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# Effect of free radical scavenger, edaravone, for patients with carbon monoxide poisoning

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ABSTRACT

*Objective:* Chronic neurological symptoms after carbon monoxide (CO) poisoning are caused by various biological processes in the damaged brain, with free radicals playing roles as mediators in establishing pathological processes leading to chronic neurological symptoms under CO poisoning. This study aimed to clarify the effects of a free radical scavenger, edaravone, in patients with CO poisoning.
*Methods:* We retrospectively compared two groups comprising patients treated with hyperbaric oxygenation alone (Group A, $n = 25$) or edaravone in addition to hyperbaric oxygenation (Group B, $n = 25$). Edaravone was administrated intravenously at 30 mg every 12 h for 7 days. Patient characteristics, general conditions on admission, and frequency of chronic neurological symptoms were compared between groups. Among patients showing chronic neurological symptoms, cognitive function and daily activity were also compared between groups.
*Results:* No significant differences in characteristics or general conditions on admission were identified between groups. In Group B, no patients presented with marked complications caused by edaravone. Although chronic persisting symptoms were less frequent in Group B ($n = 1$, 0.04%) than in Group A ($n = 5$, 20%), this difference was not significant. In the 11 patients showing chronic symptoms, scores for cognitive function and daily activity in the chronic phase were better in Group B than in Group A, but no significant differences were apparent.
*Conclusions:* The present results suggest that edaravone represents a tolerable and feasible treatment for CO-poisoned patients. Further studies are needed to clarify whether edaravone can favorably influence chronic neurological symptoms caused by CO poisoning.



## 1. Introduction

Brain damage due to carbon monoxide (CO) poisoning causes a chronic neurological prognosis in patients. Among those patients who survive CO poisoning, approximately 30% present with chronic neurological symptoms, including persistent symptoms and recurrent neuropsychiatric symptoms after an interval of apparent normality, as so-called delayed neuropsychiatric sequelae (DNS) [1,2]. The development of chronic symptoms cannot be completely prevented by routine treatment with oxygen inhalation or even hyperbaric oxygenation ($HBO_2$).

The mechanisms underlying brain damage after CO poisoning are complicated [3]. CO can cause brain hypoxia, increasing levels of excitatory amino acids and leading to subsequent injuries in the cerebral cortex [4]. CO can also cause oxidative stress, cellular necrosis, apoptosis, and ongoing inflammation [5,6]. Brain damage leading to chronic symptoms has been attributed to mechanisms other than CO-associated hypoxia [7,8]. CO inhibits mitochondrial metabolism due to disorders of the cytochromes, leading to cellular

*Abbreviations:* CO, carbon monoxide; COHb, carboxyhemoglobin; DNS, delayed neuropsychiatric sequelae; FLAIR, fluid-attenuated inversion recovery imaging; GCS, Glasgow Coma Scale; $HBO_2$, hyperbaric oxygenation therapy; MBP, myelin basic protein; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; $O_2$, oxygen; T2WI, T2-weighted magnetic resonance imaging.

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respiratory dysfunction [9], and immunological and inflammatory cascades, including platelet-to-neutrophil aggregation and neutrophil degranulation, lipid peroxidation, alteration of the structure of myelin basic protein (MBP), progressive demyelination, and ongoing inflammation in the white matter [3,10,11]. Furthermore, recent experimental studies have shown the release of a variety of proteins relating to inflammatory response [12], and elevated levels of circulating microparticles leading to neutrophil-activation as a pro-inflammatory effect, resulting in tissue injuries in CO poisoning [13].

Free radicals are closely related to pathological processes in CO-medicated brain damage [3,10–12]. CO binds to platelet heme proteins, causing the release of nitric oxide. Excess nitric oxide results in the production of peroxynitrite as a pathological free radical, impairing mitochondrial function [11]. The reactive oxygen species produced by activated neutrophils, mitochondria, and xanthine oxidase, play roles as mediators in the processes of platelet-to-neutrophil aggregation, neutrophil degranulation oxidative stress, and lipid peroxidation [10,11]. In cases involving a hypoxia-hypotension process due to severe CO poisoning, brain ischemia can initiate a series of pathological free radicals. Since reoxygenation after the release of CO from hemoglobin can have more adverse impacts than seen in normal brain tissue [14], $O_2$ may involve enhanced oxidative stress from the generation of reactive oxygen species, although the majority of oxidants may be eliminated by the inherent anti-oxidant ability of tissue components such as superoxide dismutase [15].

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) was developed as a low molecular weight free radical scavenger and anti-oxidant, able to pass through the blood-brain barrier [16,17]. Edaravone shows experimental potential in quenching hydroxyl radicals and hydrogen peroxide [18], and also in decreasing the production of superoxide anions [19] under ischemic conditions in the brain. Clinical trials have shown that administration of edaravone significantly improves functional outcomes in patients with acute ischemic stroke [20–22]. The possible mechanisms underlying the effects of edaravone have been revealed to be decreased oxidative stress, protection of neurovascular units, and a reduction in the activation of microglia after ischemic stress [17]. In CO poisoning, an experimental study using an animal model showed free radicals were involved in the production of brain injuries and found that edaravone exerted favorable effects [23].

For CO-poisoned patients, elimination of the free radicals released after CO poisoning using edaravone may represent an attractive approach to reducing the severity or even preventing the occurrence of chronic neurological symptoms. The aim of this study was to clarify whether edaravone can positively affect chronic neurological symptoms in CO-poisoned patients.

## 2. Methods

### 2.1. Participant selection

All study protocols were approved by the Ethics Committee of Iwate Medical University, Morioka, Japan. Patients recruited to this study had been admitted to Iwate Medical University Hospital. The present study was conducted according to the principles expressed in the Declaration of Helsinki. Entry criteria for this study were: patients $\geq$20 years old but $\leq$70 years old who had suffered CO poisoning caused by a fire, gas or charcoal burning; no past history of brain disorder, including surgical operation, irradiation, stroke, infection, or demyelinating disease; treatment with $HBO_2$ within 24 h of the end of CO exposure; performance of magnetic resonance imaging (MRI) within 2 weeks after admission; and provision of written informed consent to participate and for publication of case details. Patients for whom the initial examinations of blood count and blood serum (including renal and hepatic functions) showed moderate disorder more than grade 2 (between 3.0 times and 5.0 times the upper limit of normal range) according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) and/or high ratio of blood urea nitrogen to creatinine suggesting dehydration were excluded from this study.

We have been maintaining a database of CO-poisoned patients since March 2008. Treatment with $HBO_2$ plus edaravone was started from November 2010. We therefore searched the database for patients admitted between March 2008 and October 2010 who met the criteria described above. In total, 25 patients were extracted from this period and defined as Group A, after excluding 15 patients who did not meet the entry criteria. Patients who were treated with $HBO_2$ plus edaravone and who met the entry criteria were recruited to this study from November 2010. We continued to recruit patients until 25 patients were collected. After excluding 16 patients who did not meet the inclusion criteria, 25 patients who were treated with $HBO_2$ plus edaravone between November 2010 and August 2013 were defined as Group B. Among the total of 31 patients excluded from this study (from Groups A and B), 16 patients did not meet the age criteria, 5 patients could not undergo initial $HBO_2$ within 24 h of the end of CO poisoning, 6 patients did not meet the criteria for blood examination, 3 patients declined to participate, and 1 patient did not undergo MRI. Groups A and B were then compared retrospectively (Fig. 1).

### 2.2. Treatment protocols

The day of the end of CO inhalation was defined as Day 1 in this study. All patients in both groups were treated with $HBO_2$ (60 min of 100% oxygen inhalation via mask at 2.8 atmospheres absolute) starting within 24 h after the end of CO exposure. $HBO_2$ was continued with a single daily session for a maximum of 7 days. $HBO_2$ was discontinued upon patient request or when all symptoms showed full-resolution under observations by the attending physicians.

For patients in Group B, we administered edaravone intravenously at 30 mg diluted in 100 mL of physiological saline solution for 30 min every 12 h until Day 7, in addition to the $HBO_2$ described above. The initial administration of edaravone was performed immediately after making a diagnosis of CO poisoning. Every session of $HBO_2$ was started immediately after completing administration of edaravone.

### 2.3. Monitoring of patient condition

In addition to blood examinations at Day 1, all patients underwent blood examinations on each of the first 3 days, and Group B underwent blood examinations every other day until Day 7 to monitor edaravone toxicity. On Day 1, we estimated level of consciousness using the Glasgow coma scale (GCS), initial symptoms, carboxyhemoglobin (COHb) concentration in arterial blood, cause and source of CO, duration of CO exposure, duration of oxygen treatment before $HBO_2$, and intervals between arrival at hospital and start of $HBO_2$, and between end of CO exposure and starting $HBO_2$. T2-weighted MRI (T2WI) or fluid-attenuated inversion recovery imaging (FLAIR) was performed for each patient as soon as possible after admission (within 2 weeks) using a 1.5-T MRI system, and whether abnormal hyperintense foci were apparent at the globus pallidus and/or cerebral white matter was evaluated.

We continuously observed the neurological conditions of all patients for 6 weeks after admission using routine physical examinations to assess cranial nerve functions, motor and sensory functions, and coordination of the face, body and extremities as cerebellar functions. At 6 weeks (Day 40–44), patients were assigned to one of three types according clinical behaviors: acute