23	3	20.8	1,269	Yes (BG, WM)
M	41	12	11	5	28.9	1,829	Yes (BG, WM)
M	49	–	21	9	3.4	4,635	Yes (BG, WM)
M	68	–	14	5	2.1	8,514	None
F	53	11	27	–	28.6	3,153	None
F	37	24	31	7	35.8	34	None
M	48	14	34	9	46.8	–	Yes (WM)
M	59	9	23	14	–	2,174	Not performed
M	40	–	35	5	20.2	31,125	None
M	68	–	22	11	22.2	1,372	Yes (BG, WM)
F	26	14	42	3	12	5,547	Yes (BG)
M	28	–	37	9	–	4,652	Yes (BG)

–, no data. BG, basal ganglion, CK, creatinine phosphokinase; COHb, carboxyhemoglobin; F, female; GCS, Glasgow Come Scale; M, male; WH, white matter.

strongly correlated to each other. Bedsore occurrence and CK elevation were significant prediction factors for DNS ($P < 0.000001$). The OR of bedsore occurrence was 26.32 ($P = 0.007$; CI = 2.44–250) and CK elevation was 0.999 ($P = 0.019$; CI = 0.999–1). The predictive value of this logistic formula, including bedsore occurrence and CK

elevation, was 92.0%; therefore, this could be considered to be effective.

DISCUSSION

AFTER ACUTE CO poisoning, some patients can continue to develop DNS. The reported incidence of DNS varies from 10% to 24%;[1,2,7,8] in line with this, 13% of patients developed DNS in our study. The symptoms of DNS typically develop after an interval of 2–40 days.[8] The time interval before the appearance of DNS symptoms in our study was 11–42 days (Table 2), with the DNS manifestations including Parkinson-like syndromes, incontinence, cognitive impairment, personality changes, memory loss, depression, and psychosis.[2,3] Many cases of DNS may be mediated by inflammatory and immune responses;[9] however, the exact mechanisms and preventive methods are yet to be elucidated.

We identified several risk factors for the development of DNS. Among these, the occurrence of bedsores and CK elevation were identified as significant risk factors using multivariate analysis.

Weaver *et al.*[4] suggested that having an age greater than 36 years was a risk factor for cognitive functional disorders 6 weeks following CO exposure. There were, however, no significant differences in age or gender in our study, similar to other reports.[2,3] Although Pepe *et al.*[2] reported a systolic blood pressure of ≤90 mmHg as a risk factor for the development of DNS, significant differences in mean BP and HR were not recognized in our study.

We observed significantly lower initial GCS scores in patients who developed DNS than those in patients who did not develop DNS. Several other studies have also suggested that lower GCS score or severe loss of consciousness could make useful predictors for DNS.[2–4,6,10,11] However, it is important to consider that CO-poisoned patients could have taken drugs and/or alcohol, which can also affect their level of consciousness. In our study subjects, 20 of 81 (24.7%) patients who inhaled CO had additionally used psychotropic drugs or consumed alcohol.

Some studies have reported prolonged CO exposure to be associated with the development of DNS.[2,4] Similar findings were observed in our study. However, we found that COHb concentration was not a predictive factor for DNS, similar to several other reports.[3,4,6,8,12] The affinity of hemoglobin for CO is approximately 220 times greater than that for oxygen.[13] Therefore, CO rapidly binds to hemoglobin after exposure and is transferred to the intracellular space where it binds myoglobin and mitochondrial cytochrome oxidase.[14] Data derived from experimental and clinical studies have suggested that the COHb half-life in patients with CO poisoning was longer than that in subjects with experimental CO exposures. Weaver *et al.* hypothesized that a greater CO burden in poisoned patients, with CO accumulation in tissues and hemoglobin, would result in a longer duration for COHb elimination.[15] Sokal *et al.* also noted that prolonged CO exposure may be related to more profound tissue hypoxia.[16] We hypothesized that patients who were exposed to CO for longer durations would have higher amounts of CO and would be more likely to develop DNS; however, in the majority of cases, we could not ascertain accurate CO exposure times. Therefore, we were limited in this aspect, being only able to express this data by a prediction of CO exposure time (Table 2). For this reason, we excluded unreliable information from the multivariate analysis.

We did not detect an association between lactate concentration and DNS or between BE and DNS, which is similar to the findings of a previous investigation[2]; this may be because the severity of acute poisoning was accompanied by markedly higher blood lactate level.[16]

An elevated CK level may be associated with the development of DNS and is indicative of both CO-mediated muscle necrosis and rhabdomyolysis in comatose patients who have remained on flat surfaces for extended periods.[2] Thus, CK elevation might reflect prolonged CO exposure and the severity of CO poisoning. The occurrence of bedsores as a risk factor for DNS may be due to a similar reason.

Several reports have identified an association between head image abnormalities presenting in the basal ganglion or cerebral white matter regions and the development of DNS.[3,7,8,11,12] In the present study, head image abnormality was seen in 7 out of 12 patients who developed DNS and in 10 out of 69 patients who did not develop DNS.

Finally, 11 out of the 12 patients who developed DNS had CO poisoning caused by burning charcoal. Although similar reports are currently unavailable, CO exposure duration attributable to burning charcoal might tend to increase because the patient's rescue was delayed for attempted suicide. As a result, the CO exposure time may be longer.

Overall, we identified several risk factors for DNS. Among these, we indicated that bedsore occurrence and CK elevation were significant risk factors using multivariate analysis. Because various factors exist depending on each patient's background, it will be necessary to continue such studies with additional patients to certify the conclusions of the present study.

Limitations

The limitations of our study included the following: (i) follow-up of some of the patients was difficult because they

had stopped visiting the hospital, (ii) as cognitive impairment was only evaluated by patient interview, mini-mental state examination, and the Hasegawa dementia scale – revised, we may have not detected some existing slight cognitive impairments, thus potentially missing DNS in some patients.

CONFLICT OF INTEREST

NONE.

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