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ORIGINAL ARTICLE

Predicting Poor Outcome in Patients with Intentional Carbon Monoxide Poisoning and Acute Respiratory Failure: A Retrospective Study

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Purpose: Intentional carbon monoxide (CO) poisoning has become the commonly used method of suicide in some Asian countries. The objective of this study was to identify the predictors that impact the outcome of intentional CO-poisoned patients with acute respiratory failure. **Materials and Methods:** This is a retrospective observational study of 796 consecutive patients diagnosed with acute CO poisoning that presented to the emergency department (ED). Patients who were CO poisoned with intentional exposure and acute respiratory failure were enrolled and divided into two groups. The poor outcome group consisted of in-hospital death, the presence of persistent neurological sequelae, and the presence of delayed neurologic sequelae. The good outcome group consisted of other enrolled patients. Demographic and clinical data of the two groups were extracted for analysis. **Results:** A total of 148 patients were enrolled in this study. Of the eligible subjects, 67.6% (100) were identified with positive toxicology screening results. On arriving ED, parameters associated with patients with a poor outcome included hypotension, myocardial injury, prolonged lag times from the first ED arrival to initiation of hyperbaric oxygen therapy, higher white blood cell count, and higher serum levels of blood urea nitrogen, creatine kinase, and troponin-I ($P < 0.05$). Positive toxicology screening result did not relate to the outcome. Multivariate analysis showed that the myocardial injury was an independent factor for poor outcome (odds ratio, 2.750; 95% confidence interval, 1.168-6.474; $P = 0.021$). **Conclusions:** Myocardial injury is an independent predictor of in-hospital death and neurologic sequelae in patients with intentional CO poisoning and acute respiratory failure.

Key words: Suicide, carbon monoxide, acute respiratory failure, myocardial injury

INTRODUCTION

Carbon monoxide (CO), a colorless and odorless toxic gas that competes with oxygen for hemoglobin binding, is the most common cause of poisoning-related deaths and complications worldwide.[1,2] CO causes a combination of tissue hypoxia by reducing oxygen delivery to tissues and direct CO-mediated damage at the cellular level. In the United States, unintentional CO poisoning is responsible for approximately 15,000 emergency department (ED) visits and nearly 500 deaths annually.[2] A large proportion of patients with severe CO poisoning have loss of consciousness and ischemic cardiac changes, resulting in acute respiratory failure through the pathophysiology of airway obstruction, atelectasis, and pulmonary edema.[3] Hyperbaric oxygen therapy (HBOT) has been considered as optimum treatment for severely poisoned patients.[4] Mechanical ventilation (MV) in a monoplace chamber is required for these patients that need HBOT.[5]

Outcome measures commonly employed in clinical studies of CO poisoning are mortality and morbidity, particularly persistent neurological sequelae (PNS) and delayed neurologic sequelae (DNS). Symptoms of these sequelae include vegetative state, hemiplegia, monoplegia, aphasia, movement disorders, cognitive deficits, newly developed mood disorder, and incontinence. PNS is characterized by immediate neurological symptoms following acute poisoning while DNS is manifested by the delayed neurological manifestations after a symptom-free lucid interval. Prognostic factors associated with outcomes, such as age, history of exposure, consciousness, myocardial injury, lactic acidosis, carboxyhemoglobin (COHb), serum biochemistry markers, and pallidoreticular lesion (necrosis) on brain image have been proposed.[4,6-9]

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In the last decade, intentional CO poisoning is a commonly used method in suicide in some Asian countries such as Taiwan, Japan, and Korea. It has spread to other countries such as England and the United States.[3,10-14] In our previous study which examined the predictors for the duration of MV, it is noted that a high ratio of intentional CO poisoning in patients with severe CO poisoning and acute respiratory failure in Taiwan.[15] Although previous study has reported the prognostic factors associated with clinical outcome in CO-poisoned patients with acute respiratory failure,[7] there is a paucity of literature regarding the factors that impact the outcome of CO-poisoned patients with acute respiratory failure due to suicidal behavior. The objective of this retrospective study was to identify factors that predict the outcome of this specific patient group. Clinicians in the ED and Intensive Care Unit (ICU) accordingly could use these predictors to refine patient management.

MATERIALS AND METHODS

Design, setting, and patients

This retrospective observational study was performed at HBOT Center at Tri-Service General Hospital, which is a 1700-bed regional referral center of critical CO poisoned patients in urban Taiwan, with 24-h chamber availability for patients with MV. Medical records of 796 consecutive patients diagnosed with acute CO poisoning from January 2005 to December 2011 were reviewed. Patients with intentional CO poisoning and acute respiratory failure were enrolled. HBOT was arranged under the criteria of COHb level of >25% or COHb level of <25% with significant symptoms such as any period of unconsciousness. We excluded patients who were <16 years of age. The study protocol was reviewed and approved by Tri-Service General Hospital Institutional Review Board.

Intubation was performed either in the referring or our hospital according to the clinical decision of emergency physicians. Patients' consciousness and hemodynamic variables were evaluated every hour at ED or ICU. Ventilator management and weaning were performed by respiratory therapists according to an approved protocol.

In stable hemodynamic status, patients with acute CO poisoning and acute respiratory failure consented to at least three 90 min period, protocol-directed sessions in hyperbaric chambers. The first hyperbaric chamber session was performed as soon as possible at admission to ED. Ideally, the interval between two chamber sessions was 6-12 h, and the interval between the initiation of first and third chamber session was <24-h.[16] Prolonged interval was considered for patients with the hemodynamic imbalance. Patients were exposed to 100% oxygen at 3 atmospheres absolute (ATA) for the first chamber session, and then to 100% oxygen at 2.5 ATA for the following chamber sessions. All chamber sessions consisted of three 25-min oxygen-breathing periods with two 5-min air break.

Measurement

For enrolled patients, the following characteristics were collected and analyzed: Age, sex, body weight, history of psychological disease, the length of hospital stay, the length of ICU stay, the duration of MV, the numbers of HBO treatment, in-hospital mortality, neurologic sequelae at discharge, DNS, the referral, the initial Glasgow coma scale (GCS) and blood pressure on arriving ED, COHb level, and arterial blood gas data. The initially laboratory data were collected including white blood cell (WBC) count, serum levels of glucose, aspartate aminotransferase (AST), alanine aminotransferase, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), troponin-I, qualitative analysis of blood ethanol concentration, and qualitative analysis of urine benzodiazepine, amphetamine, and opiate by dipstick. Time lag from the end of CO exposure to the first ED arrival and time lag from the first ED arrival to initiation of the HBOT were also recorded.

Definitions

Delayed neurologic sequelae was defined as delayed development of new symptoms or signs after a period of days to weeks following acute CO poisoning, including apathy, disorientation, memory impairment, hypokinesia, mutism, irritability, and bizarre behavior, without other apparent cause. PNS was defined as the immediate and persistent neurological symptoms following acute CO poisoning, without the subsequent development of DNS. Hypotension was defined as a calculated mean arterial pressure <65 mmHg. Metabolic acidosis was defined as a calculated base excess <−2.0 mmol/L. Myocardial injury was defined as an ischemic electrocardiogram (ECG) change (ST segment elevation ≥1 mm, depression ≥0.05 mm, or T wave inversion ≥2 mm in two consecutive lead) or troponin-I >0.05 ng/mL. The definition of ethanol abuse was >200 mg/dL of blood ethanol concentration, which is equal to 0.2% blood ethanol content, a cut-off level of stupor and unconsciousness.

The main outcome measures were mortality and neurologic morbidities. A poor outcome was defined as an in-hospital death, the presence of neurologic sequelae at discharge, and the presence of DNS after discharge.

Statistical analysis

The differences of clinical characteristics and prognostic factors between two groups were evaluated by *t*-test for continuous variables (e.g., hospital stay, ICU stay, numbers of

HBO treatment). Chi-square or Fisher's exact test was employed for categorical variables (e.g., in-hospital mortality, neurologic sequelae, sex). A $P < 0.05$ was considered statistically significant, and all P values were two-sided. Collinearity between variables was evaluated. A multivariate logistic regression model was applied with prognostic factors that were significantly associated with the poor outcome group in a univariate analysis ($P < 0.1$). The statistics software SPSS 21 (International Business Machines Corporation) was used for data management and modeling.

RESULTS

Characteristics of the study patients

During the 7-year study period, 796 patients diagnosed with an acute CO poisoning were sent to our ED. Of these patients, 183 exhibited acute respiratory failure. A total of 148 patients (80.9%) were of intentional CO poisoning and enrolled. Thirty-five patients were ineligible and excluded because of unintentional causes. Of the enrolled patients, 3 patients with unstable vital signs due to multiple organ dysfunction syndrome or brain death did not receive HBOT. Sources of CO exposure other than suicidal behavior included water heaters (29 patients), house fires (4 patients), and charcoal stove (2 patients). The good and poor outcome groups had 90 and 58 patients, respectively [Figure 1].

Of 148 eligible patients, males and females were 75 and 73, respectively. The median age was 39.1 years (range: 17-85). Psychological history was found in 94 patients (63.5%). Most patients (82.4%) were referred from other hospitals. On arriving ED, the average GCS was 4.9 (range: 3-8). The average COHb was 39.3%. Twenty-one patients had hypotension (14.2%). Metabolic acidosis was found in 82 patients (55.4%). Myocardial injury was found in 77 patients (52.0%). Positive toxicology screening result was found in 100 patients (67.6%). Disease severity of the study groups is summarized in Table 1. The poor outcome group had more MV day, hospital stay, ICU stay, and numbers of HBO treatment.

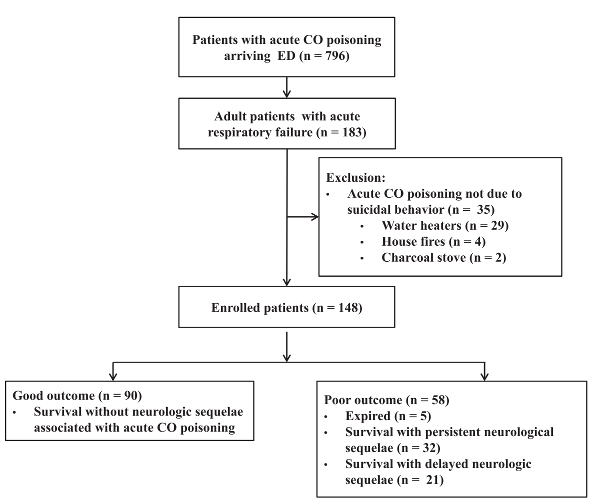

Figure 1. Flowchart of the study

Variables according to good and poor outcomes

Univariate logistic regression analysis was performed to investigate factors predictive of poor outcome [Table 2]. Variables including age, sex, body weight, referral, psychological history, hypotension, GCS, COHb, toxicology screens, laboratory findings, and HBO treatments were analyzed. On arriving ED, parameters associated with patients with a poor outcome included hypotension, myocardial injury, prolonged lag times from the first ED arrival to initiation of HBOT, higher WBC count, and higher serum levels of BUN, CK, and troponin-I ($P < 0.05$).

Multivariate stepwise logistic regression analysis

A multivariate logistic regression model was performed to investigate prognostic factors that were associated with poor outcome group in a univariate analysis that $P < 0.1$ [Table 3]. After evaluating collinearity, we chose hypotension, WBC count, AST, BUN, myocardial injury, and time from the first ED arrival to initiation of HBOT in the multivariate regression analysis. The correlation coefficients were weak between all variables included in the regression analysis. Only myocardial injury was an independent factor for poor outcome (odds ratio, 2.750; 95% confidence interval, 1.168-6.474; $P = 0.021$).

DISCUSSION

In the present study, we demonstrated that myocardial injury assessed at ED arrival was an independent predictor of poor outcome in patients with intentional CO poisoning and acute respiratory failure. To the best of our knowledge, this is the first study to investigate this issue.

Cardiovascular sequelae of acute CO poisoning have been well-described. Satran *et al*. investigated heart involvement

Table 1. Disease severity of the study groups

Variables	Total (n = 148)	Good outcome (n = 90)	Poor outcome (n = 58)	P
Mechanical ventilation (day)	3.8±5.8	2.1±1.7	6.5±8.3	<0.001
Hospital stay (day)	11.1±13.5	7.2±7.3	17.2±18.0	<0.001
ICU stay (day)	3.9±5.8	2.2±2.0	6.7±8.2	<0.001
Numbers of HBO treatment	6.1±4.8	5.0±3.3	8.0±6.1	0.001

Continuous data are expressed as mean ± SD. HBO = Hyperbaric oxygen; SD = Standard deviation; ICU = Intensive care unit assessed by biomarkers or ECG in moderate to severe CO poisoning and found that 37% of patients exhibited myocardial injury.[17] The clinical spectrum of myocardial injury after CO poisoning encompasses cardiomyopathy, angina attack, myocardial infarction, arrhythmias, and heart failure up to myocardial stunning and cardiogenic shock.[18]

Henry *et al*. reported the association between myocardial injury and long-term mortality in patients with moderate to severe CO poisoning. Myocardial injury frequently occurred in patients hospitalized and was a significant predictor of mortality.[8] In addition, myocardial injury remained a good predictor for mortality and short-term neurologic sequelae in patients with acute CO poisoning and MV.[7] A possible explanation of the findings is that the most vulnerable organs to acute CO poisoning are the heart and the brain due to their high metabolic rate. Therefore, myocardial injury may represent the severity of other tissue damage, especially the brain injury, after CO poisoning clinically.[19] In addition, myocardial injury following CO poisoning itself may also lead to pump failure that reduce the blood supply to the brain, which cause further damage.

Our results revealed a high percentage of positive toxicology screens (67.6%) in patients with intentional CO

Table 2. Clinical characteristics, events on ED arrival, laboratory data, and HBOT of the study groups

Variables	Total (n = 148)	Good outcome (n = 90)	Poor outcome (n = 58)	P
Characteristics				
Age (year)	39.1±13.5	39.7±13.6	38.3±13.3	0.549
Female	73 (49.3)	42 (46.7)	31 (53.4)	0.501
Body weight (kg)	60.7±11.6	60.2±11.6	61.6±11.7	0.508
Referral from other hospital	122 (82.4)	73 (81.1)	49 (84.5)	0.663
Psychological history	94 (63.5)	54 (60.0)	40 (69.0)	0.298
Arriving ED				
Hypotension	21 (14.2)	9 (10.0)	12 (20.7)	0.009
GCS	4.7±2.0	4.7±1.9	4.7±2.0	0.789
COHb (%)	39.3±14.3	40.0±15.3	38.4±12.6	0.528
Positive toxicology screening result	100 (67.6)	64 (71.1)	36 (62.1)	0.283
Benzodiazepine	81 (54.7)	52 (57.8)	29 (50.0)	0.399
Opiate	6 (4.1)	3 (3.3)	3 (5.2)	0.679
Ethanol	21 (14.2)	15 (16.7)	6 (10.3)	0.340
Amphetamine	15 (10.1)	12 (13.3)	3 (5.2)	0.163
Metabolic acidosis	82 (55.4)	48 (53.3)	34 (58.6)	0.487
BE (mmol/L)	−6.2±5.5	−6.1±5.5	−6.3±5.7	0.771
Hemoglobin (mg/dl)	14.2±2.1	14.4±2.1	14.0±2.2	0.295
WBC (/μL)	16,341±7009	15,318±6956	17,996±6835	0.025
Glucose (mg/dl)	142.1±59.0	143.7±66.2	139.7±45.5	0.674
BUN (mg/dl)	17.6±9.1	16.3±8.4	19.6±9.9	0.046
Creatinine (mg/dl)	1.14±0.53	1.08±0.50	1.25±0.57	0.066
AST (U/L)	101.6±311.7	53.1±59.4	178.7±488.7	0.061
ALT (U/L)	150.5±357.9	36.8±35.7	309.7±521.5	0.062
Myocardial injury	77 (52.0)	35 (38.9)	42 (72.4)	<0.001
CK (U/L)	3766±11,709	1776±3890	6820±17,674	0.040
Troponin-I (ng/mL)	1.45±2.15	0.98±1.78	2.18±2.46	0.002
HBOT				
Time from the end of CO exposure to first ED arrival (min)	47.2±24.0	45.8±21.5	49.5±27.6	0.405
Time from the first ED arrival to initiation of HBOT (h)	9.0±6.7	8.0±5.7	11.5±7.8	0.048

Continuous data are expressed as mean ± SD, and categorical data are expressed as n (%). SD = Standard deviation; ED = Emergent department; HBOT = Hyperbaric oxygen therapy; GCS = Glasgow coma scale; COHb = Carboxyhemoglobin; BE = Base excess; WBC = White blood cell; BUN = Blood urea nitrogen; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; CK = Creatine kinase; CO = Carbon monoxide

Table 3. Variables associated with poor outcome in a multivariate logistic regression

Variable	OR	95% CI	*P*
Hypotension	0.633	0.182-2.200	0.472
WBC	1.000	1.000-1.000	0.317
AST	1.003	0.998-1.007	0.210
BUN	1.022	0.978-1.068	0.325
Myocardial injury	2.750	1.168-6.474	0.021
Time from the first ED arrival to initiation of HBOT (h)	1.037	0.972-1.107	0.272

OR = Odds ratio; CI = Confidence interval; WBC = White blood cell; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; ED = Emergency department; HBOT = Hyperbaric oxygen therapy

poisoning and acute respiratory failure. There is a paucity of literature evaluating CO poisoning and co-ingestion of drugs. In a retrospective study of 426 patients treated for intentional CO poisoning in the United States, 42% had ingested one or more poisons in addition to CO.[11] However, the severity and outcome of these patients were not mentioned. In the current study, positive benzodiazepine screen was the most common, accounting for 54.7% of all enrolled patients. Our previous study has shown that positive toxicology screening result is a predictor for early extubation.[15] It is postulated that administration of hypnotic agents, especially benzodiazepine, before acute CO poisoning may provide protection to the brain. However, the protective effect of co-ingesting these hypnotic agents toward mortality and neurologic sequelae was nonspecific in the present study. The endotracheal intubation may be performed in suicidal patients for alteration of consciousness that co-ingestion of hypnotic agents majorly causes overestimation of the severity of intentional CO poisoning.

The optimal time to HBO treatment remains unclear. Our hospital provided availability of 24-h monoplace chamber with MV for patients need HBOT. We found that lag times from the first ED arrival to initiation of HBOT was significant ($P = 0.048$) to predict the poor outcome in the univariate logistic regression analysis. Although there was no significance in the multivariate logistic regression analysis, this finding implied that delay in administration of HBOT may have influences on the patient's outcome. In addition, properly conducted trials would be desirable in guiding the time to HBOT for these patients.

There are some limitations to this study. First, because our study was retrospective and based on chart reviews, we could not assess the actual duration of CO exposure. The previous central nervous system (CNS) disease (i.e., stroke, dementia, head trauma, etc.) and the neurological exam in the ED that could possibly influence the measurement of outcome were poorly documented. Some parameters that may be associated with the outcome, such as CK-MB level and brain computed tomography findings were infeasible in this study. Second, some parameters associated with the critical care, such as Acute Physiology and Chronic Health Evaluation score and ventilator settings might have been missing. Third, although toxicology screens were routinely ordered in ED for patients with unconsciousness, many agents (antidepressants, anticonvulsant, and CNS stimulants other than amphetamine etc.) were not screened in our study. Among the screened drugs, benzodiazepine, amphetamine, and opiate were qualitatively analyzed. We had no information about the serum concentration of these agents.

CONCLUSION

Myocardial injury is an independent predictor of in-hospital mortality and neurologic sequelae in patients with intentional CO poisoning and acute respiratory failure. Accordingly, clinicians should be able to use this predictor to identify patients with an increased risk of poor prognosis and administrate HBOT as soon as possible.

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