Management of delayed encephalopathy after CO poisoning
An evidence-based narrative review
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Abstract
Background: Approximately 10% to 30% patients develop delayed encephalopathy after acute CO poisoning (DEACMP). No specific treatment is available and poor prognosis is a characteristic of this disease. We aimed to evaluate the efficacy and safety of all therapies that have been tried in randomized controlled trial (RCT) for DEACMP.

Methods: We conducted a systematic search of the Cochrane, Embase, PubMed, and Web of Science databases.

Results: Overall, 4 RCTs were identified in our study. Both hyperbaric oxygen (HBO) and mesenchymal stem cell (MSC) transplantation were effective in DEACMP, and MSC seemed to be superior to HBO. The addition of dexamethasone, N-butylphthalide, or XingZhi-YiNao granules into HBO, or butylphthalide into MSC could achieve better neurological recovery in DEACMP patients but did not significantly increase the incidence of adverse events.

Conclusion: Several therapies have shown positive results in treating DEACMP and need to be proven by further studies.

Abbreviations: ACOP = acute carbon monoxide poisoning, ADL = activity of daily living, ARWMC = age related white matter changes, CO = carbon monoxide, DEACMP = delayed encephalopathy after carbon monoxide poisoning, HBO = hyperbaric oxygen, MMSE = Mini-Mental State Examination, MoCA = Montreal cognitive assessment, MSC = mesenchymal stem cell, NIHSS = National Institutes of Health Stroke Scale, XZYN = XingZhi-YiNao.

Keywords: delayed encephalopathy after CO poisoning, hyperbaric oxygen, therapies

1. Introduction
Carbon monoxide (CO) is the main environmental cause of acute poisoning worldwide, which is associated with high morbidity and mortality.1–3 Approximately 10% to 30% patients develop delayed encephalopathy after acute CO poisoning (DEACMP),4 which is a group of neuropsychologic disorders that occur after a transient improvement or a symptom-free interval of acute carbon monoxide poisoning (ACOP).5–9 These patients show acute symptoms as memory loss, motor dysfunction, mental behavior abnormality, disturbance of intelligence, and bladder/bowel dysfunction after a latent period of pseudo-recovery for 2 days to 1 year.4,10,11

Previous studies have demonstrated that CO-mediated delayed neuropathology were associated with the enhancement of lipid peroxidation, increased reactive oxygen species (ROS), depletion of antioxidant defense systems, cytochrome aa3 binding, and disruption of intracellular oxygen utilization of brain.12–14 The exact mechanism of DEACMP remains unclear.

No specific treatment is available15 for DEACMP, and poor prognosis is one of the characteristics of this disease. The present review was, therefore, to evaluate the efficacy and safety of all therapies that have been tried in RCT for DEACMP in order that appropriate or better treatment strategies may be found.

2. Methods
2.1. Data sources and search strategy
A systematic search of the Cochrane, PubMed, Embase, and Web of Science databases was conducted in May 2019 using the search terms such as “carbon monoxide,” “poison,” “encephalopathy,” “delayed,” and “DEACMP.” Details of search strategies were shown in Supplemental Table, http://links.lww.com/MD/D426 (Results of the systematic search strategy.). Only papers in English were included. To avoid omitting relevant randomized controlled trials (RCTs), conference summaries and reference lists of all identified related publications were also searched.
2.2. Selection criteria

The inclusion criteria to identify studies were as follows: RCTs involving patients with a diagnosis of DEACMP. Clinical trials evaluating all therapies for the treatment of DEACMP. Clinical trials comparing therapies with placebo or other treatments; trials that compared a combined treatment with the same monotherapy were also included. Trials irrespective of the type of administration or setting, reporting complete efficacy outcome(s).

Exclusion criteria were as follows: mixed poisoning such as CO plus a drug or other toxic gases as may be encountered in fires; animal trials, reviews, dissertations, duplicate secondary analyses, or case reports.

2.3. Data extraction and quality assessment

Two authors independently screened the titles and abstracts of each literature for possibly relevant trials and retrieved these articles in full to identify suitable studies meeting the selection criteria. Data extracted from the RCTs included the key characteristics of studies, methods, and results. The methodological quality of the trials was assessed by the “risk of bias” tool from the Cochrane Handbook[16] (Fig. S1, http://links.lww.com/MD/D425. “Risk of bias” summary: review authors’ judgements about each risk of bias item for each included trails). All disagreement and discrepancy were resolved by consensus. Due to the heterogeneity of trials and limited data reporting, a narrative approach was adopted to analyze the findings of the included studies.

3. Results

3.1. Study selection and characteristics

Our literature search for RCTs of DEACMP yielded 4 references covering 4 treatment options that met our inclusion criteria[4,17–19] (Fig. 1. Flowchart of study selection.). Therapies involved MSC transplantation, butylphthalide, HBO, dexamethasone, and XingZhi-YiNao (XZYN). The details were present in Table 1. (The outcomes of treatments for DEACMP.)
| Study       | Intervention                                                                 | CO-exposure time, h | Latent phase, d | Coma time               | COHb levels (%) | Outcome measure | Follow-up time | Adverse events                                                                 |
|-------------|------------------------------------------------------------------------------|---------------------|----------------|-------------------------|-----------------|-----------------|----------------|-----------------------------------------------------------------------------|
| Qin 2017[19] | XZYN (twice daily × 2 months) + HBO vs HBO (once daily × 2 months) vs placebo | 38 vs 32            | 10.1 vs 10.8   | 15.8 vs 15.2           | 6.5 h vs 7.0 h  | ADL, MoCA, MMSE, P300, ARWMC | 2 M            | No apparent adverse reactions                                               |
| Wang 2016[4] | MSC transplantation (1–2 × 10^7 MSCs, alternatively injected into the subarachnoid space and the carotid artery each time within 5–7 days intervals × 4/8 injections) + butylphthalide (100 mL, intravenously infused twice daily × 14 days) vs MSC transplantation vs HBO | 14 vs 15            | NR             | 25 vs 24               | 3.0 d vs 3.1 d | MMSE, Barthel index, Neuroimages | 6 M            | Low fever in MSC plus butylphthalide group                                  |
| Xiang 2017a[18] | Dexamethasone (5 mg/10mg daily × 5 d/wk × 4 weeks) + HBO vs HBO (0.25 MPa absolute pressure for 80 min/d × 5 d/wk × 4 weeks) | 60 vs 60            | 5.41 vs 5.22   | 20.3 vs 18.9           | NR              | MMSE, NIHSS     | 4 W            | Dexamethasone plus HBO: mild nausea, vomiting, headache, dizziness, loss of appetite; HBO: mild nausea, headache, loss of appetite |
| Xiang 2017b[17] | N-Butylphthalide (0.2 g orally tid × 5 d/wk × 8 weeks) + HBO vs HBO (0.25 MPa absolute pressure, 80 min/d × 5 d/wk × 8 weeks) | 94 vs 90            | 5.08 vs 5.31   | 21.23 vs 19.11         | NR              | MMSE, NIHSS     | 8 W            | N-Butylphthalide plus HBO: mild abdominal discomfort, nausea, minor skin irritations. |
3.2. Efficacy outcomes

3.2.1. Cognitive function. Wang et al.\(^4\) was the first publication that explored the treatment program for DEACMP patients via RCT. Forty-two patients received one therapy of combined MSC transplantation and butylphthalide, MSC transplantation, or HBO in a randomized order. It is resulted that MSC transplantation was superior to HBO (MD = 14.53; 95% CI = 10.67–18.39; P = <.00001) and combined MSC transplantation and butylphthalide was superior to MSC transplantation alone (6M: MD = 6.70; 95% CI = 2.52–10.88; P = .002) in improving Mini-Mental State Examination (MMSE) scores after 1 month, 3 months, and 6 months of observation after the treatment.

Xiang published 2 randomized trials on DEACMP the same year. One trial compared 4 weeks of dexamethasone plus HBO to 4 months, and 6 months of observation after the treatment. Mini-Mental State Examination (MMSE) scores after 1 month, 3 months, and 6 months of observation after the treatment.

3.2.2. Remission rate. Two studies\(^17,18\) had investigated the remission rate defined by the percentage of complete recovery according to MMSE scores (MMSE > 24). It showed that combined HBO and dexamethasone (41.6% vs 23.3%; P = .032) or N-butylphthalide (47.9% vs 33.3%; P = .045) resulted a significantly higher remission rate compared with HBO as monotherapy in DEACMP patients. Furthermore, there is no statistical difference between 5mg/10mg daily of dexamethasone. (P = .432).

3.2.3. Neurological function. Compared with HBO monotherapy, HBO combined dexamethasone (P = .002) or N-butylphthalide (P = .011) achieved better efficacy in neurological function assessed by National Institutes of Health Stroke Scale (NIHSS) score.\(^17,18\) No statistical difference was observed between dexamethasone 5mg/d and dexamethasone 10mg/d (P = .195).

3.2.4. Activities of daily living. Both the activities of daily living (ADL) scale and the Barthel index were included to evaluate the ability of daily living. According to Wang et al.\(^4\) MSC transplantation is effective in improving the ability of daily living of DEACMP patients (MSC vs HBO: MD = 73.00; 95% CI = 63.76–82.24; P = <.00001). And when combined with butylphthalide, the effect seemed to be better (MSC plus butylphthalide vs HBO: MD = 162.23; 95% CI = 79.93–94.53; P = <.00001; MSC plus butylphthalide vs MSC: MD = 14.23; 95% CI = 3.92–24.54; P = .007). In another trial, Qin et al.\(^19\) found that HBO can improve the daily exercise ability of patients with DEACMP (MD = 36.10; 95% CI = 32.14–40.06; P = <.00001), and the efficacy of combined HBO and XZYN granules is more effective in DEACMP patients (HBO plus XZYN vs control: MD = 46.70; 95% CI = 42.75–50.65; P = <.00001; HBO plus XZYN vs HBO: MD = 10.60; 95% CI = 6.49–14.71; P = <.00001).

3.2.5. Neuroimaging. Age related white matter change (ARWMC) scale\(^20\) and there vised scale\(^21\) were used to evaluate the severity and extent of white matter lesions in one trial. Qin et al.\(^19\) found that the ARWMC score was significantly decreased at 2 months of treatment both in HBO (MD = –6.80; 95% CI = –8.85 to –4.73; P = <.00001) and XZYN plus HBO (MD = –7.0; 95% CI = –9.76 to –5.44; P = <.00001) groups compared with control group, suggesting that HBO therapy can significantly reduce the lesion degree of white matter in DEACMP patients. However, our calculated data revealed that combination of HBO and XZYN therapy did not result a better ARWMC score compared with HBO as monotherapy (MD = –0.90; 95% CI = –2.58 to 0.98; P = .38).

In another trial,\(^4\) combined-therapy of MSC and butylphthalide resulted a significantly higher radiological response rate than that in the MSC (92.9% vs 60.0%; Risk ratios (RR) = 1.55; 95% CI = 1.10–2.40; P = .05) and HBO groups (92.9% vs 38.5%; RR = 2.41; 95% CI = 1.20–4.88; P = .01). Moreover, patients in MSC group had better neurological recovery rate than those in HBO group but the result was not statistically significant (60.0% vs 38.5%; RR = 1.56; 95% CI = 0.70–3.48; P = .28).

3.2.6. Side effect. None of these treatment programs in our review was found to cause serious adverse events or a significant alteration for blood glucose, blood lipids, and liver or kidney function during the whole treatment period. Reported adverse events included nausea, vomiting, abdominal discomfort, skin irritations, headache, dizziness, loss of appetite, and low fever. And most of these patients could recover by themselves and did not require additional treatment.

4. Discussion and conclusions

DEACMP is the most common neurological complication after ACOP and often causes great damage to the human body.\(^17,19\) This is the first comprehensive evidence-based review to describe all therapies that have been tried in RCT for the treatment of
DEACMP. Due to the paucity of research, this review is not sufficient to comprehensively guide physicians in the management of DEACMP, and additional research is needed. Nevertheless, the findings of this review provide some information on the current status and trends of DEACMP therapy.

Overall, we included 4 published trials investigating the management of DEACMP, involving a total of 435 DEACMP patients. Only 1 study has compared HBO to the placebo, and the results indicated that the application of HBO could improve the cognitive function, daily exercise ability, and lesion degree of white matter in patients with DEACMP. All of these 4 studies have set the HBO treatment as a control treatment. And the results showed that the addition of dexamethasone or N-butylpthalide in HBO therapy could achieve better cognitive and neurological function, and the addition of XZYN granules in HBO therapy could achieve better cognitive function and daily exercise ability of patients with DEACMP than HBO therapy alone. Furthermore, there was no statistical difference between dexamethasone 5 mg/d and dexamethasone 10 mg/d.

It seemed to be that MSC transplantation was superior to HBO, and combined-therapy of MSC and butylphthalide was superior to MSC transplantation alone, in improving cognitive function, activities of daily living, and neurological recovery rate assessed by neuroimages for DEACMP patients. The authors suggested that MSCs could activate endogenous neural stem cells and differentiate into nerve cells to replace damaged cells. And butylphthalide, as a lipid-soluble drug, might help the MSCs pass the blood–brain barrier, induce MSCs to vivo to rebuild the nerve tracts and repair nerve functions.

Based on the aforementioned results, both the clinical applicability of HBO and MSC transplantation were effective in DEACMP. And the addition of dexamethasone, N-butylpthalide, or XZYN granules into HBO, or butylphthalide into MSC could achieve better neurological recovery in DEACMP patients but did not significantly increase the incidence of adverse events. Preliminary data are promising, but larger and longer studies are necessary before these therapies are routinely prescribed for DEACMP as these evidences were insufficient and weak.

Limitations of this review also should be addressed. First, because of the limited research available, there are very few RCTs that we can include, which in turn limits our ability to draw conclusions about treatments options for the disease. Second, most of the included trials containing a relatively small number of DEACMP patients, the results are not convincing enough to reveal the potential therapeutic effects. Third, the treatment duration of the recruited trials was 1 or 2 months. It was not adequate to show the maximal response or the long-term effect of the treatment on DEACMP, which might prevent us from further revealing the potential role of the treatment. Fourth, all the included trials were conducted in China, and all patients were Chinese. Therefore, site-specific bias could not be ruled out and it might limit the clinical application of the findings. Further studies recruiting heterogeneous populations are required. Finally, pooling of data or further assessment was not possible owing to the heterogeneity in terms of treatment protocols and outcomes reported. Therefore, our ability to draw a conclusion on treatment options for DEACMP was extremely limited.

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References
[1] Kuroda H, Fujihara K, Kushimoto S, et al. Novel clinical grading of delayed neurologic sequelae after carbon monoxide poisoning and factors associated with outcome. Neurotoxicology 2015;48:35–43.
[2] Hosseminejad SM, Amnahimadshin H, Goli Khazar J, et al. Carbon monoxide poisoning in Iran during 1999–2016: a systematic review and meta-analysis. J Forensic Leg Med 2018;53:87–96.
[3] Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. Am J Respir Crit Care Med 2017;195:596–606.
[4] Wang H, Li Y, Wu Q, et al. Combination of butylphthalide with umbilical mesenchymal stem cells for the treatment of delayed encephalopathy after carbon monoxide poisoning. Medicine (Baltimore) 2016;95:e5412.
[5] Hu H, Pan X, Wan Y, et al. Factors affecting the prognosis of patients with delayed encephalopathy after acute carbon monoxide poisoning. Am J Emerg Med 2011;29:261–4.
[6] Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. Intensive Care Med 2011;37:486–92.
[7] Buckley NA, Juurlink DN, Isbister G, et al. Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2011; CD002041.
[8] Weaver JK. Carbon monoxide poisoning, Polski Tygodnik Lekarski 1999;15:297–317.
[9] Weaver JK. Clinical practice. Carbon monoxide poisoning, N Engl J Med 2009;360:1217–25.
[10] Harper A, Croft-Baker J. Carbon monoxide poisoning: undetected by both patients and their doctors. Age Ageing 2004;33:105–9.
[11] Hsiao CL, Kuo HC, Huang CC. Delayed encephalopathy after carbon monoxide intoxication–long-term prognosis and correlation of clinical manifestations and neuroimages. Acta Neurol Taiwan 2004;13:64–70.
[12] Chen X, Li Y, Chen W, et al. Protective effect of hyperbaric oxygen on cognitive impairment induced byd-galactose in mice. Neurochem Res 2016;41:3032–41.
[13] Wang P, Zeng T, Zhang C-L, et al. Lipid peroxidation was involved in the memory impairment of carbon monoxide-induced delayed neuron damage. Neurochem Res 2009;34:1293–8.
[14] Liao SC, Mao YC, Yang KJ, et al. Targeting optimal time for hyperbaric oxygen therapy following carbon monoxide poisoning for prevention of delayed neuropsychiatric sequelae: a retrospective study. J Neurol Sci 2019;396:187–92.
[15] Weaver JK. Carbon monoxide poisoning. N Engl J Med 2009;360:1217–23.
[16] Huggins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. London, UK: The Cochrane Collaboration; 2011.
[17] Xiang W, Xue H, Wang B, et al. Efficacy of N-butylpthalide and hyperbaric oxygen therapy on cognitive dysfunction in patients with delayed encephalopathy after acute carbon monoxide poisoning. Med Sci Monit 2017;23:1501–6.
[18] Xiang W, Xue H, Wang B, et al. Combined application of dexamethasone and hyperbaric oxygen therapy yields better efficacy for patients with delayed encephalopathy after acute carbon monoxide poisoning. Drug Des Devel Ther 2017;11:513–9.

[19] Qin L, Meihua C, Dadong G, et al. Efficacy of combined XingZhi-YiNao granules and hyperbaric oxygen therapy for cognition and motor dysfunction in patients with delayed encephalopathy after acute carbon monoxide poisoning. Evid Based Complement Alternat Med 2017;2017:1323297.

[20] Wahlund L.O, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318–22.

[21] Xiong Y, Yang J, Wong A, et al. Operational definitions improve reliability of the age-related white matter changes scale. Eur J Neurol 2011;18:744–9.