● PERSPECTIVES

Acute carbon monoxide poisoning and delayed neurological sequelae: a potential neuroprotection bundle therapy

Currently, there is no known optimal therapy for carbon monoxide (CO) poisoning and CO-associated delayed neurological sequelae. Hyperbaric oxygen therapy (HBOT) is a well-known treatment method, but its use for CO poisoning patients is controversial to use due to lack of evidences regarding its efficacy. Thus, it is unlikely that HBOT alone will be accepted as the standard treatment method. In this article, current and potential treatment methods of CO poisoning are presented as well as the tentative multi-factorial pathophysiology. A series of treatments are suggested for use as a bundle therapy, with targeted temperature management as the base treatment method. Such a therapy holds a great potential, especially for the cases where HBOT is not readily available. We suggest further investigations for elucidating the effects of these suggested treatments and their roles in terms of the complex pathophysiology of CO poisoning. Future acceptance of this therapy based on the improved scientific and clinical knowledge may result in injury prevention and minimization of the signs and the symptoms in CO poisoning.

CO poisoning: CO gas is odorless, colorless, and non-irritating. Still, it is very toxic, and inhalation in even small quantities can cause serious injuries in humans. CO poisoning is still one of the most common poisoning deaths in the world (Braubach et al., 2013). In South Korea, the number of CO poisoning deaths has rapidly increased in recent years, which is associated with the increasing number of suicidal attempts by ignite charcoal burning. In CO poisoning, the common morbidity involves the organs with high oxygen demands such as the heart and the brain. Types and severity of the symptoms may vary with different levels and durations of CO exposure. For those who survived the acute CO poisoning, delayed neurological sequelae (DNS) is a real concern. After the disappearance of initial symptoms, DNS may develop in 2 to 40 days in up to 40% of the survivors of acute CO poisoning. During the acute phase, the signs and the symptoms of toxicity include headaches, dizziness, syncope, loss of consciousness, seizure, coma, and death. During the delayed phase, the signs and the symptoms include memory loss, movement disorders, Parkinson-like syndrome, communication disturbances, depressed mood, dementia and psychosis.

Cerebral injuries in CO poisoning: Cerebral injuries subject to CO intoxication may occur during the acute phase as well as during the sub-acute phase, resulting in the development of neurological and neuropsychiatric symptoms. Radiological findings of neuropathologic abnormalities can usually be made in CT and MRI images for early and late brain damages. These are possibly caused by white matter demyelination, diffuse brain atrophy, injury to basal ganglia, and infarct of the globus pallidus. The most common feature known is the symmetrical bilateral basal ganglia abnormality. Acute brain lesions are observed commonly in basal ganglia and corpus callosum, and more clearly in bilateral globus pallidus. During the delayed phase, brain lesions are typically observed in deep white matter and diffuse inflammations in semicentrum ovale or periventricular regions (Parkinson et al., 2002).

Pathophysiological mechanisms of CO poisoning: Pathophysiology of CO poisoning and subsequent DNS is very complex and remains poorly understood. A well-known underlying pathophysiological mechanism in CO poisoning is hypoxic stress. However, tissue hypoxia and impaired oxygen transport to the cells does not fully explain the complexity of cerebral injuries in CO poisoning. CO can affect the tissues in the brain directly, and inflammatory responses and cell structure changes are involved in the pathophysiological cascade. Therefore, there should be more explanations about various pathophysiological factors like apoptosis, abnormal inflammatory responses, ischemia/reperfusion injuries. Additional potential mechanisms are lipid peroxidation, the degradation of unsaturated fatty acids, and oxidative stress induced by reactive oxygen species, free radicals, and neuronal nitric oxide. Lipid peroxidation, if triggered, can lead to the delayed demyelination of white matter. In acute CO poisoning, dysregulated release nitric oxide by vascular endothelium and platelet cells may be triggered, hence the formation of oxygen free radicals such as peroxynitrite. This can lead to mitochondrial dysfunction, capillary leakage, leukocyte sequestration, and apoptosis.

A theory regarding catecholamine crisis was recently suggested as a novel underlying pathophysiologic mechanism in acute CO poisoning (Park et al., 2014). It is notable that acute CO poisoning patients and some consumers of cocaine, heroin and methamphetamine share similar characteristics of the lesions in the bilateral basal ganglia and globus pallidus (Verrico et al., 2007). In acute CO poisoning, sympathetic activities and subsequent catecholamine levels are likely to increase in synapses or nerve terminals, particularly in the limbic system in the brain. CO-associated hypoxia in striatum shows an increase of dopamine and a decrease of dopamine turnover rates. Thus, dopamine excess could be a major contributor to neurotoxicity, triggered by associated hypoxia and ischemia. During the acute phase of CO intoxication, dopamine excess in synaptic cleft of mesolimbic system can cause neuronal destruction at synapses and nucleus. Striatal lesions in mesolimbic system may appear in bilateral basal ganglia and globus pallidus. After CO withdrawal, dopamine excess can sustain for several weeks in the synapses in deep white matter enhancing oxidative metabolism of dopamine generating reactive species and triggering abnormal inflammatory responses. As a result, serotonergic axonal injury and secondary myelin damage may lead to the delayed leukoencephalopathy or CO-asso-

ciated DNS, in which leukoencephalopathy can be found in the white matter. Leukoencephalopathy and striatal injury can be caused not only in CO poisoning patients but also in 3,4-methylenedioxy-methamphetamine (MDMA) consumers. In leukoencephalopathy, toxins target at myelin, axons, oligodendrocytes, astrocytes, and white matter vasculature. MDMA is known to target at axons, but the targets of CO are not clearly known. Further scientific validation is requested in these areas.

A new critical care neuro-protection bundle therapy implications in CO poisoning: Single effective treatment method for minimizing the risk of CO-associated brain injuries at both acute and delayed phases is currently unavailable. Thus, a series of effective treatments should be considered for use as a bundle. Based on the current tentative pathophysiology, potential treatment methods were presented as in **Figure 1**. Underlying pathophysiological mechanisms were shown to be hypoxic stress, oxidative stress, lipid peroxidation, and catecholamine crisis. Complex interactions between these pathophysiological mechanisms and risk factors may progress to cause hypoxic injury, ischemia/reperfusion injury, demyelination, and neuronal apoptosis. If not treated properly, cerebral lesions can be formed in the globus pallidus at an acute stage and in the deep white matter at a delayed stage.

Hyperbaric oxygen therapy: Supplemental oxygen is the key for treating CO intoxication. For the patients diagnosed with CO poisoning, 100% oxygen is usually indicated. Hyperbaric oxygen is warranted for patients with serious intoxication showing loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, and carboxyhemoglobin greater than 25%. HBOT facilitates oxygen transport to the tissues eliminating CO effectively compared to normobaric oxygen therapy. It is known as the most common method for treating CO poisoning and preventing DNS by far, but its use is controversial due to insufficient evidences of efficacy (Chiew and Buckley 2014). Because hypoxic stress is not the only pathophysiologic mechanism in CO poisoning, the role of HBOT is likely over-rated, although generally suggested for patients showing moderate to severe symptoms. HBOT alone seems largely limited in delivering the most effective treatment, and its therapeutic effect may be enhanced if combined with other treatments. Further investigation is necessary for clarifying its role and for the side effects including middle ear barotrauma and conditions derived from oxygen toxicity.

Targeted temperature management and sympatholytics: Targeted temperature management with mild therapeutic hypothermia (TTM-TH) is used for patients with post-cardiac arrest or hypoxic-ischemic brain injury. It seems that TTM-TH is a promising treatment for DNS subject to acute CO poisoning. Brain injuries caused by systemic inflammations, hypoxic injuries, ischemia/reperfusion injuries, or apoptosis may be prevented by TTM-TH. Thus, prognosis of the patients with acute CO poisoning may be altered by way

of managing the body temperature. In hypothermia, formation of reactive oxygen species, subsequent lipid peroxidation and delayed encephalopathy are likely to be suppressed. In a study by Feldman et al. (2013), a combined therapy of HBOT and therapeutic hypothermia was performed to produce successful result. In this study, neurological sequelae turned out to have been mitigated by the initial intravascular cooling and subsequent chamber treatment, while hypothermia was sustained by using ice bags inside the chamber. In validating the effects of TTM, an objective and accurate neurological evaluation is of great importance (Oh et al., 2014). Further studies are warranted regarding the effects of targeted temperature management for CO poisoning patients.

Based on the 'catecholamine crisis' theory, minimization of systemic responses to acute stressor (CO) is paramount in treating CO poisoning patients. For example, initial stabilization of the patients by way of sedatives administration may help suppressing sympathetic nervous activities by precluding catecholamine surge and dopamine excess. Administration of sympatholytics such as dexmethetomidine or remifentanil may also be beneficial for inhibition of the postganglionic functions of the sympathetic nervous system. Effects of sympatholytics could be verified, for example, by analyzing heart rate variability (HRV), a quantitative index of sympathetic nervous activities. Exemplary studies based on HRV analysis are: 1) fetal HRV, correlated with maternal carboxyhemoglobin levels, showed the initial lows and the patterns variations with the ongoing therapies. 2) The changes of HRV were suppressed in patients with coronary artery disease exposed to the environmental levels of CO. 3) A moderate increase of carboxyhemoglobin did not contribute to acute sympathetic effects in cigarette-smoking healthy individuals as much as stress. Several environmental studies also showed stress as an important factor that increases HRV. One advantage with sympatholytic treatment is that it could be relatively easily carried out simultaneously with TTM-TH, since sedatives and paralytics are usually administered for preventing shivering in hypothermic induction.

Anti-oxidants, steroids, erythropoietin, and other potential treatments: A potent anti-oxidant such as N-acetylcysteine can be used as a treatment in CO poisoning. N-acetyl cysteine is largely effective for traumatic brain injury, cerebral ischemia, and other neurological disorders (Bavarsad Shahripour et al., 2014). N-acetylcysteine restores the intracellular levels of glutathione and the ability of cells to resist the reactive oxygen species mechanisms. In animal studies, the effects of N-acetylcysteine on oxidative damages were already verified for neurological disorders. The results from human studies, however, are rather inconsistent. Its side effects will have to be thoroughly examined before using in human patients. Additionally, special caution is required for the patients taking nitroglycerin, since N-acetylcysteine increase the effects of nitroglycerin.

Potent anti-inflammatory and immuno-suppressant steroids such as dexamethasone or methylprednisolone could be used for severe inflammations in CO poisoning. A patient
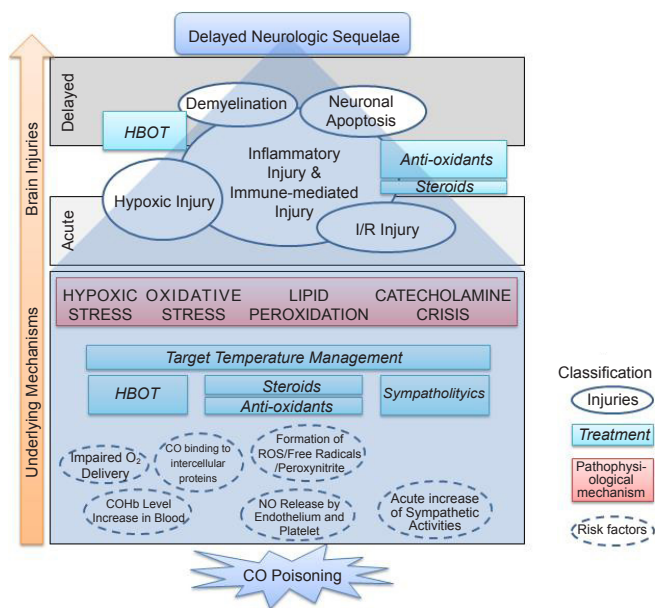
Figure 1 Underlying pathophysiologic mechanisms and therapeutic suggestions in acute CO poisoning and CO-associated delayed neurologic sequelae.
CO: Carbon monoxide; COHb: carboxyhemoglobin; NO: nitric oxide; ROS: reactive oxygen species; HBOT: hyperbaric oxygen therapy; I/R: ischemia/reperfusion.

with CO poisoning revived by a series of 3 HBOT sessions and steroid treatments from semi-coma state, and no sign or symptom of DNS appeared (Yee and Brandon 1983). Steroid pulse (methylprednisolone) and memantine hydrochloride was given to a patient who developed DNS even after HBOT, which made the patient recover from neurological deficits (Iwamoto et al., 2014).

Erythropoeitin is a glycoprotein hormone that produces red blood cells. In a hypoxic state as in stroke, erythropoeitin may be protective of neuronal cells by reducing S100B and preventive from neurological sequelae. It was shown that erythropoeitin manages cardiac complications subject to CO poisoning. Neuronal damages were also shown to have been prevented by erythropoeitin in a rat study, although the effect was partial. In a human study, neurological outcomes were shown to be improved with reduced incidence of DNS (Pang et al., 2013).

For a patient who developed persisting DNS after receiving a series of treatments including HBOT, an effective atypical antipsychotic, ziprasidone, successfully treated for delayed encephalopathy due to CO (Hu et al., 2006).

Conclusion: There is currently no optimal treatment for CO poisoning and CO-associated DNS. The use of HBOT, a well-known treatment method, has become controversial, and it is unlikely that HBOT alone will be accepted as the standard optimal treatment in CO poisoning in any case. Pathophysiologic mechanisms can work as the ground for the invention of new treatment tactics. In this article, current and potential treatment methods of CO poisoning are presented as well as the tentative multi-factorial pathophysi-

ology. A series of treatments is suggested for use as a bundle therapy with targeted temperature management as the base treatment method. A series of potent treatments in combination could bring a greater benefit.

Future investigation is necessary for elucidation of the pathophysiology and treatments in CO poisoning and CO-associated DNS. The effects of individual treatment and their combinations should be verified. Improved scientific and clinical knowledge may eventually result in injury prevention and minimization of the signs and the symptoms in CO poisoning.

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