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Critical Care Medicine

The Significance of the Level of Methemoglobin among Patients with Carboxyhemoglobin

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Abstract: This study retrospectively investigated the significance of the MetHb level in patients with carbon monoxide (CO) poisoning.We conducted a medical chart review of patients treated from October 2012 to March 2018. The inclusion criterion was patients who were treated in our department due to CO poisoning. The subjects were divided into two groups based on the outcome (survival vs. death). The following variables measured at arrival were analyzed by a review of medical charts based on the patients' sex, age, and cause of CO poisoning, cardiac arrest on arrival, vital signs on arrival, COHb, MetHb, base excess, and treatments.Thirty-one patients were defined as subjects in this study. There were no significant differences associated with the sex, age, cause of CO poisoning or ratio of hyperbaric oxygen therapy between the dying and surviving cases. The Glasgow Coma Scale, systolic blood pressure, heart rate, oxygen saturation and level of BE in the dying group were lower than in the surviving group. The level of COHb and MetHb and frequency of tracheal intubation in the dying group were greater than those in the surviving group. A weak correlation was noted between the MetHb level and the age, oxygen saturation, BE and COHb. The MetHb level at the time of arrival was higher in CO poisoning cases that died than in those that survived, and MetHb had a weak positive correlation with COHb. Therefore, physicians should pay attention to the MetHb level when treating patients with severe CO poisoning.
Keywords: methemoglobin; carboxyhemoglobin; outcome.

INTRODUCTION

Methemoglobin (MetHb) formation is the result of an oxidative process during which one or more of the four iron atoms in the hemoglobin molecule convert to a ferric state, becoming incapable of binding oxygen. Endogenous MetHb is produced when naturally produced nitric oxide (NO) interacts with hemoglobin, while MetHb is converted to hemoglobin enzymatically by MetHbreductase. Therefore, MetHb is maintained at a constant level [1].

Clinically, methemoglobinemia in mild cases may go undiagnosed. Fatigue, flulike symptoms and headaches may be the only manifestations in the initial phase. Symptoms are proportional to the MetHb level and include cyanosis. As levels of MetHb rise above 15%, neurologic and cardiac symptoms arise as a consequence of hypoxia. Levels higher than 70% are usually fatal [2].

Methemoglobinemia can be congenital or acquired. A large proportion of intoxication-induced MetHb is secondary to the use of nitrites and nitrates [2].Some patients fatally injured in fires or through the intentional inspiration of exhaust may demonstrate high levels of MetHb as well as carbon monoxide (CO) poisoning. However, no study has investigated the level of MetHb among surviving patients with CO poisoning or compared findings between dead and surviving cases among patients with CO poisoning. Juntendo Shizuoka Hospital routinely performed blood gas analyses including levels of both carboxyhemoglobin (COHb) and MetHb for patients who were transported to this hospital by ambulance. Therefore, this study retrospectively investigated the significance of the level of MetHb in patients with CO poisoning.

METHODS

This study was a retrospective chart analysis and it was approved by the Institutional Review Board of Juntendo Shizuoka Hospital. The serum COHb and

MetHb levels were evaluated using a blood gas analyzer at our hospital (ABL 800 FLEX Radiometer®, Copenhagen, Denmark). We conducted a medical chart review of patients treated from October 2012 to March 2018. The inclusion criterion was patients who were treated in our department due to CO poisoning. The exclusion criterion was patients without acute CO poisoning.

The subjects were divided into two groups based on the outcome (survival vs. death). The following variables measured at arrival were analyzed by a review of medical charts based on the patients' sex, age, cause of CO poisoning, cardiac arrest on arrival, vital signs on arrival (Glasgow Coma Scale, systolic blood pressure, heart rate, oxygen saturation), COHb, MetHb, base excess (BE), tracheal intubation and hyperbaric oxygen therapy.

In addition, concerning MetHb, differences in the sex, cause of CO poisoning, and relationship by age, vital signs on arrival, BE and COHb were analyzed.

Statistical analyses were performed using Student's unpaired *t*-test, the chi-squared test or a correlation analysis. Differences with P-values of less than 0.05 were considered to be statistically significant.

RESULTS

There were 32 patients who were treated by this department for CO poisoning during the investigation period. Among them, one patient with delayed neurological syndrome after CO poisoning was excluded. The remaining 31 patients were defined as subjects in this study.

The background of the subjects is summarized in Table 1. All subjects who were in cardiac arrest on arrival ultimately died without obtaining spontaneous circulation under advanced cardiac life support.

The findings of the groups defined by the outcome are summarized in Table 2. There were no significant differences associated with the sex, age, cause of CO poisoning or ratio of hyperbaric oxygen therapy between the dying and surviving cases. The Glasgow Coma Scale, systolic blood pressure, heart rate, oxygen saturation and level of BE in the dying group were lower than in the surviving group. The level of COHb and MetHb and frequency of tracheal intubation in the dying group were greater than those in the surviving group. In subsequent univariate analyses, the vital signs of the dead cases were found to be a confounding factor, so the Glasgow Coma Scale, systolic blood pressure, heart rate and oxygen saturation were initially evaluated, with the Glasgow Coma Scale and heart rate ultimately selected. A multivariate analysis of the Glasgow Coma Scale, heart rate, COHb, MetHb and BE showed that the heart rate and Glasgow Coma Scale were independent predictors of fatality, with a Log worth of 1.88 ($p=0.01$) and 1.63 ($p<0.05$), respectively.

The results of the subanalysis concerning MetHb are shown in Table 3. There were weak correlations between the MetHb levels and the age, oxygen saturation, BE and COHb.

Table-1: Background of the subjects

Male/female	22/9
Age (years old)	48.4 ± 20.3
Cause of carbon monoxide intoxication	
Charcoal	15
Fire	13
Incomplete combustion	2
Exhaust gas	1
Cardiac arrest on arrival	5
Glasgow Coma Scale	Median 14 (8, 15)
Systolic blood pressure (mmHg)	109.5 ± 53.5
Heart rate (beat per minute)	76.6 ± 38.2
Level of carboxyl hemoglobin (%)	20.9 ± 19.8
Methemoglobin (%)	1.83 ± 0.69
Tracheal intubation	15
Hyperbaric oxygen therapy	13
Mortality	6

Table-2: Comparison between the Survival and Fatal groups

	Survival (n=25)	Fatal (n=6)	p value
Sex (male/female)	18/7	4/2	n.s.
Age	44.8 + 18.9	63.6 + 20.6	0.05
Fire or exhaust gas (yes/no)	11/14	3/3	n.s.
Glasgow Coma Scale	14 (13.5, 15)	3 (3)	p < 0.01
Systolic blood pressure (mmHg)	131.9 + 21.9	20.0 + 48.9	p < 0.001
Heart rate (rate per minute)	92.8 + 17.1	11.6 + 28.5	p < 0.001
Oxygen saturation (%)	98.0 + 2.1	16.3 + 40.0	p < 0.001
Base excess (mmol/l)	-1.1 + 5.0	-18.0 + 11.9	p < 0.01
Carboxyl hemoglobin (%)	14.0 + 9.7	49.5 + 26.2	p = 0.01
Methemoglobin (%)	1.6 + 0.5	2.6 + 0.7	p = 0.01
Tracheal intubation (yes/no)	9/16	6/0	p<0.01
HBO therapy (yes/no)	12/13	1/5	n.s.

HBO: Hyperbaric oxygen therapy

Table-3: Results of analysis concerning methemoglobin

Sex	Male (22)	1.78 $\pm$ 0.82 %	n.s.
	Female (9)	1.94 $\pm$ 0.25 %	
Age	R = 0.49	p < 0.01	
Fire or exhaust gas			
yes (14)	1.92 $\pm$ 0.56	n.s.	
no (17)	1.7 $\pm$ 0.21		
Glasgow Coma Scale	R = -0.2	n.s.	
Blood pressure	R = -0.2	**n.s.**	
Heart rate	R = -0.1	**n.s.**	
Oxygen saturation	R = -0.41	p=0.01	
Base excess	R = -0.47	p < 0.01	
Carboxyl hemoglobin	R = 0.53	p < 0.01	

HBO: Hyperbaric oxygen therapy

DISCUSSION

This is the first report to show that the MetHb level at the time of arrival was higher in CO poisoning cases that died than in those that survived, and MetHb had a weak positive correlation with COHb. However, compared with the vital signs, the level of MetHb was not an important prognostic factor for predicting the outcome of CO poisoning.

Previous reports have shown that patients fatally injured in fires or through the intentional inspiration of exhaust gas might demonstrate high levels of Met Hb [3-5].The major immediate toxic threats in fire situations are carbon monoxide, a multitude of irritating organic chemicals in the smoke, oxygen depletion and heat. Synthetic polymers have been introduced in buildings, many of which contain nitrogen or halogens, resulting in the release of hydrogen cyanide and inorganic acids during fires as additional toxic threats and inducing the production of MetHb by heat denaturation and inhalation of oxides of nitrogen [3, 6].The present study included patients injured in fires or through the intentional inspiration of exhaust gas, which may increase the level of MetHb. Hoffman *et al*. reported in their case series that relatively low levels of MetHbcould complicate concomitant CO poisoning by additive or synergistic effects on oxygen binding and delivery [7].

Recently, variability in the COHb and MetHb levels for patients with endogenous diseases, such as asthma, pulmonary embolism or malaria, has been reported [8-10].Increased initial MetHb levels were found to be accompanied by increased disease severity and more prominent gas exchange impairment upon admission among patients with pulmonary embolism [8]. A previous study found that elevated MetHb levels are secondary to pathologic conditions, such as sickle cell crisis, and gastrointestinal infections in children [2].In addition, elevated MetHb levels have been reported in patients with sepsis or septic shock, possibly due to the enhanced production of NO that accompanies sepsis [11].In critically ill patients, the production of NO was found to be increased [12].In addition, tissue hypoxia may increase the production of endogenous MetHb[13].In cases of severe CO poisoning, patients enter shock and suffered from hypoxia. Accordingly, such a mechanism may increase the production of endogenous MetHb. The level of MetHb in patients with CO poisoning was not very high in the present study; however, increases in both the COHb and MetHb levels result in a vicious cycle affecting the transport of oxygen to peripheral tissues in humans. Thus,

physicians should pay attention to the levels of MetHb when they treat patients with severe CO poisoning.

Limitations associated with our study include its retrospective nature, small number of subjects and lack of healthy controls. Accordingly, further prospective studies including healthy control are therefore needed to determine to confirm significance of MetHb among patients with CO poisoning in the future.

CONCLUSION

The MetHb level at the time of arrival was higher in CO poisoning cases that died than in those that survived, and MetHb had a weak positive correlation with COHb. Therefore, physicians should pay attention to the MetHb level when treating patients with severe CO poisoning.

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