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원 저

의식이 명료한 일산화탄소 중독환자를 대상으로 응급실에서 시행한 간이정신상태검사의 임상적 의의

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Incidence and Features of Cognitive Dysfunction Identified by Using Mini-mental State Examination at the Emergency Department among Carbon Monoxide-poisoned Patients with an Alert Mental Status

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Purpose: Because carbon monoxide (CO)-intoxicated patients with an alert mental status and only mild cognitive dysfunction may be inadequately assessed by traditional bedside neurologic examination in the emergency department (ED), they may not receive appropriate treatment.

Methods: We retrospectively investigated the incidence and features of cognitive dysfunction using the Korean version of the Mini-Mental State Examination (MMSE-K) in ED patients with CO poisoning with alert mental status. We conducted a retrospective review of 43 consecutive mild CO poisoned patients with a Glasgow Coma Scale score of 15 based on documentation by the treating emergency physician in the ED between July 2014 and August 2015.

Results: Cognitive dysfunction, defined as a score of less than 24 in the MMSE-K, was diagnosed in six patients (14%) in the ED. In the MMSE-K, orientation to time, memory recall, and concentration/calculation showed greater impairments. The mean age was significantly older in the cognitive dysfunction group than the non-cognitive dysfunction group (45.3 yrs vs. 66.5 yrs, p<0.001). Among the initial symptoms, experience of a transient change in mental status before ED arrival was significantly more common in the cognitive dysfunction group (32.4% vs. 100%, p=0.003).

Conclusion: Patients with CO poisoning and an alert mental status may experience cognitive dysfunction as assessed using the MMSE-K during the early stages of evaluation in the ED. In the MMSE-K, orientation to time, memory recall, and concentration/calculation showed the greatest impairment.

Key Words: Carbon monoxide, Cognitive disorder, Emergency care

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Introduction

Carbon monoxide (CO) is a colorless, odorless, and nonirritating toxic gas commonly encountered in daily life. CO poisoning is particularly damaging to organs with high oxygen requirements, such as the brain[1)]. Therefore, CO can cause various neuropsy-

chological symptoms, including impairment in cognitive function, mood disorders, irritability and coma[2-5]. Additionally, unique and problematic complications of CO poisoning can lead to delayed neuropsychological sequelae (DNS), including impairment in cognitive functions, akinetic mutism, anxiety and depression, sphincter incontinence, temperament changes, dystonia, parkinsonism, and amnesia, which may develop in some patients after a period of apparent recovery from acute symptoms[3-5]. DNS develops in 3% to 23% of cases of CO poisoning[6,7] and appears 1 to 4 weeks after poisoning[7,8].

Although the neurotoxic effect of moderate to severe CO poisoning is well-established[9-11], CO poisoning in patients with an alert mental status has received relatively little attention and the extent of neuropsychological damage is controversial[12]. Although traditional methods of assessment such as the bedside neurologic examination can readily identify unconscious or severely affected patients, many CO-poisoned patients with only mild cognitive impairment are inadequately assessed by such methods[13]. Failure to assess the cerebral functioning of patients exposed to CO may result in neuropsychological sequelae. To the best of our knowledge, there has not been a report on the evaluation of cognitive dysfunction using neuropsychological screening tests in patients with CO poisoning and an alert mental status in an emergency department (ED) setting in Korea. Since July 2014, our ED has been investigating cognitive dysfunction using the Korean version of the Mini-Mental State Examination (MMSE-K), which was developed for use in a Korean population (Table 1)[14,15].

We retrospectively investigated the incidence and features of cognitive dysfunction using the MMSE-K in ED patients with CO poisoning with alert mental status.

Methods

1. Study design and data

This was a retrospective observational study that collected data from consecutive patients diagnosed with acute CO poisoning in an ED between July 2014 and August 2015. The ED was located in a single urban, tertiary-care hospital, which experiences more than 45,000 annual visits and is staffed 24 hours per day by board-certified emergency physicians.

All patients with the word "CO poisoning" in ED discharge codes registered in the computerized hospital records were initially considered. For selected patients, a diagnosis of CO poisoning was made according to medical history and carboxyhemoglobin

Table 1. The Korean version of the mini-mental state examination (MMSE-K)

Max	Variables	Check points	Score
5	Orientation to time	What is the (year) (season) (date) (day) (month)?	(5)
5	Orientation to place	a) Where are we (province/city) (town)? Or where is this place? (school or market or hospital or home)?	(4)
		b) What place is here?	(1)
3	Memory registration	Name 3 objects: 1 second to say each. Then ask the patient to repeat all 3 after you have said them.	(3)
3	Memory recall	Ask for the 3 objects repeated above. Give 1 point for each correct answer.	(3)
5	Concentration/calculation	Serial subtraction from 100 by 7 (For example, 100-7, 93-7…) Or spell "sam-cheon-ri-gang-san" backward.	(5)
7	Language function	a) Ask patient to name a pencil and watch.	(2)
		b) Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."	(3)
		c) Copy the design shown.	(1)
		d) Repetition: "Gan jang Gong jang Gong jangjang"	(1)
2	Comprehension/judgement	a) Why do you wash your clothes?	(1)
		b) What should I do if I find an ID card on the road?	

(CO-Hb) level of ⟩5% (⟩10% in smokers). Mild CO poisoning was defined as patients with a Glasgow Coma Scale (GCS) score of 15, which relied on the documentation by the treating emergency physician, upon arrival to the ED. All patients complaining of acute CO poisoning were treated with 100 % high-flow oxygen therapy and, if indicated[16], hyperbaric oxygen therapy (HBOT). Exclusion criteria were a history of a previous stroke or dementia, inability to perform MMSE-K for unavoidable reasons, and a GCS less than 15. The reasons for these exclusions were as follows: 1) in patients with a history of stroke or dementia, it was not possible to prove whether the cognitive dysfunction occurred as a result of the current event. 2) Patients with a GCS less than 15 were excluded because we wanted to investigate the results of cognitive dysfunction using the MMSE-K in patients with CO poisoning and no deficits in mental status.

Data were collected by retrospectively reviewing the electronic medical records. Data collection was conducted by two emergency physicians blinded to the study objectives and hypothesis; if there was inter-observer disagreement in the interpretation of the clinical data, the two emergency physicians reviewed the case together to come to a conclusion. Training of the abstractors was conducted prior to data collection to reduce bias. The clinical parameters assessed were age, gender, intentionality of CO poisoning, duration of CO exposure, ED arrival time, medical history, initial symptoms, and vital signs. The duration of CO exposure was ascertained from patient history via the patients themselves or through interviews with guardians and was thus recorded as an estimated maximum duration of CO exposure, measured from the time of normal consciousness to the time of detection or reported CO exposure. The laboratory parameters assessed were the initial CO-Hb level from pre-hospital sources or the level obtained at our hospital, creatinine kinase (CK) to evaluate muscle injury, high sensitivity troponin I (hs-TnI) to evaluate myocardial injury, base excess (BE), and lactate to evaluate tissue hypoperfusion.

Patients available for testing underwent the MMSE-K administered in the ED to measure the presence and severity of cognitive function. The MMSE-K includes 7 subsets that evaluate higher cognitive functions, including orientation to time, orientation to place, memory registration, memory recall, concentration/calculation, language function, and comprehension/judgement (Table 1)[14,15]. The cognitive dysfunction group included those with an MMSE-K score less than 24 in test performed in the ED. Two experienced rehabilitation physicians (S.H.K and J.H.K) interpreted the test findings while blinded to the patients' clinical data.

The primary outcome of this study was to investigate the early incidence and features of cognitive dysfunction in patients with CO poisoning and an alert mental status using the MMSE-K performed in an ED. This study was approved by the Institutional Review Board of Wonju College of Medicine, Yonsei University.

2. Statistical analysis

Data are expressed according to the properties of the variable. Continuous variables are presented as the mean and standard deviation, median and interquartile range, or range after assessment for normality using the Shapiro-Wilk test. Categorical variables are presented as frequency and percentage. The Chi-square test or Fisher's exact test was used for comparison of categorical variables, while the two-sample t-test or Mann-Whitney U-test was used to compare continuous variables. P values less than 0.05 were considered statistically significant, and all statistical analyses were performed using SPSS 20 Ver. (IBM, Armonk, NY, USA).

Results

1. Characteristics of the study subjects

Between July 2014 and August 2015, a total of 47,005 patients visited our hospital ED. A total of 55 consecutive patients with acute CO poisoning and a GCS score 15 was identified during the study period. The following patients were excluded: those unable

to undergo the MMSE-K for unavoidable reasons including refusal to undergo the examination and difficulties associated with test performance (6 patients) and a history of stroke or dementia (6 patients). Therefore, we ultimately included 43 of the 55 total patients with CO poisoning and an alert mental status.

Of the 43 patients analyzed, 76.7% were men, and the mean age was 48.3 years (range, 12-82 years). Intentional CO poisoning accounted for 27.9% of cases, and the median duration of CO exposure was 2.8 hours. Hypertension (20.9%) was the most common finding in the medical history. The most common symptom at initial presentation was dizziness (60.5%). The median initial CO-Hb level was 19.8%, and the median serum lactate levels was 1.82 mmol/L (Table 2, 3).

2. The incidence and features of cognitive dysfunction identified in the ED

Acute cognitive dysfunction, defined as an abnormal score on MMSE-K, was diagnosed in 6 patients

Table 2. General characteristics according to the presence of cognitive dysfunction in patients with CO poisoning and an alert mental status

Variables	Total (N=43)	Non-cognitive dysfunction group (N=37; 86%)	Cognitive dysfunction group (N=6; 14%)	*p*-value
Age (years)	48.3±20.4*	45.3±20.3*	66.5±7.7*	<0.001
Male sex	33 (76.7%)	29 (78.4%)	4 (66.7%)	0.611
Intentionality	12 (27.9%)	12 (32.4%)	0 (0%)	0.163
CO exposure times (hrs)	2.8 (1.0-9.5)†	2.3 (0.9-8.8)†	9.0 (2.3-11.8)†	0.185
ED arrival times (mins)	165 (123-263)†	165 (123-274)†	163 (129-177)†	0.440
History				
DM	3 (7.0%)	3 (8.1%)	0 (0%)	1.000
HTN	9 (20.9%)	8 (21.6%)	1 (16.7%)	1.000
Dyslipidemia	3 (7.0%)	3 (8.1%)	0 (0%)	1.000
Lung disease	2 (4.7%)	2 (5.4%)	0 (0%)	1.000
Smoking	19 (44.2%)	16 (43.2%)	3 (50%)	1.000
Alcohol co-ingestion	9 (20.9%)	8 (21.6%)	1 (16.7%)	1.000
Symptoms				
Transient mental change	18 (41.9%)	12 (32.4%)	6 (100%)	0.003
Headache	18 (41.9%)	14 (37.8%)	4 (66.7%)	0.218
Dizziness	26 (60.5%)	22 (59.5%)	4 (66.7%)	1.000
Dyspnea	12 (27.9%)	10 (27%)	2 (33.3%)	1.000
Chest pain	3 (7.0%)	2 (5.4%)	1 (16.7%)	0.370
General weakness	6 (14.0%)	5 (13.5%)	1 (16.7%)	1.000
SBP	129 (117-150)†	129 (117-150)†	141 (123-158)†	0.430
PR	86 (75-97)†	86 (75-98)†	87 (77-90)†	0.806

* mean±standard deviation, † Median (interquartile range)
CO: carbon monoxide, ED: emergency department, DM: diabetes mellitus, HTN: hypertension, SBP: systolic blood pressure, PR: pulse rate

Table 3. Laboratory findings according to the presence of cognitive dysfunction in patients with CO poisoning and an alert mental status

Variables	Total (N=43)	Non-cognitive dysfunction group (N=37; 86%)	Cognitive dysfunction group (N=6; 14%)	*p*-value
CO-Hb (%)	19.8 (11.4-36.7)†	20.3 (10.4-36.7)†	17.2 (15.6-41.6)†	0.483
Creatinine kinase (U/L)	119 (78-169)†	119 (80-186)†	97 (65-195)†	0.335
Troponin I (ng/mL)	0.015 (0.015-0.047)†	0.015 (0.015-0.025)†	0.131 (0.015-0.280)†	0.085
Base excess (mmol/L)	-1.8 (-3.7- -1.0)†	-2.0 (-4.2- -0.8)†	-1.3 (-3.4- -0.9)†	0.587
Lactate (mmol/L)	1.82 (1.15-3.07)†	1.82 (1.13-2.97)†	1.65 (1.21-3.59)†	0.902

* mean±standard deviation, † Median (interquartile range)
CO-Hb: carboxyhemoglobin

(14%). In the MMSE-K, orientation to time, memory recall, and concentration/calculation showed the greatest impairment (Table 2-4). All of the 6 patients received once HBOT at the ED. They were follow-up test before discharge and normalized score of MMSE-K. For the 6 patients with cognitive dysfunction, we attempted to contact each patient or their guardian to inquire about the patient' s current condition, including newly developed DNS symptoms after discharge. All of these 6 patients were successfully contacted and verified that they did not experience any DNS symptoms. A comparison of the baseline characteristics of the study participants is shown in Table 2. The mean age was significantly older in the cognitive dysfunction group than in the non-cognitive dysfunction group (45.3 yrs vs. 66.5 yrs, $p<0.001$). Among the initial symptoms, experience of a transient change in mental status before ED arrival was significantly more common in the cognitive dysfunction group (32.4% vs. 100 %, $p=0.003$). There was no statistical difference in terms of intentionality, CO exposure time, and past medical history. Initial CO-Hb, CK, hs-TnI, and lactate levels were not significantly different between the cognitive dysfunction group and the non-cognitive dysfunction group (Table 3).

Discussion

It would be easy for emergency physicians to conclude that patients have no neuropsychiatric abnormalities, such as cognitive dysfunction, if the patient is alert as assessed using traditional assessment methods such as bedside neurologic examination. Although bedside neurologic examination can readily identify unconscious or severely affected patients, such methods may inadequately assess many CO-poisoned patients with only mild cognitive impairment[13]. In this study, we included patients with a GCS score of 15 as assessed by the treating emergency physician. However, the incidence of cognitive dysfunction as assessed by tests performed in the ED was as high as 14% in patients with CO poisoning and an alert mental status, with orientation to time, memory recall, and concentration/calculation showing the greatest impairment. There was a large fraction of patients with disorientation to time and/or place, which would automatically reduce their GCS to 14 (losing 1 point for a disoriented verbal response). In other words, this means that the preliminary neurologic examination was relatively insensitive and inconsistent. Therefore, cognitive function tests such as the MMSE-K may be required

Table 4. Result of cognitive function tests (MMSE-K)

MMSE-K	Category (range)	Number/median (IQR)
Orientation to time	Normal (5)	24 (55.8%)
	Abnormal (<5)	19 (44.2%)/4 (3-4)
Orientation to place	Normal (5)	37 (86.0%)
	Abnormal (<5)	6 (14.0%)/3 (2-4)
Memory registration	Normal (3)	42 (97.7%)
	Abnormal (<3)	1 (2.3%)/2
Memory recall	Normal (3)	22 (51.2%)
	Abnormal (<3)	21 (48.8%)/1 (0-2)
Concentration/calculation	Normal (5)	19 (44.2%)
	Abnormal (<5)	24 (55.8%)/3 (1.3-4)
Language function	Normal (7)	37 (86.0%)
	Abnormal (<7)	6 (14.0%)/5 (3.8-6)
Comprehension/judgement	Normal (2)	33 (76.7%)
	Abnormal (<2)	9 (20.9%)/1
Total	Normal (24-30)	37 (86.0%)/28 (26.5-29)
	Abnormal (<24)	6 (14.0%)/18.5 (13.5-22.3)

MMSE-K: Korean version of the Mini-Mental State Examination, IQR: interquartile range

to identify patients with cognitive dysfunction.

Although various areas of the brain can be damaged in acute CO poisoning, the temporal lobe and the hippocampus are particularly vulnerable areas[17] and are responsible for many of the aspects of cognitive function evaluated by the MMSE, including orientation to time and place, memory recall, and language[18]. Therefore, the MMSE may be one of useful methods for assessing cognitive function. Amitai et al. reported that the cognitive dysfunction resulting from low-level exposure to CO may be extensive and may involve memory, concentration, temporal and spatial orientation, construction skills, visuomotor coordination, and visuospatial function[19]. The authors used the Carbon Monoxide Neuropsychological Screening Battery (CONSB), which includes 6 subsets that evaluate higher cognitive functions including memory, visuomotor coordination, visuospatial planning and processing, temporospatial orientation, and constructive skills. Although one advantage of the CONSB is that it can be conducted in a short amount of time[20], Rottman et al. reported that the CONSB does not appear to be as useful in cases of low-level CO poisoning[21].

In this study, age differed between the patient groups, with the cognitive dysfunction group being older than the non-cognitive dysfunction group ($p<0.001$). This result may be explained by the lack of physiologic functional reserve in older patients. A history of transient mental status change before arrival at the ED was significantly more common in the cognitive dysfunction group than in the group without cognitive dysfunction ($p=0.003$) (Table 2). Even if patients only lose consciousness for a short period of time, their brains may have already been injured by the exposure and the recovery of consciousness may not positively correlate with the level of brain injury resulting from the CO poisoning.

There were some limitations to this study. First, the study was conducted using a retrospective design at a single hospital. As a result, not all relevant assessment parameters were included. Second, we did not compare the usefulness of the MMSE-K with that of other tests such as the CONSB, because the length of time required for testing makes it difficult to conduct cognitive function tests in CO-poisoned patients. Third, we did not evaluate the long-term outcomes of patients with mild CO poisoning with only cognitive dysfunction. Long term outcomes, such as DNS, in mild CO-poisoned with only reversible cognitive dysfunction should be investigated. Fourth, our exclusion criteria may have resulted in bias and we did not administer the MMSE-K to all patients with mild CO poisoning. Additional prospective studies with a larger sample size are required to validate our results.

Conclusion

Our study demonstrated that patients with CO poisoning and an alert mental status may experience cognitive dysfunction as assessed using the MMSE-K during the early stages of evaluation in the ED. In the MMSE-K, orientation to time, memory recall, and concentration/calculation show the greatest impairment.

Conflict of interests

The authors report no declarations of interest.

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