Received: 2019.04.19
Accepted: 2019.06.26
Published: 2019.10.13

Effect of Hyperbaric Oxygen on Neurologic Sequelae and All-Cause Mortality in Patients with Carbon Monoxide Poisoning: A Meta-Analysis of Randomized Controlled Trials

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDE 1,2 **Weiqliang Wang**
BC 3 **Jincheng Cheng**
CF 1 **Jun Zhang**
B 1,4,5 **Kai Wang**

1 Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P.R. China
2 Department of General Practice, Suzhou Hospital of Anhui Medical University/ Suzhou Municipal Hospital, Suzhou, Anhui, P.R. China
3 Department of Neurology, No. 123 Hospital of Nanjing Military Command, Chinese People's Liberation Army (CPLA), Bengbu, Anhui, P.R. China
4 Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health, Hefei, Anhui, P.R. China
5 Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, Hefei, Anhui, P.R. China

Corresponding Author: Kai Wang, e-mail: wangkai1964@126.com
Source of support: Departmental sources

Background: Hyperbaric oxygen (HBO) is used in patients with carbon monoxide (CO) poisoning to prevent the occurrence of delayed neurological sequelae. However, inconsistent results were obtained regarding the treatment effects of HBO. Therefore, the current meta-analysis was conducted based on published randomized controlled trials (RCTs) to determine the effect of HBO on neurologic sequelae and all-cause mortality in patients with CO poisoning.

Material/Methods: Electronic databases MedLine, EmBase, and the Cochrane Library were searched for relevant RCTs from inception to March 1, 2019. The pooled relative risks (RRs) and weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate the outcomes by using a random-effects model. Sensitivity, subgroup, and publication bias analyses were also conducted.

Results: Seven RCTs, including 9 cohorts and a total of 2023 patients with CO poisoning, were enrolled in this study. The summary results revealed that HBO showed an association with lower risk of memory impairment compared to patients receiving normobaric oxygen (NBO), whereas 2 sessions of HBO showed an association with higher risk of memory impairment compared to those who received 1 session of HBO. Moreover, HBO was associated with increased neuropsychologic scores of block design and trail making when compared with NBO. No other significant differences regarding the treatment effects of HBO were observed.

Conclusions: These results indicate that HBO therapy significantly reduces the risk of memory impairment compared to NBO, but 2 sessions of HBO might not be better for memory impairment than 1 session of HBO.

MeSH Keywords: **Carbon Monoxide Poisoning • Hyperbaric Oxygenation • Meta-Analysis • Safety**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/917065>

3336 2 14 38

Background

Carbon monoxide (CO) is produced when the combustion of carbon-based compounds is incomplete. Inhalation of CO causes severe tissue hypoxia, as it binds to hemoglobin (Hb) more significantly than oxygen [1]. CO poisoning results in tissue hypoxia and direct cell-level damage, and is subsequently associated with serious cardiovascular and neurological complications [2–4]. The mortality rates of patients with CO poisoning at 1 and 3 months are 1.6% and 5.0%, respectively [5], and nearly 40% of the survivors have permanent neurocognitive and emotional deficits. Oxygen inhalation can accelerate the elimination of COHb, relieving tissue hypoxia [6]. Normobaric oxygen (NBO) includes high-flow nasal catheters and oxygen mask, and it is a simple and effective strategy for reducing COHb [7,8].

According to a previous retrospective study, administration of hyperbaric oxygen (HBO) is associated with better prognosis use of NBO [9]. Liao et al. reported that HBO should be performed as early as possible, which should be within 22.5 h after CO poisoning [10]. Moreover, HBO can prevent the late-onset neurological sequelae of CO poisoning, reducing the risk of mortality due to acute CO poisoning [11–14]. However, Huang et al. demonstrated that the risk of neurological sequelae in patients receiving HBO was significantly higher than in those who did not receive HBO [15]. Simonsen et al. suggested that HBO showed no association with all-cause mortality [16]. Meta-analyses conducted in the Cochrane collaboration group indicated no significant difference between HBO and NBO with regard to the risk of adverse neurologic outcomes, and pointed out that these results required further study to define the effect of HBO in patients with CO poisoning [17,18]. However, whether the incidences of neurologic outcomes differ between HBO and NBO was not addressed. Therefore, the effect of HBO on neurologic sequelae and all-cause mortality in patients with CO poisoning was evaluated by conducting a meta-analysis of the available randomized controlled trials (RCTs).

Material and Methods

Data Sources, Search Strategy, and Selection Criteria

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [19]. Studies designed as RCTs and the studies that investigated the role of HBO on neurologic sequelae and all-cause mortality in CO-poisoned patients were considered eligible for this meta-analysis. The electronic databases MedLine, EmBase, and Cochrane Library were systematically searched for potentially relevant articles from their inception

to March 1, 2019. The core search terms used were: “carbon monoxide poisoning” and (“hyperbaric oxygen” or “HBO” or “hyperbaric oxygen therapy” or “HBOT”) and “randomized controlled trials”. The reference lists of the obtained studies were assessed by manual searching for any new eligible study. The study selection process was based on PICOS (patients, intervention, control, outcomes, and study design) criteria.

Literature search and study selection processes were carried out by 2 independent reviewers, and any inconsistencies between them were resolved by group discussion to reach a consensus. The details of study inclusion criteria in this study were: (1) patients: studies with CO-poisoned patients; (2) intervention and control: HBO versus NBO or 2-session HBO versus 1-session HBO; (3) outcomes: recovered (defined as an absence of symptoms reported on the self-assessment questionnaire with a normal physical exam), moderate sequelae (defined as one or more symptoms on the questionnaire and normal physical findings), severe sequelae (defined as any objective abnormality at patient’s examination), all-cause death, asthenia, headache, memory impairment, disturbed sleep, difficulty in concentrating, visual disturbances, behavioral impairment, resumption of former activity, and neuropsychologic subtest scores (including block design, trail making, digit span and digit-symbol); and (4) study design: all the included studies must have RCT design.

Data collection and quality assessment

Two independent reviewers collected the data and performed quality assessment, and any inconsistency between them was settled by an additional reviewer by referring to the original article. The collected data items included the first author’s surname, publication year, country, sample size, mean age, percentage male, CO poisoning, intervention, control, follow-up duration, and the incidence of investigated outcomes in intervention and control groups. The Jadad scale was used to evaluate the quality of included studies based on randomization, allocation concealment, blinding, loss to follow-up, and the use of intention-to-treat analysis [20].

Statistical analysis

The relative risk (RR) with 95% confidence interval (CI) in each included trial was calculated based on the prevalence of investigated outcomes in the intervention and control groups before pooling the data. Moreover, the weighted mean difference with its 95% CI for continuous data was presented as mean, standard deviation, and sample size in each group in individual trials. After that, the pooled RRs or WMDs and 95% CIs for HBO versus NBO or 2-session HBO versus 1-session HBO outcomes were evaluated by random-effects model [21,22]. Heterogeneity was evaluated by using I-square and Q statistics, and P value

Figure 1. Flow diagram of literature search and trials selection process.

for Q statistic of <0.10 was considered to be significant heterogeneity [23,24]. Sensitivity analyses for investigated outcomes reported >3 cohorts to assess the impact of a single cohort on overall analysis [25]. Moreover, subgroup analyses were conducted based on control strategy, and interaction tests were

conducted to compare the differences between subgroups [26]. Publication biases for investigated outcomes reported >3 cohorts for assessment by using funnel plot and Egger [27] and Begg [28] test results. The P values for all pooled results are two-sided, and 0.05 was considered as the inspection level. Statistical analyses were conducted using STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

The initial search of MedLine, EmBase, and the Cochrane Library produced 162 records; 139 of these were considered duplicates and irrelevant topics and were thus excluded. The remaining 23 potentially relevant studies were selected, and 16 of these were excluded after detailed evaluation because patients received other interventions, the study explored prognostic factors, or it did not report the investigated outcomes. Finally, 7 RCTs involving 9 cohorts were included for the final analysis [29–35]. After reviewing the reference lists of these eligible studies, no additional eligible study was found. Figure 1 shows the detailed study selection process.

Table 1. Baseline characteristics of included studies.

Study	Publication year	Country	Sample size	Mean age (years)	Percentage Male (%)	CO poisoning time	Intervention	Control	Follow-up	Study quality
Raphael [29]	1989	France	173/170	35.4	48.7% (167/176)	<12 hours	HBO 1 (2.0 ATA, 2 hours)+NBO (4 hours)	NBO (6 hours)	1.0 month	4
Raphael [29]	1989	France	141/145	37.4	43.0% (123/163)	<12 hours	HBO 2 (2.0 ATA, 2 hours) + NBO (4 hours)	HBO 1 (2.0 ATA, 2 hours) + NBO (4 hours)	1.0 month	4
Thom [30]	1995	US	33/32	37.0	52.3% (34/31)	<6 hours	HBO (2.8 ATA, 30 minutes, then 2.0 ATA, 90 minutes)	NBO	4.0 weeks	2
Ducasse [31]	1995	France	13/13	NA	NA	<12 hours	HBO (2.5 ATA, 2 hours) + NBO (100% O ₂ , 4 hours +50%O ₂ , 6 hours)	NBO (100% O ₂ , 6 hours +50% O ₂ , 6 hours)	21 days	4
Mathieu [32]	1996	France	299/276	NA	NA	<12 hours	HBO (2.5 ATA, 90 minutes)	NBO (12 hours)	1.0 month	2
Scheinkestel [33]	1999	Australia	104/87	36.3	81.7% (156/35)	Not limited	HBO (2.8 ATA, 60 minutes)	NBO (100 minutes)	1.0 month	4
Weaver [34]	2002	US	76/76	35.5	71.1% (108/44)	<24 hours	HBO 1 (3.0 ATA, 1 hours and 2.0 ATA, 1 hours) + HBO 2 (2.0 ATA, 2 hours)	NBO	6.0 weeks	5
Annane [35]	2011	France	93/86	33.0	41.3% (74/105)	<12 hours	HBO 1 (2.0 ATA, 2 hours) + NBO (4 h)	NBO (6 hours)	1.0 month	3
Annane [35]	2011	France	105/101	37.5	43.2% (89/117)	<12 hours	HBO 2 (2.0 ATA, 2 hours) + NBO (4 h)	HBO 1 (2.0 ATA, 2 hours) +NBO (4 hours)	1.0 month	2

ATA – atmosphere absolute; HBO – hyperbaric oxygen; NBO – normobaric oxygen.

Figure 2. Effect of HBO on recovery rate.

Figure 3. Effect of HBO on moderate sequelae rate.

Study characteristics

Seven RCTs with 2023 CO-poisoned patients were enrolled in this study, and the baseline characteristics of studies included are presented in Table 1. Two of the included cohorts compared 2-session HBO with 1-session HBO, and the remaining 7 cohorts compared the treatment effects of HBO with NBO. The follow-up duration ranged from 21 days to 6 weeks, and 26 to 575 patients were included in each trial. Four of the included trials were conducted in France, 2 in the USA, and 1 in Australia. Four trials included CO poisoning in patients within 12 h, 1 trial included CO poisoning in patients within 24 h, 1 trial included CO poisoning in patients within 6 h, and 1 trial did not mention the CO poisoning time. The quality of studies was evaluated by Jadad scale. One cohort scored 5 points, 4 cohorts scored 4 points, 1 cohort scored 3 points, and the remaining 3 cohorts scored 2 points.

Recovered

Data from 882 patients were used to evaluate the effect of HBO on recovery, and included 526 events of recovered patients. The results revealed that HBO showed no association with the incidence of recovery rate (RR: 0.92; 95% CI: 0.78–1.08; P=0.307; significant heterogeneity; Figure 2). Also, the conclusion was not altered by sequential exclusion of an individual trial (data

Figure 4. Effect of HBO on severe sequelae rate.

Figure 5. Effect of HBO on all-cause death rate.

not shown). The recovery rate was not affected by whether it was HBO or NBO (RR: 1.01; 95% CI: 0.88–1.15; P=0.916; with no evidence of heterogeneity; Figure 2) or whether it was 2 versus 1 session of HBO (RR: 0.82; 0.59–1.15; P=0.257; significant heterogeneity; Figure 2).

Moderate sequelae

Data on the effect of HBO on the incidence of moderate sequelae were obtained from 8 cohorts, and the incidence of moderate sequelae did not differ between HBO and control (RR: 0.95; 95% CI: 0.78–1.16; P=0.639; significant heterogeneity; Figure 3). The results were stable after sequential exclusion of each included study (data not shown). No significant differences were observed between HBO and NBO (RR: 0.87; 95% CI: 0.69–1.09; P=0.227; significant heterogeneity; Figure 3) or between 2-session versus 1-session HBO (RR: 1.20; 95% CI: 0.83–1.75; P=0.337; moderate heterogeneity; Figure 3) for the risk of moderate sequelae.

Severe sequelae and all-cause death

The breakdown of the number of studies available for each outcome was 2 cohorts and 3 cohorts for severe sequelae and all-cause mortality, respectively. The summary RRs indicated no significant differences between HBO and NBO for the risk of severe sequelae (RR: 2.15; 95% CI: 0.44–10.40; P=0.343; unimportant heterogeneity; Figure 4) and all-cause death (RR: 0.90; 95% CI: 0.32–2.53; P=0.841; with no evidence of heterogeneity; Figure 5).

Figure 6. Effect of HBO on asthenia rate.

Figure 7. Effect of HBO on headache rate.

Moderate sequelae

Asthenia

Data on the effect of HBO on the incidence of asthenia were available from 5 cohorts. The results of HBO on the risk of asthenia demonstrated no significant effect (RR: 1.11; 95% CI: 0.84–1.47; P=0.468; with moderate heterogeneity; Figure 6), and this conclusion was not altered by sequentially excluding each individual trial (data not shown), irrespective of HBO versus NBO (RR: 1.02; 95% CI: 0.67–1.56; P=0.917; with unimportant heterogeneity; Figure 6) or 2-session versus 1-session HBO (RR: 1.22; 95% CI: 0.72–2.08; P=0.461; significant heterogeneity; Figure 6).

Headache

Data on the effect of HBO on the incidence of headache were available from 6 cohorts. The results revealed that HBO was not associated with the risk of headache (RR: 1.07; 95% CI: 0.75–1.52; P=0.723; unimportant heterogeneity; Figure 7), and the sensitivity analysis results indicated this was a stable conclusion (data not shown). Also, this risk was unaltered by whether the study was in HBO versus NBO (RR: 0.83; 95% CI: 0.43–1.59; P=0.571; with moderate heterogeneity; Figure 7) or

Figure 8. Effect of HBO on memory impairment rate.

2-session versus 1-session HBO (RR: 1.24; 95% CI: 0.78–1.98; P=0.359; with unimportant heterogeneity; Figure 7).

Memory impairment

Data regarding the effect of HBO on the incidence of memory impairment were available from 5 cohorts, and the risk of memory impairment showed an insignificant association between HBO and control (RR: 1.05; 95% CI: 0.60–1.84; P=0.867; significant heterogeneity; Figure 8). Sensitivity analysis indicated the summary conclusion was not altered by excluding any particular trial (data not shown). However, we noted that HBO versus NBO was associated with lower risk of memory impairment (RR: 0.67; 95% CI: 0.46–0.97; P=0.035; unimportant heterogeneity; Figure 8), whereas 2-session versus 1-session HBO was associated with increased risk of memory impairment (RR: 1.95; 95% CI: 1.21–3.13; P=0.006; with no evidence of heterogeneity; Figure 8). These results showed significant difference between the subgroups (P<0.001, Table 2).

Disturbed sleep

Data regarding the effect of HBO on the incidence of disturbed sleep were available from 4 cohorts. HBO and control regarding the risk of disturbed sleep (RR: 1.02; 95% CI: 0.75–1.40; P=0.884; with no evidence of heterogeneity; Figure 9) showed no significant difference, and the summary conclusion was stable (data not shown), irrespective of HBO versus NBO (RR: 0.87; 95% CI: 0.54–1.41; P=0.573; with no evidence of heterogeneity; Figure 9) or 2-session versus 1-session HBO (RR: 1.15; 95% CI: 0.76–1.75; P=0.498; with no evidence of heterogeneity; Figure 9).

Difficulty in concentrating

Data regarding the effect of HBO on the incidence of difficulty in concentrating were available from 6 cohorts. We noted that HBO was not associated with the risk of difficulty in concentrating (RR: 1.04; 95% CI: 0.63–1.71; P=0.883; significant heterogeneity; Figure 10), and the pooled conclusion was stable

Table 2. Subgroup analyses for investigated outcomes based on comparisons.

Outcomes	Groups	Number of cohorts	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity	P value between subgroups
Recovered	HBO vs. NBO	2	1.01 (0.88–1.15)	0.916	0.0	0.657	0.103
	2 vs. 1 session HBO	2	0.82 (0.59–1.15)	0.257	71.5	0.061	
Moderate sequelae	HBO vs. NBO	6	0.87 (0.69–1.09)	0.227	47.9	0.088	0.065
	2 vs. 1 session HBO	2	1.20 (0.83–1.75)	0.337	58.8	0.119	
Asthenia	HBO vs. NBO	3	1.02 (0.67–1.56)	0.917	32.2	0.229	0.543
	2 vs. 1 session HBO	2	1.22 (0.72–2.08)	0.461	73.5	0.052	
Headache	HBO vs. NBO	4	0.83 (0.43–1.59)	0.571	50.0	0.112	0.518
	2 vs. 1 session HBO	2	1.24 (0.78–1.98)	0.359	33.4	0.220	
Memory impairment	HBO vs. NBO	3	0.67 (0.46–0.97)	0.035	24.0	0.268	<0.001
	2 vs. 1 session HBO	2	1.95 (1.21–3.13)	0.006	0.0	0.568	
Disturbed sleep	HBO vs. NBO	2	0.87 (0.54–1.41)	0.573	0.0	0.965	0.385
	2 vs. 1 session HBO	2	1.15 (0.76–1.75)	0.498	0.0	0.521	
Difficulty in concentrating	HBO vs. NBO	4	0.76 (0.54–1.06)	0.105	0.0	0.489	0.006
	2 vs. 1 session HBO	2	1.97 (0.99–3.94)	0.054	27.7	0.240	
Visual disturbances	HBO vs. NBO	2	0.62 (0.15–2.61)	0.513	70.1	0.067	0.677
	2 vs. 1 session HBO	2	0.88 (0.31–2.52)	0.818	54.0	0.140	
Behavioural impairment	HBO vs. NBO	2	0.52 (0.08–3.32)	0.489	77.5	0.035	0.416
	2 vs. 1 session HBO	2	1.18 (0.53–2.62)	0.693	31.5	0.227	
Resumption of former activity	HBO vs. NBO	2	0.99 (0.96–1.02)	0.520	0.0	0.752	0.285
	2 vs. 1 session HBO	2	0.96 (0.90–1.03)	0.249	42.7	0.187	

and not altered by any individual trial (data not shown). Also, HBO might have a more beneficial effect on difficulty in concentrating than NBO (RR: 0.76; 95% CI: 0.54–1.06; $P=0.105$; with no evidence of heterogeneity; Figure 10), whereas 2 sessions of HBO might produce an increased risk of difficulty in concentrating as compared to 1 session of HBO (RR: 1.97; 95% CI: 0.99–3.94; $P=0.054$; with unimportant heterogeneity; Figure 10). Moreover, there was significant difference between subgroups for the risk of difficulty in concentrating ($P=0.006$; Table 2).

Visual disturbances

Data regarding the effect of HBO on the incidence of visual disturbances were available from 4 cohorts. There was no significant difference between HBO and control on the risk of visual disturbances (RR: 0.77; 95% CI: 0.37–1.57; $P=0.469$; moderate heterogeneity; Figure 11), and the pooled conclusion was not altered by sequentially excluding individual trials (data not shown). This result was stable whether HBO was compared with NBO (RR: 0.62; 95% CI: 0.15–2.61; $P=0.513$; significant heterogeneity; Figure 11) or 2-session with 1-session HBO (RR: 0.88; 95% CI: 0.31–2.52; $P=0.818$; non-significant heterogeneity; Figure 11).

Figure 9. Effect of HBO on disturbed sleep rate.

Figure 12. Effect of HBO on behavioral impairment rate.

Figure 10. Effect of HBO on difficulty in concentrating rate.

Figure 13. Effect of HBO on resumption of former activity rate.

Figure 11. Effect of HBO on visual disturbances rate.

Behavioral impairment

Data regarding the effect of HBO on the incidence of behavioral impairment were available from 4 cohorts. The summary RR indicated no association of HBO with the risk of behavioral impairment (RR: 0.89; 95% CI: 0.41–1.92; P=0.760; significant heterogeneity; Figure 12), irrespective of HBO compared with NBO (RR: 0.52; 95% CI: 0.08–3.32; P=0.489; significant heterogeneity; Figure 12) or 2-session with 1-session HBO (RR: 1.18; 95% CI: 0.53–2.62; P=0.693; unimportant heterogeneity; Figure 12). Sensitivity analyses results indicated that the

Figure 14. The summary results of HBO versus NBO on block design, trail making, digit span, and digit-symbol.

pooled conclusion for behavioral impairment was stable and not altered by excluding any particular trial (data not shown).

Resumption of former activity

Data regarding the effect of HBO on the incidence of resumption of former activity were available from 4 cohorts. There was no significant difference between HBO and control on

the incidence of resumption of former activity (RR: 0.98; 95% CI: 0.96–1.01; $P=0.178$; with no evidence of heterogeneity; Figure 13), and the conclusion was unchanged after sequential exclusion of individual trials (data not shown). Moreover, HBO and NBO (RR: 0.99; 95% CI: 0.96–1.02; $P=0.520$; with no evidence of heterogeneity; Figure 13) or 2-session and 1-session HBO (RR: 0.96; 95% CI: 0.90–1.03; $P=0.249$; moderate heterogeneity; Figure 13) on the incidence of resumption of former activity showed no significant differences.

Neuropsychologic scores

The summary results for neuropsychologic subtest scores after HBO and NBO treatment are presented in Figure 14. The pooled WMD indicated that HBO was associated with higher scores in block design (WMD: 3.95; 95% CI: 2.99–4.90; $P<0.001$) and trail making (WMD: 3.03; 95% CI: 1.10–4.96; $P=0.002$) than in those who received NBO. However, no significant differences between HBO and NBO for the levels of digit span (WMD: 0.55; 95% CI: –2.22–3.32; $P=0.698$) and digit-symbol (WMD: 0.96; 95% CI: –0.44–2.35; $P=0.179$) were observed.

Publication bias

There were no significant publication biases for recovery rate (P value for Egger: 0.763 and Begg: 1.000), moderate sequelae (P value for Egger: 0.196; P value for Begg: 0.133), asthenia (P value for Egger: 0.956; P value for Begg: 0.308), headache (P value for Egger: 0.080; P value for Begg: 0.221), memory impairment (P value for Egger: 0.874; P value for Begg: 0.806), disturbed sleep (P value for Egger: 0.787; P value for Begg: 0.734), difficulty in concentrating (P value for Egger: 0.359; P value for Begg: 0.806), visual disturbances (P value for Egger: 0.122; P value for Begg: 0.734), behavioral impairment (P value for Egger: 0.678; P value for Begg: 0.734), and resumption of former activity (P value for Egger: 0.765; P value for Begg: 1.000) (data not shown).

Discussion

The present meta-analysis investigated the effect of HBO on neurologic sequelae and all-cause mortality for patients with CO poisoning, based on published RCTs. This comprehensive quantitative study recruited 2023 patients with CO poisoning from 7 RCTs (9 cohorts) with a wide range of patient characteristics. The results of this meta-analysis suggested that HBO has no significant effects on recovery, moderate sequelae, severe sequelae, all-cause death, asthenia, headache, memory impairment, disturbed sleep, difficulty in concentrating, visual disturbances, behavioral impairment, or resumption of former activity. Moreover, HBO versus NBO reduced the risk of memory impairment, whereas 2-session versus 1-session

HBO produced additional risk of memory impairment. Finally, the neuropsychologic subtest scores of block design and trail making in patients who received HBO showed significantly higher scores than in those who received NBO, whereas no significant differences were observed between HBO and NBO for digit span and digit-symbol.

Several systematic review and meta-analyses have already addressed the treatment effects of HBO in patients with CO poisoning [17,18,36]. Juurlink et al. performed a systematic review and meta-analysis of 6 trials, revealing no evidence of the superiority of HBO over NBO regarding the risk of adverse neurologic outcomes in patients with CO poisoning [17], and an updated meta-analysis by Buckley et al. reported similar results [18]. However, the treatment effects of HBO on specific events of neurologic outcomes were not found. Moreover, the treatment effects of HBO versus NBO on the neuropsychologic subtest scores were not addressed. In addition, Lin et al. conducted a meta-analysis of 6 RCTs and found that HBO versus NBO showed an association with headache, memory impairment, difficulty concentrating, disturbed sleep, and delayed neurological sequelae, and they also found that 2-session HBO increased the risk of memory impairment and difficulty concentrating compared to those who received 1-session HBO. However, some data abstracted from the included studies had mistakes and the neuropsychologic subtest scores were not calculated [36]. Therefore, the current quantitative meta-analysis was conducted to systematically evaluate the treatment effects of HBO in patients with CO poisoning.

The summary results showed no significant effects of HBO on the incidence of recovery, moderate sequelae, severe sequelae, and all-cause death. Most of the included cohorts reported similar results, while Annane et al. indicated that 2-session HBO showed reduced incidence of recovery and increased the risk of moderate sequelae [35]. The main reason for this could be that recovery and moderate sequelae are non-specific, and may not be related to the intoxication, and potential bias might also exist in the rates of recovery and moderate sequelae. Moreover, none of the included studies reported significant differences between sequelae and all-cause death, as these events were infrequent, irrespective of whether they received HBO therapy. These results were associated with a wide range of 95% CIs, causing no significant differences in the results.

We noted that the incidence of asthenia, headache, memory impairment, disturbed sleep, difficulty in concentrating, visual disturbances, behavioral impairment, and resumption of former activity did not differ between HBO and NBO. However, several included studies reported inconsistencies in the results. Raphael et al. indicated that HBO had lower incidence of visual disturbances and behavioral impairment compared with

NBO [29]. Moreover, Weaver et al. indicated that the risk of memory impairment was significantly lower in patients receiving HBO [34]. Furthermore, Annane et al. indicated that 2-session HBO was associated with greater risk of asthenia and difficulty in concentrating and lower incidence of resumption of former activity as compared with 1-session HBO. The reason for this might be that although HBO improved cellular respiration, it could increase the peroxide product [37,38].

The summary of WMDs indicated that HBO was associated with higher scores for block design and trail making of the neuropsychologic subtest scores as compared with NBO, whereas the digit span and digit-symbol showed no differences between HBO and NBO. However, these results were based on only 2 trials [30–34], and further large-scale RCTs should be conducted to confirm the treatment effects of HBO on neuropsychologic subtest scores.

There are several limitations in the present study that need to be noted. (1) There were fewer trials that compared 2-session with 1-session HBO, and the treatment effects of HBO might

vary and need further RCTs to verify; (2) subgroup analyses based on various patient characteristics were not conducted; (3) publication bias was inevitable as this analysis was based on published articles; and (4) the analysis of this study was based on pooled data and detailed analysis could not be carried out.

Conclusions

The results of this study indicate that HBO has lower risk of memory impairment compared with NBO, and 2-session HBO therapy had higher risk of memory impairment compared to 1-session HBO. Moreover, patients who received HBO had better scores in block design and trail making of the neuropsychologic subtest scores as compared to those who received NBO. The results of this study should be further confirmed by conducting large-scale RCTs.

Conflict of interests

None.

References:

- Prockop LD, Chichkova RI: Carbon monoxide intoxication: An updated review. *J Neurol Sci*, 2007; 262: 122–30
- Garg J, Krishnamoorthy P, Palaniswamy C et al: Cardiovascular abnormalities in carbon monoxide poisoning. *Am J Ther*, 2018; 25: e339–48
- Betterman K, Patel S: Neurologic complications of carbon monoxide intoxication. *Handb Clin Neurol*, 2014; 120: 971–79
- Mouthon-Reignier C, Biberon J, De Toffol B, Mondon K: A delayed neurological syndrome after carbon monoxide intoxication. *Rev Neurol (Paris)*, 2017; 173: 237–38
- Huang CC, Ho CH, Chen YC et al: Demographic and clinical characteristics of carbon monoxide poisoning: Nationwide data between 1999 and 2012 in Taiwan. *Scand J Trauma Resusc Emerg Med*, 2017; 25: 70
- Rose JJ, Nouraie M, Gauthier MC et al: Clinical outcomes and mortality impact of hyperbaric oxygen therapy in patients with carbon monoxide poisoning. *Crit Care Med*, 2018; 46: e649–55
- Tomruk O, Karaman K, Erdur B et al: A new promising treatment strategy for carbon monoxide poisoning: High flow nasal cannula oxygen therapy. *Med Sci Monit*, 2019; 25: 605–9
- Ozturan IU, Yaka E, Suner S et al: Determination of carboxyhemoglobin half-life in patients with carbon monoxide toxicity treated with high flow nasal cannula oxygen therapy. *Clin Toxicol (Phila)*, 2019; 57: 617–23
- Kusuba Y, Taki K, Ohta A: Questionnaire results of hyperbaric oxygen therapy for acute carbon monoxide poisoning in Japan. *Undersea Hyperb Med*, 2012; 39: 639–45
- 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
- Thom SR, Bhopale VM, Fisher D: Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental carbon monoxide toxicity. *Toxicol Appl Pharmacol*, 2006; 213: 152–59
- Murata M, Suzuki M, Hasegawa Y et al: Improvement of occipital alpha activity by repetitive hyperbaric oxygen therapy in patients with carbon monoxide poisoning: A possible indicator for treatment efficacy. *J Neurol Sci*, 2005; 235: 69–74
- Lo CP, Chen SY, Chou MC et al: Diffusion-tensor MR imaging for evaluation of the efficacy of hyperbaric oxygen therapy in patients with delayed neuropsychiatric syndrome caused by carbon monoxide inhalation. *Eur J Neurol*, 2007; 14: 777–82
- Huang CC, Ho CH, Chen YC et al: Hyperbaric oxygen therapy is associated with lower short- and long-term mortality in patients with carbon monoxide poisoning. *Chest*, 2017; 152: 943–53
- Huang CC, Ho CH, Chen YC et al: Impact of hyperbaric oxygen therapy on subsequent neurological sequelae following carbon monoxide poisoning. *J Clin Med*, 2018; 7: pii: E349
- Simonsen C, Thorsteinsson K, Mortensen RN et al: Carbon monoxide poisoning in Denmark with focus on mortality and factors contributing to mortality. *PLoS One*, 2019; 14: e0210767
- Juurlink DN, Buckley NA, Stanbrook MB et al: Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*, 2005; (1): CD002041
- Buckley NA, Juurlink DN, Isbister G et al: Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2011; (4): CD002041
- Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*, 2009; 6: e1000097
- Jadad AR, Moore RA, Carroll D et al: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*, 1996; 17: 1–12
- DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials*, 1986; 7: 177–88
- Ades AE, Lu G, Higgins JP: The interpretation of random-effects meta-analysis in decision models. *Med Decis Making*, 2005; 25: 646–54
- Deeks JJ, Higgins JPT, Altman DG: Analyzing data and undertaking meta-analyses. In: Higgins J, Green S (eds.) *Cochrane handbook for systematic reviews of interventions* 501. Oxford, UK: The Cochrane Collaboration, 2008
- Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. *BMJ*, 2003; 327: 557–60
- Tobias A: Assessing the influence of a single study in meta-analysis. *Stata Tech Bull*, 1999; 47
- Altman DG, Bland JM: Interaction revisited: the difference between two estimates. *BMJ*, 2003; 326: 219
- Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 1997; 315: 629–34
- Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics*, 1994; 50: 1088–101

29. Raphael JC, Elkharrat D, Jars-Guincestre MC et al: Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet*, 1989; 2: 414–19
30. Thom SR, Taber RL, Mendiguren II et al: Delayed neuropsychologic sequelae after carbon monoxide poisoning: Prevention by treatment with hyperbaric oxygen. *Ann Emerg Med*, 1995; 25: 474–80
31. Ducasse JL, Celsis P, Marc-Vergnes JP: Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? *Undersea Hyperb Med*, 1995; 22: 9–15
32. Mathieu D, Wattel F, Mathieu-Nolf M et al: Randomized prospective study comparing the effect of HBO vs. 12 h NBO in noncomatose CO-poisoned patients: Results of the preliminary analysis. *Undersea Hyperb Med*, 1996; 23
33. Scheinkestel CD, Bailey M, Myles PS et al: Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: A randomised controlled clinical trial. *Med J Aust*, 1999; 170: 203–10
34. Weaver LK, Hopkins RO, Chan KJ et al: Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*, 2002; 347: 1057–67
35. 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
36. Lin CH, Su WH, Chen YC et al: Treatment with normobaric or hyperbaric oxygen and its effect on neuropsychometric dysfunction after carbon monoxide poisoning: A systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*, 2018; 97: e12456
37. Jang DH, Khatri UG, Shortal BP et al: Alterations in mitochondrial respiration and reactive oxygen species in patients poisoned with carbon monoxide treated with hyperbaric oxygen. *Intensive Care Med* 2018; 6: 4
38. Chen W, Liang X, Nong Z et al: The multiple applications and possible mechanisms of the hyperbaric oxygenation therapy. *Med Chem*, 2018 [Epub ahead of print]