Risk Factors for Delayed Neuropsychiatric Sequelae in Carbon Monoxide Poisoning: Ten Years’ Experience in a Pediatric Emergency Department -

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Abstract

Objective: The occurrence of Delayed Neuropsychiatric Sequelae (DNS) after Carbon Monoxide (CO) poisoning is uncommon in children. Early identification of risk factors for the development of DNS in pediatric emergency departments is important. The objective of this study was to analyze risk factors for DNS after CO poisoning.

Methods: We retrospectively analyzed children with CO poisoning admitted to the pediatric emergency department from 2001 to 2010. Clinical, demographic, and laboratory data were collected; chi-square and univariate analyses were performed to assess risk factors for DNS.

Results: Among 68 children with CO poisoning, seven (10.3%) developed DNS. Clinical parameters such as Glasgow Coma Scales (GCS), Methemoglobin (MetHb), troponin-I, CPK level, myocardial injury, and neuroimaging abnormalities, were important associated risk factors for DNS. Decreased GCS level (OR = 0.701) and Methemoglobin (MetHb) ≥ 0.8% (OR = 19.54) are associated with DNS. Carboxyhemoglobin, and inadequate HBO therapy were not risk factor.

Conclusions: Prompt treatment of CO poisoning and identify risk factor for DNS is still challenge in PED. Our data demonstrate that decreased GCS level and increased MetHb level were independent risk factors associated with DNS. Early recognition and prompt treatment is important to prevent further neurological damage.

Keywords: Delayed neuropsychiatric sequelae; Carbon monoxide poisoning; Children; Methemoglobin; Hyperbaric oxygen

Introduction

Carbon Monoxide (CO) poisoning is one of the important causes of inhalational poisoning in Pediatric Emergency Departments (PEDs). Presenting symptoms are non-specific, and acute diagnosis is initially a challenge for the pediatric emergency physician. The prognosis for CO poisoning is variable; although most cases have a good outcome, some have devastating complications, including cardiopulmonary compromise, Delayed Neuropsychiatric Sequelae (DNS), and death. Following the introduction of Hyper Baric Oxygen (HBO) therapy and associated with the development of DNS and to reevaluate previous recommendations with respect to prompt HBO treatment in PEDs.

Materials and Methods

Study design

We retrospectively analyzed the medical records of 68 children with CO poisoning who were admitted to the PED of Chang Gung Children’s Hospital between January 2001 and December 2010. The study was approved by the institutional review board of this hospital. Inclusion criteria included COHb level greater than 5% with exposure history in age lesser than 18 years old. Patients with COHb level lesser than 5%, previous neuropsychological disorders, and insufficient information for diagnosis of CO were excluded.

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DNS was diagnosed as the presence of neurological, cognitive, or affective disorders, developing after hospital discharge, as assessed by a pediatric neurologist or pediatric psychologist. Myocardial injury was defined as cardiac dysrhythmias, elevated troponin-I levels, or electrocardiogram abnormalities.

Data on the following variables were collected: age, sex, accidental or intentional exposure, presence of the same symptoms in family members, transient loss of consciousness or mental change, seizures, headache, vital signs, evidence of cardiac dysfunction, dyspnea, CO-oximeter panel including \(\text{O}_2\text{Hb}\) and \(\text{COHb}\), methemoglobin (\(\text{MetHb}\)), metabolic acidosis (\(\text{pH} < 7.20\)), and \(p\text{aO}_2\) in an arterial blood sample at the PED. White Blood Cell count (WBC), troponin-I, and Creatine Phosphor Kinase (CPK) concentration in a venous blood sample obtained on arrival at the PED or on admission were also collected. Treatment modality for HBO, 100% non-rebreathing mask, or 100% Normal Baric Oxygen (NBO) was also recorded.

Inadequate HBO treatment was defined as patients not receiving HBO therapy in circumstances in which it is currently recommended; that is, candidate patients presenting with at least one of these signs or symptoms before or upon hospital admission were identified as inadequately treated: \(\text{COHb} > 25\%\) or lower with intubation, < 1 years old, GCS < 8, any period of unconsciousness, metabolic acidosis, or myocardial injury \([1, 14-16]\).

### Statistical analyses

The chi-square test, Fisher’s exact test for categorical variables, and the Mann–Whitney \(U\)-test for continuous variables were used for comparative analyses between patients with and without DNS. Univariate analysis was performed using a logistic regression model to estimate the Odds Ratio (OR) of developing DNS, along with the 95% Confidence Interval (CI). Variables significantly related to DNS development were selected; a multivariate analysis was then performed via a step-wise forward regression model, and the OR was estimated. For all tests, two-sided \(p\)-values less than 0.05 were considered to indicate statistical significance. In the text and tables, variables are expressed as means ± Standard Deviations (SDs). Statistical analyses were conducted using SPSS software (ver. 17.0; SPSS Inc.).

### Results

#### Demographic characteristics

Presenting symptoms and signs of acute carbon monoxide poisoning are listed in Table 1. Of the 68 cases of CO intoxication, 34 (50.0%) were males and 34 (50.0%) were females. The mean age was ranging between 0 years and 16 years (mean ± SD, 8.15 ± 4.53).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DNS children (N = 7; 10.3%)</th>
<th>Non DNS children (N = 61; 89.7%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>3 (42.9%)</td>
<td>33 (50.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fire accident</td>
<td>1 (14.3%)</td>
<td>0 (0.0%)</td>
<td>0.103</td>
</tr>
<tr>
<td>Intention</td>
<td>1 (14.3%)</td>
<td>2 (3.3%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Heater in poorly ventilated indoor</td>
<td>5 (71.4%)</td>
<td>51 (83.6%)</td>
<td>0.598</td>
</tr>
<tr>
<td>Charcoal</td>
<td>2 (28.6%)</td>
<td>2 (3.3%)</td>
<td>0.050</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (14.3%)</td>
<td>41 (67.2%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (14.3%)</td>
<td>24 (39.3%)</td>
<td>0.248</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2 (28.6%)</td>
<td>21 (34.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>0 (0.0%)</td>
<td>4 (6.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Mental change</td>
<td>7 (100%)</td>
<td>21 (34.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS</td>
<td>10.14 ± 4.91</td>
<td>14.56 ± 1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lab findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{COHb})</td>
<td>26.71 ± 12.48</td>
<td>21.54 ± 9.21</td>
<td>0.338</td>
</tr>
<tr>
<td>(\text{MetHb})</td>
<td>0.85 ± 0.29</td>
<td>0.41 ± 0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>12842 ± 5009</td>
<td>11357 ± 4209</td>
<td>0.437</td>
</tr>
<tr>
<td>Troponin I</td>
<td>3.52 ± 6.57</td>
<td>0.24 ± 0.36</td>
<td>0.009</td>
</tr>
<tr>
<td>CPK</td>
<td>15555.8 ± 1421.4</td>
<td>95.82 ± 58.72</td>
<td>0.002</td>
</tr>
<tr>
<td>Acidosis</td>
<td>2 (28.6%)</td>
<td>0 (0.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neuroimaging abnormalities</td>
<td>4 (57.1%)</td>
<td>1 (1.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intubation</td>
<td>1 (14.3%)</td>
<td>1 (1.6%)</td>
<td>0.197</td>
</tr>
<tr>
<td>Only NBO</td>
<td>1 (14.3%)</td>
<td>33 (54.1%)</td>
<td>0.105</td>
</tr>
<tr>
<td>HBO</td>
<td>5 (71.4%)</td>
<td>20 (32.8%)</td>
<td>0.091</td>
</tr>
<tr>
<td>Candidate for HBO*</td>
<td>7 (100%)</td>
<td>34 (55.7%)</td>
<td>0.167</td>
</tr>
<tr>
<td>Inadequate HBO</td>
<td>2 (33.3%)</td>
<td>21 (35.3%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

DNS indicates delayed neuropsychological sequelae; SD, standard deviation; GCS, Glasgow coma scales; NBO, normal baric oxygen; HBO, hyperbaric oxygen; Candidate for HBO*, initial COHb>25%, mental change, or myocardial injury.

Table 2: Clinical profiles of patients with and without delayed neuropsychological sequelae

The most common symptom on pediatric emergency department was dizziness (61.8%), followed by mental changes (41.2%), headache (36.8%), nausea or vomiting (33.8%), weakness (16.2%), syncope (10.3%), chest pain (5.9%), and seizure (2.9%) (Table 2). A gas water heater improperly installed in a poorly ventilated indoor situation was the most common reason for CO poisoning (82.4%), followed by intentional charcoal burning (4.4%), electrical heaters (2.9%), fire accidents (1.5%), Barbecue (1.5%) and unclassified.

Most patients (86.8%) were treated with normal baric oxygen treatment; 25 cases (36.8%) were treated with HBO. No patient expired and 7 (10.3%) cases developed DNS.

### Comparative analysis of DNS

Table 2 summarizes the clinical and demographic factors relevant to the development of DNS. Comparisons of the DNS patients showed a significant increase in \(\text{MetHb}\) (0.85 ± 0.29 vs. 0.41 ± 0.21; \(P = 0.001\)), troponin-I level (3.52 ± 6.57 vs. 0.24 ± 0.36; \(P = 0.009\)), and CPK level (15555.8 ± 1421.4 vs. 95.8 ± 58.7; \(P = 0.002\)), but a significant decrease in GCS level (10.14 ± 4.91 vs. 14.56 ± 1.74; \(P < 0.001\)). Factors showing significant differences were charcoal burning (\(P = 0.050\)), dizziness (\(P = 0.011\)), metabolic acidosis (\(P < 0.001\)) and mental changes (\(P = 0.001\)). However, no significant differences were observed in COHb level (\(P = 0.338\)).
CI indicates confidence interval. MetHb, methemoglobin; GCS, Glasgow child protection and stayed in foster care. Early recognition of victims include them in a family suicide. These two children were transferred to
identified only three cases (4.4%) those were associated with intentional burning were the most common reasons for DNS [7]. However, we
HBO treatment were not significantly associated with the development of DNS in these subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>0.681</td>
<td>0.002</td>
</tr>
<tr>
<td>Initial COHb level</td>
<td>1.053</td>
<td>0.185</td>
</tr>
<tr>
<td>MetHb ≥ 0.8</td>
<td>22.1</td>
<td>0.002</td>
</tr>
<tr>
<td>White blood count</td>
<td>1.00</td>
<td>0.407</td>
</tr>
<tr>
<td>Troponin I</td>
<td>9.63</td>
<td>0.042</td>
</tr>
<tr>
<td>PH value</td>
<td>0.00</td>
<td>0.07</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow coma scales; CI, confidence interval.

Table 3: Univariate analysis of Predictive risk factors of DNS development.

Discussion

In this study, DNS was identified in seven of 68 children (10.3%) with CO poisoning. Initial GCS level and MetHb ≥ 0.8% were found to be independent risk factors for DNS in this study. We also observed that troponin-I was increased in the DNS group. In contrast, age, sex, fire accident, WBC, COHb level, blood glucose level, and inadequate HBO treatment were not significantly associated with the development of DNS in these subjects.

A previous report revealed that suicide attempts and charcoal burning were the most common reasons for DNS [7]. However, we identified only three cases (4.4%) those were associated with intentional charcoal burning; one case was a suicide attempt and the other two were children with CO poisoning following an attempt by their parents to include them in a family suicide. These two children were transferred to child protection and stayed in foster care. Early recognition of victims of such child neglect/abuse is important for pediatric emergency physicians to prevent recurrences.

In our study, a correlation was observed between change in MetHb and development of DNS in CO poisoning. MetHb in the blood has not previously been associated with DNS. Increased MetHb indicating hypoxia increased by reduced ability to release oxygen to tissues and produces tissue hypoxia. Toxins can oxidize hemoglobin to MetHb through direct oxidation of hemoglobin, indirect oxidative pathways, and via metabolic activation [17]. Severe hypoxia leads to severe damage in the gray matter such as the cortex rather than the white matter, because the gray matter is more vulnerable under hypoxia than the white matter in development of DNS. Further prospective studies are planned to establish whether the increase in MetHb is truly predictive of the development of DNS.

We identified several predictive clinical and laboratory markers associated with developing DNS in a pediatric group. Specifically, low level of GCS and increased MetHb had significant predictive value for developing DNS. Thus, low level of GCS may be a useful predictor for the neurological injury. Recently, consistent with previous studies, GCS score was identified as a risk factor for the development of DNS, whereas COHb was not a predictor [10,18]. The mechanism of DNS is incompletely understood, but it probably occurs through brain lipid peroxidation by xanthine oxidase, resulting in reversible demyelination of white matter in the central nervous system; this condition can lead to edema and focal necrosis within the brain [19]. These processes are thought to occur as a result of post-ischemic reperfusion injuries and the production of oxygen free radicals [20–21]. Additionally, brain injury is related to susceptibility to oxidative stress, antioxidiant capacity, and autoregulation of brain blood flow [3,22]. Furthermore, post-CO damage-induced inflammation may contribute to more damage [16].

COHb level was not associated with developing DNS in our case series; this is, consistent with a previous study that also showed that COHb level did not correlate with clinical condition [15]. However, others have reported that COHb increased the risk of developing neurological impairment or correlated with clinical prognosis [9,23-24]. These differences may be influenced by several factors, such as CO exposure time, timing of blood collection, pre-hospital oxygen support available in transportation, and individual genetic variation.

In our study, we did not find a statistically significant association between inadequate HBO therapy and developing DNS. Our results are consistent with several previous reports [12,15,25-26]. However, several previous randomized clinical trials have demonstrated the benefits of HBO therapy [2,16,27]. It seems likely that the timing of 100% O2 antioxidant capacity, and autoregulation of brain blood flow [3,22]. Furthermore, post-CO damage-induced inflammation may contribute to more damage [16].

Discussion

        Table 4: Multivariate regression of relationship for development of DNS

        | B     | S.E.   | Wald | df | Sig. | Exp(B) | 95% C.I. for EXP(B) |
        |-------|--------|------|----|------|--------|---------------------|
        | MetHb ≥ 0.8% | 2.972 | 1.132 | 6.900 | 0.009 | 19.540 | 2.127 – 179.54 |
        | GCS   | -0.355 | 0.163 | 4.725 | 0.030 | 0.701  | 0.509 – 0.966 |

CI indicates confidence interval; MetHb, methemoglobin; GCS, Glasgow Coma Scales.

Table 4: Multivariate regression of relationship for development of DNS (95% CI).

Variables Odds ratio (95% CI) P value

0.338), white blood count (P = 0.437), age (P = 0.887), sex (P = 1.00), HBO therapy (0.091) or inadequate HBO therapy (P = 1.000).

The variables identified by the univariate analysis as associated with DNS were GCS (P = 0.002), MetHb ≥ 0.8% (P = 0.002), and troponin-I (P = 0.042). However, COHb level, pH value, and white blood count were not associated with DNS (P = 0.185, P = 0.07, and P = 0.407, respectively; Table 3). Using multivariate logistic analyses, GCS (OR 0.701; P = 0.03) and MetHb ≥ 0.8% (OR 19.54; P = 0.009) were identified as independent predictors of DNS development (Table 4).

Forty-one patients (60.3%) presented with signs or symptoms currently considered indications for HBO; of these patients, 21 (21/41, 51.2%) were not treated with HBO. Of these cases of inadequate HBO therapy, only two patients (9.5%) developed DNS (P = 0.238). Of the patients who ultimately suffered from DNS, all children present signs or symptoms currently considered indications for HBO at admission. None of the patients suffered adverse effects from HBO therapy and no cases of mortality occurred.

The most common sequela consisted of impaired learning; personality changes; attention deficits; recent memory impairment; slurred speech; delirium; insomnia; difficulty calculating, writing, or reading; and involuntary movements. Abnormal neurological signs were seen in three patients; these were primarily related to cerebellar and basal ganglia injury: postural instability, increased deep tendon reflex, clamping, impaired coordination, and dysarthria.

Discussion

In this study, DNS was identified in seven of 68 children (10.3%) with CO poisoning. Initial GCS level and MetHb ≥ 0.8% were found to be independent risk factors for DNS in this study. We also observed that troponin-I was increased in the DNS group. In contrast, age, sex, fire accident, WBC, COHb level, blood glucose level, and inadequate HBO treatment were not significantly associated with the development of DNS in these subjects.

A previous report revealed that suicide attempts and charcoal burning were the most common reasons for DNS [7]. However, we identified only three cases (4.4%) those were associated with intentional charcoal burning; one case was a suicide attempt and the other two were children with CO poisoning following an attempt by their parents to include them in a family suicide. These two children were transferred to child protection and stayed in foster care. Early recognition of victims
arterial lactate level, and the duration of unconsciousness from the scene to the institute. The time interval between exposure to CO and MetHb measurements was not controlled. Additionally, the management of children who had experienced CO poisoning during the period prior to arrival at our PED was not standardized. The treatment guidelines for HBO administration were not followed consistently. Although HBO was administered in more clinically severe cases, this was not done or was done less frequently in less severe cases, adding a bias. The small changes in MetHb levels may make this a relatively insensitive means of assessing the risk of developing DNS. In future studies, changes in MetHb and metabolic acidosis need to be correlated with clinical condition. If a positive correlation is observed between changes in MetHb and clinical presentation, then assessment of MetHb levels may provide an early biomarker for the detection of development of DNS.

Conclusion

Prompt treatment of CO poisoning and identify risk factor for DNS is still challenge in PED. Our data demonstrate that decreased GCS and increased MetHb level were independent risk factors associated with DNS. Further prospective studies are needed to assess whether HBO truly prevents DNS in children in the context of early recognition and prompt treatment.

References


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