Systematic Review and Meta-Analysis

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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 *aa*3 binding, and disruption of intracellular oxygen utilization of brain.[12–14] The exact mechanism of DEACMP remains unclear.

No specific treatment is available[15] 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.

Editor: Massimo Tusconi.

Ethics: As this is a review article, the ethical approval was not necessary.

This work was supported by the Science and Technology Support Project of Science & Technology Department of Sichuan (No.14ZC0063).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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How to cite this article: Xu XM, Luo H, Rong Bb, Zheng XM, Wang Ft, Zhang SJ, Li ZX. Management of Delayed Encephalopathy After CO Poisoning (DEACMP): an evidence-based narrative review. Medicine 2019;98:49(e18199).

Received: 19 July 2019 / Received in final form: 25 October 2019 / Accepted: 31 October 2019

http://dx.doi.org/10.1097/MD.0000000000018199

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.).

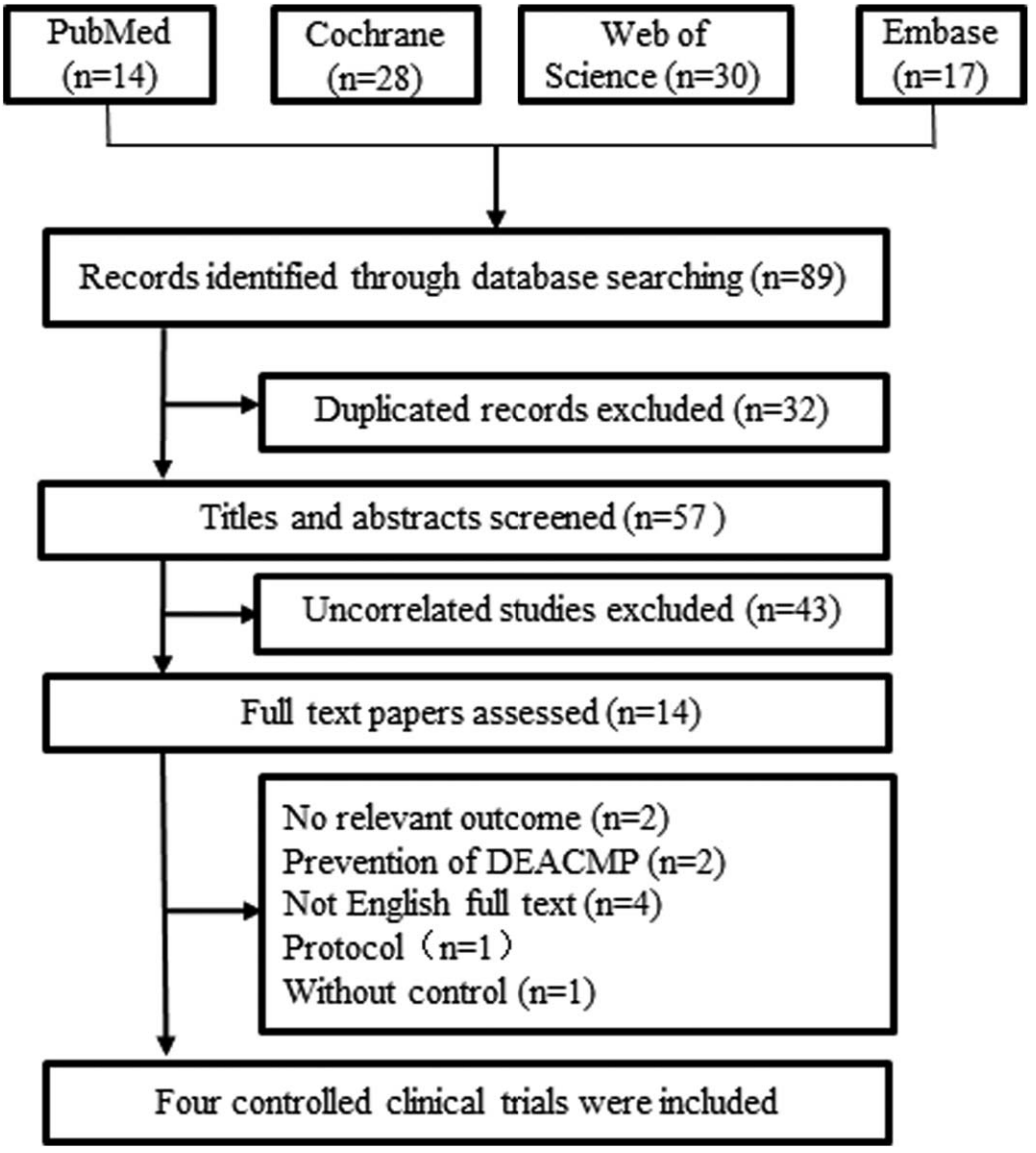

Figure 1. Flowchart of study selection.

Table 1

The outcomes of treatments for DEACMP.

Study	Treatment groups	Intervention versus placebo (n)	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 vs 19	10.1 vs 10.8 vs 9.6	15.8 vs 13.5 vs 15.2	6.5 h vs 7.0 h vs 6.8 h	26.9% vs 25.7% vs 28.0%	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 vs 13	NR	25 vs 24 vs 25	3.0 d vs 3.1 d vs 3.0 d	NR	MMSE, Barthel index, Neuroimages	6 M	Low fever in MSC plus butylphthalide group
Xiang 2017a[18]	Dexamethasone (5 mg/10 mg 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	21.3% vs 20.7%	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	23.72% vs 21.05%	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. Fourty-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 (6 M: 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 HBO as monotherapy,[18] another trial compared 8 weeks of N-butylphthalide plus HBO to HBO alone.[17] Results showed that all of these treatment programs could significantly increase the average MMSE scores of DEACMP patients. In addition, the average MMSE score in the dexamethasone plus HBO ($P = .037$) or N-butylphthalide plus HBO group ($P = .012$) was significantly higher than that in the HBO group. There is no statistically significant difference between dexamethasone 5 mg/d and dexamethasone 10 mg/d ($P = .204$), but dexamethasone 10 mg/d showed a trend toward better improvement.

The first controlled trial exploring traditional Chinese medicine in DEACMP patients was conducted in 2017.[19] Eighty-nine DEACMP patients were randomly divided into XZYN plus HBO group, HBO group, and control group. The XZYN granules is made by 8 types of boil-free granules of traditional Chinese medicine extracts: Coptis Rhizome, 10 g; PanaxGinseng, 10 g; Poria cum Radix Pini, 10 g; Acorus tatarinowii Schott, 20 g; Milkworts, 10 g; Salvia miltiorrhiza, 30 g; Radix Puerariae, 10 g; Bile Arisaema, 10 g. And its therapeutic effect was "promoting blood circulation, detoxifying, dissolving phlegm, removing obstruction, unraveling wisdom, and replenishing essence." Results showed that patients in both XZYN plus HBO group (MMSE: MD = 7.50; 95% CI = 4.97–10.03; $P < .00001$; MoCA: MD = 7.50; 95% CI = 5.3–9.7; $P < .00001$; Latency of P300: MD = –50.60; 95% CI = –69.06 to –32.14; $P < .00001$; amplitude of P300: MD = 2.50; 95% CI = 1.65–3.35; $P < .00001$) and HBO group (MMSE: MD = 4.70; 95% CI = 2.11–7.29; $P = .0004$; MoCA: MD = 4.50; 95% CI = 2.39–6.61; $P < .0001$; latency of P300: MD = –26.5; 95% CI = –44.54 to –8.46; $P = .004$; amplitude of P300: MD = 1.60; 95% CI = 0.75–2.45; $P = .0002$) manifested better cognitive function than those in control group after 2 months of treatment. Moreover, compared with HBO as monotherapy, combined HBO and XZYN was more effective in improving cognitive function of patients with DEACMP (MMSE: MD = 2.80; 95% CI = 0.50–5.10; $P = .02$; MoCA: MD = 3.00; 95% CI = 0.95–5.05; $P = .004$; latency of P300: MD = –24.10; 95% CI = –40.40 to –7.80; $P = .004$; amplitude of P300: MD = 0.90; 95% CI = 0.07–1.73; $P = .03$).

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 5 mg/10 mg 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 5 mg/d and dexamethasone 10 mg/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 = 87.23; 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. Neuroimages. 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 –4.75; $P < .00001$) 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 = –0.80; 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 = 1.00–2.40; $P = .05$) 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-butylphthalide 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 in 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-butylphthalide, 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, since 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 trails 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.

Author contributions

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