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급성일산화탄소 중독환자에서 고압산소치료의 압력에 따른 예후 비교

김정윤[1], 임지혜[2], 김성화[2], 한상일[1,3], 차용성[1,3]

연세대학교 원주의과대학 [1]응급의학교실, [2]의통계학과, [3]고압의과학연구소

Comparison of hyperbaric oxygen therapy pressures for acute carbon monoxide poisoning

Jeong Yun Kim, M.D.[1], Jihye Lim, B.S.[2], Sung Hwa Kim, B.S.[2], Sang Il Han, M.D.[1,3], Yong Sung Cha, M.D., Ph.D.[1,3]

[1]Department of Emergency Medicine, [2]Department of Biostatistics and Center of Biomedical Data Science, and [3]Research Institute of Hyperbaric Medicine and Science, Yonsei University Wonju College of Medicine, Wonju, Korea

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Corresponding author:
Yong Sung Cha
Department of Emergency Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea
Tel: +82-33-741-1615
Fax: +82-33-742-3030
E-mail: emyscha@yonsei.ac.kr

Purpose: No consensus currently exists regarding the maximal pressure of hyperbaric oxygen (HBO_2) therapy performed within 24 hours of acute carbon monoxide (CO) poisoning. This study aimed to evaluate the difference in therapeutic effects according to the first HBO_2 pressure (3.0 atmospheres absolute [ATA] vs. 2.8 ATA).

Methods: We used prospectively collected registry data on CO poisoning at a tertiary academic hospital in the Republic of Korea. Adult patients with acute CO poisoning treated with HBO_2 within 24 hours after arrival at the emergency department and without the use of additional HBO_2 after 24 hours between January 2007 and February 2022 were included. Data from 595 patients were analyzed using propensity score matching (PSM). Patients with mild (non-intubated) and severe (intubated) poisoning were also compared. Neurocognitive outcomes at 1 month after CO poisoning were evaluated using the Global Deterioration Scale combined with neurological impairment.

Results: After PSM, the neurocognitive outcomes at 1-month post-CO exposure were not significantly different between the 2.8 ATA (110 patients) and 3.0 ATA (55 patients) groups (p=1.000). Similarly, there was also no significant difference in outcomes in a subgroup analysis according to poisoning severity in matched patients (165 patients) (mild [non-intubated]: p=0.053; severe [intubated]: p=1.000).

Conclusion: Neurocognitive sequelae at 1 month were not significantly different between HBO_2 therapy pressures of 2.8 ATA and 3.0 ATA in patients with acute CO poisoning. In addition, the 1-month neurocognitive sequelae did not differ significantly between intubated and non-intubated patients.

Keywords: Carbon monoxide poisoning, Hyperbaric oxygen therapy, Prognosis

INTRODUCTION

Carbon monoxide (CO) is a colorless, tasteless, and odorless gas, and thus, CO poisoning is not perceptible to those exposed to it[1]. In the United States, approximately 50,000 people are brought to the emergency departments (EDs) annually due to CO poisoning, and an average of 1,500 people die from CO poisoning[2,3]. Headache, dizziness, weakness, nausea, vomiting, confusion, misdirection, blindness, and difficulty breathing are the common symptoms of CO poisoning[1]. Cognitive sequelae occur in 25%–50% of people with acute CO poisoning[4], and

those with severe poisoning may develop convulsions and cardiopulmonary arrest[1].

Hyperbaric oxygen therapy (HBO_2) reduces neurocognitive complications in symptomatic patients with acute CO poisoning[4,5]. Weaver et al.[4] conducted a double-blind randomized controlled trial (RCT) of HBO_2 therapy thrice with a maximum pressure of 3.0 atmospheres absolute (ATA) within 24 hours in patients with acute CO poisoning. The results showed that neurocognitive complications were significantly decreased after 6 weeks and 12 months. In another RCT performed by Thom et al.[5], the maximum pressure of HBO_2 was 2.8 ATA, and HBO_2 treatment reduced the incidence of neurocognitive complications in patients with mild-to-moderate CO poisoning[6].

One of most effective mechanisms of HBO_2 therapy for the inflammatory reaction of CO poisoning is the inhibition of human β_2-integrin-dependent adherence of HBO_2, which is observed at 2.8 or 3.0 ATA[7]. To date, all reports of using 2.0 ATA showed no therapeutic effect of HBO_2[8,9], whereas using 3.0 ATA had a therapeutic effect[4,5,10]. In addition, because previous RCTs showed the effectiveness of HBO_2 therapy in reducing neurocognitive sequelae, both 3.0 ATA and 2.8 ATA may be a reasonable recommended pressure within 24 hours of CO poisoning for symptomatic patients[4,5]. However, the optimal pressure (3.0 ATA versus 2.8 ATA) with respect to neurocognitive outcomes in acute CO poisoning remains unclear.

Therefore, this study aimed to evaluate the difference in therapeutic effect according to the first HBO_2 pressure (3.0 ATA versus 2.8 ATA) used in patients with acute CO poisoning who received HBO_2 therapy within 24 hours after CO poisoning.

METHODS

1. Study design and population

This cohort study extracted data from a cohort of a single tertiary academic hospital in the Republic of Korea. Patients who visited the ED of Wonju Severance Christian Hospital for acute CO poisoning between January 2006 and February 2022 were included. Since January 2006, a CO poisoning registry has been used to prospectively collect consecutive patient data in our hospital. From August 2020, data were prospectively collected with the "CARE CO cohort" informed consent (ClinicalTrials.gov identifier: NCT04490317). This study was approved by the institutional review board of Wonju Severance Christian Hospital (approval number: CR322003) and was conducted according to the tenets of the Declaration of Helsinki.

Adult patients with CO poisoning treated with HBO_2 within 24 hours after rescue from CO exposure and without use of additional HBO_2 after 24 hours from ED arrival (EDA) were eligible. We excluded patients aged < 16 years; those aged > 70 years were also excluded owing to aging-related senile changes in neurocognitive function. The patients with the following characteristics were also excluded: (1) previous stroke or neurocognitive disorder, (2) previous CO poisoning, (3) serious illness such as advanced cancer, (4) other specific treatment (therapeutic hypothermia or steroid), (5) no follow-up for neurocognitive outcome at 1 month, and (6) missing data for important variables.

2. Treatment protocol

In our institute, acute CO poisoning is diagnosed according to the patient's or guardian's history report and carboxyhemoglobin levels (CO-Hb) > 5% (> 10% for heavy smokers). Patients with CO poisoning are treated with 100% oxygen therapy through a facemask with a reservoir bag. Patients with any loss of consciousness intervals, neurocognitive symptoms or signs, cardiovascular dysfunction, elevated cardiac enzymes, ischemic electrocardiogram changes, severe acidosis, or CO-Hb ≥ 25% were treated with HBO_2[6]. First, HBO_2 was delivered at a pressure of 2.8 ATA or 3.0 ATA for 45 minutes and then maintained at a pressure of 2.0 ATA for 60 minutes (Fig. 1A, B). Additional HBO_2 was delivered at a pressure of 2.0 ATA for 90 minutes without air break (Fig. 1C). Treatment was performed with a maximum pressure of 2.8 ATA until January 2021 and 3.0 ATA after February 2021.

3. Variables and definitions

Information on the following clinical variables were collected: age, sex, intentionality, source of CO poisoning (charcoal, gas and oil, and fire), number of HBO_2 therapies within 24 hours after ED arrival, CO exposure time (hr), time from rescue to HBO_2 (hr), drug co-ingestion, Glasgow Coma Scale (GCS) score at the site of rescue or ED arrival, comorbidities (diabetes mellitus, hypertension, cardiovascular disease, psychiatric disease), smoking history, symptoms or signs (loss of conscious-

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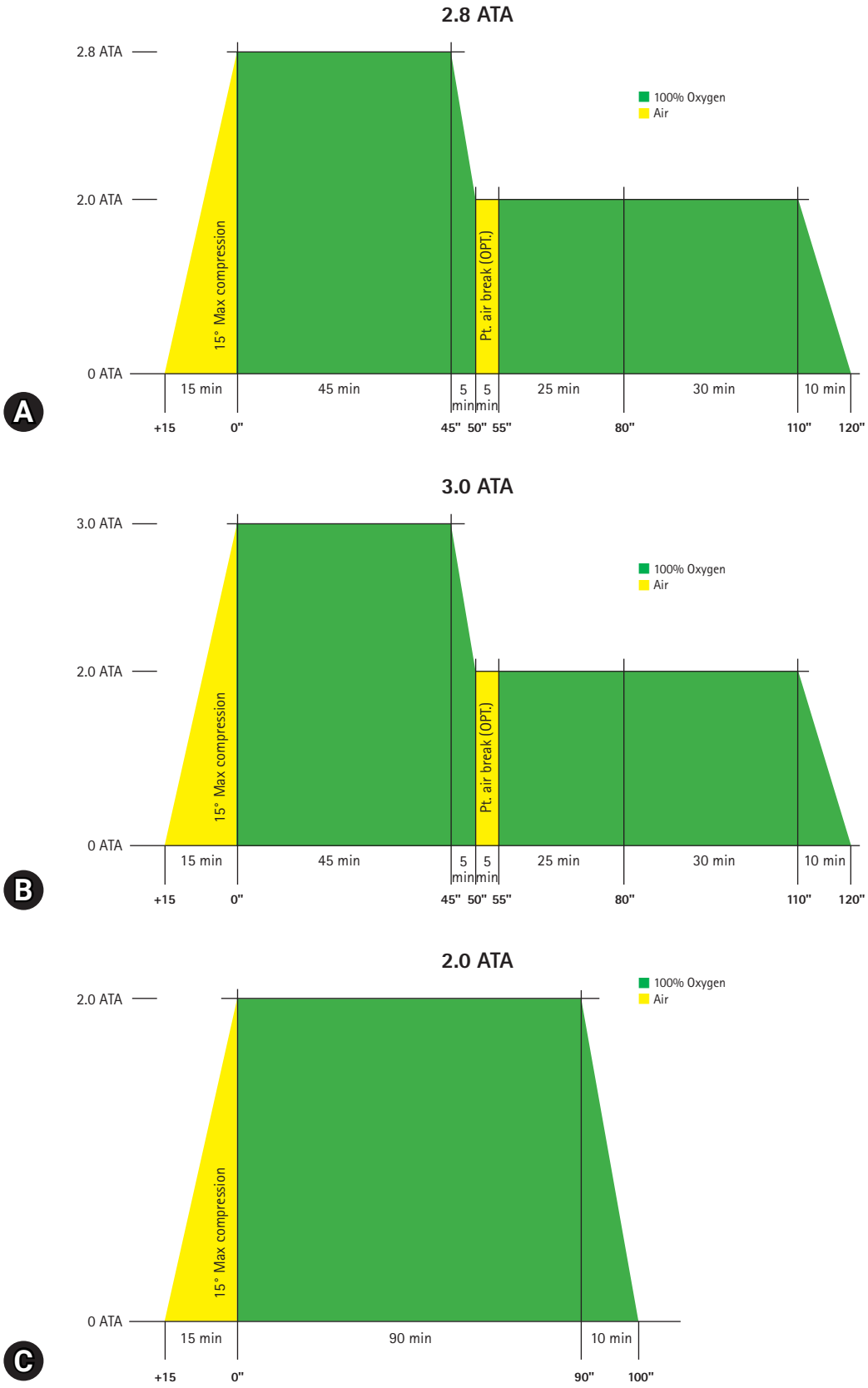

Fig. 1. Protocols of hyperbaric oxygen therapy. (A) 2.8 Atmospheres absolute (ATA). (B) 3.0 ATA. (C) 2.0 ATA. PT: patient, OPT: optional.

ness, shock, or seizure), laboratory findings (CO-Hb, bicarbonate, lactate, creatinine, creatine kinase, and troponin I), and intubation.

The patients were classified into two groups as the 2.8 ATA and 3.0 ATA treatment groups. In subgroup analysis, mildly and severely poisoned patients were defined as those not requiring and requiring intubation, respectively[11]. Neurocognitive outcomes after CO poisoning were evaluated using the Global Deterioration Scale (GDS) combined with neurological impairment at 1-month post-CO exposure on visits to the rehabilitation outpatient department[12]. Guardians of patients in poor condition who were unable to visit the rehabilitation outpatient department were interviewed to assess the patients' conditions. The GDS was divided into seven stages from stages 1 to 7. Stage 1 was defined as no cognitive decline; stage 4, moderate cognitive decline; and stage 7, very severe cognitive decline. GDS stages 1–3 were classified as the favorable outcome group, while GDS stages 4–7 were classified as the poor outcome group. However, patients belonging to the favorable outcome group, but with neurological impairment, (e.g., motor weakness or dysarthria) were assigned to the poor outcome group. Patients who had CO-related death within 1 month after CO poisoning were classified as having GDS stage 7.

4. Outcome measures

The primary outcome measure was to compare the difference in 1-month neurocognitive outcomes according to the maximum treatment pressure of HBO_2 (2.8 ATA versus 3.0 ATA) in patients with acute CO poisoning. The secondary outcome measures included neurocognitive outcomes at 1-month post-CO exposure in the 2.8 ATA group compared with those in the 3.0 ATA group according to the severity of poisoning (mild [non-intubated] versus severe [intubated]).

5. Statistical analyses

Propensity score matching (PSM) using the nearest neighbor method was conducted to reduce selection bias in the observational study and control for confounding variables. Propensity scores were estimated through logistic regression with statistically and clinically significant variables. The score assigned to each patient was used to reduce bias in estimating treatment effects[13]. The matching ratio between the treatment group and the control group is generally 1:1 or 1:2[14]. In this study, the ratio was 1:2 because the 2.8 ATA group was larger than the 3.0 ATA group. The caliper width was set as 0.2 based on previous findings[15]. Matching balance was confirmed based on the absolute value of the standardized mean difference within 0.25[16].

Data are reported as the median (interquartile range) for continuous variables and as frequencies (percentages) for categorical variables, before and after matching. The normality of distribution of continuous variables was assessed using the Shapiro-Wilks test. Comparisons between the 2.8 ATA and 3.0 ATA groups were performed using the chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables. All statistical analyses were performed using SAS statistical software ver. 9.4 (SAS Institute Inc., Cary, NC, USA) and R ver. 4.1.2 (R Core Team, Vienna, Austria). Statistical significance was confirmed at $p < 0.05$.

RESULTS

1. Patient characteristics

In total, 1,020 patients were identified, and 595 were included in the final analysis. Among them, 540 patients and 55 patients received initial HBO_2 therapy with 2.8 ATA and 3.0 ATA, respectively (Fig. 2). The median age of the total cohort was 45.0 years, and 65.4% were male individuals. The most common source of CO poisoning was charcoal (76.5%). HBO_2 therapy was performed only once within 24 hours of ED arrival in 497 patients (83.5%). The median CO exposure time and the time from rescue to HBO_2 therapy were 3.0 hours and 5.3 hours, respectively. The most common comorbidity was hypertension (14.5%). In total, 48 patients (8.1%) were intubated. We showed that baseline patient characteristics before and after PSM in the total cohort in Table 1.

A total of 560 patients (94.1%) and 35 patients (5.9%) had favorable outcomes (GDS 1–3) and unfavorable outcomes (GDS 4–7), respectively. Three patients with GDS stages 4, 5, and 6 had neurological symptoms (motor weakness, speech disturbance, or peripheral neuropathy). Therefore, the neurocognitive outcome group classified by GDS stage combined with neurological impairment was not different from the outcome group categorized by GDS stage alone. In the analysis of whether the 1-month GDS stage changed 6 months after CO poisoning, 559 patients were followed up for up to 6 months. The GDS stage remained unchanged in 517 patients (92.5%) before PSM, while it improved in 40 (7.1%) and worsened in 2

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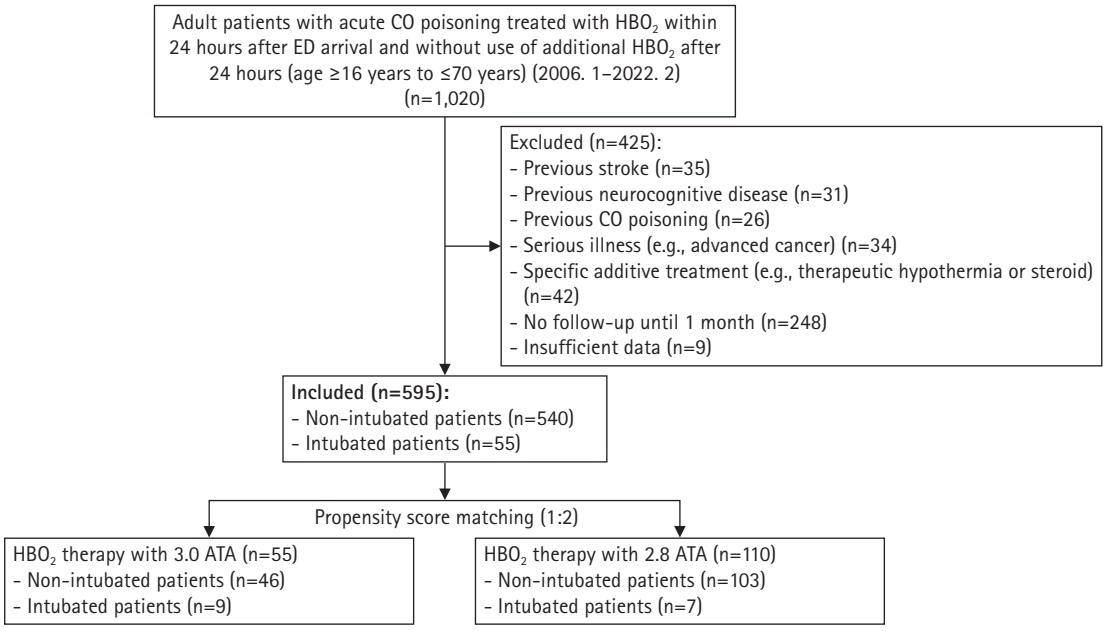

Fig. 2. Study flowchart. CO: carbon monoxide, HBO_2: hyperbaric oxygen, ED: emergency department, ATA: atmospheres absolute.

(0.4%). There was no significant difference in neurocognitive outcomes between 1-month and 6-month GDS stage ($p=1.000$) (Table 2).

2. Patient characteristics according to HBO_2 pressure

There were significant differences in intentionality, CO source, CO exposure time, time from rescue to HBO_2, drug co-ingestion, GCS score, shock, bicarbonate, troponin I, and intubation rates between the 2.8 ATA and 3.0 ATA groups. However, the groups were well balanced after PSM, as confirmed based on the absolute value of the standardized mean difference within 0.25 (Fig. 3)[16]. Before matching, there was a difference in the distribution of propensity scores between the 2.8 ATA and 3.0 ATA groups, although the distribution was generally consistent after matching, confirming group homogeneity (Fig. 4).

3. Neurocognitive outcomes

Intentionality, source of CO poisoning, CO exposure time, time from rescue to HBO_2, drug co-ingestion, GCS score, shock, bicarbonate, and troponin I were significantly different between the 2.8 ATA and 3.0 ATA groups. Therefore, PSM for these variables were performed. In addition, because variables with no significant difference (age, sex, number within 24 hours after EDA, creatine kinase) were considered to be clinically important, PSM was performed with these variables. There was no difference in neurocognitive outcome after PSM between the 2.8 ATA and 3.0 ATA groups (Table 1). In subgroup analysis according to intubation in matched patients (n=165), no significant differences were observed between the 2.8 ATA and 3.0 ATA groups (Tables 3, 4).

DISCUSSION

The optimal pressure for initial HBO_2 therapy for acute CO poisoning is yet to be established. This study found no significant difference in the 1-month neurocognitive outcome between maximum pressures of 2.8 ATA and 3.0 ATA of HBO_2 therapy as initial treatment in patients with acute CO poisoning. Subgroup analysis according to severity of poisoning (mild [non-intubated] versus severe [intubated]) also showed no significant difference in neurocognitive complications between these HBO_2 pressures. Convulsions due to oxygen toxicity, which is a complication of HBO_2 therapy, are more frequent in higher treatment pressures[17]. Other complications such as barotrauma of the middle ear, nasal sinus, and teeth can also occur due to increased pressure in HBO_2 therapy. In this study, the seizure rate was 1.1% (6/540) in the 2.8 ATA group and 1.8% (1/55) in the 3.0 ATA group. Although there was no sig-

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Table 1. Baseline patient characteristics before and after PSM in the total cohort

Characteristic	Before PSM				After PSM		
	Total (n=595)	2.8 ATA (n=540)	3.0 ATA (n=55)	*p*-value	2.8 ATA (n=110)	3.0 ATA (n=55)	*p*-value
Age (yr)	45.0 (35.0–56.0)	45.0 (35.0–56.0)	42.0 (33.0–58.0)	0.464	43.0 (33.0–54.0)	42.0 (33.0–58.0)	0.847
Sex (male)	389 (65.4)	358 (66.3)	31 (56.4)	0.140	57 (51.8)	31 (56.4)	0.581
Intentionality	228 (38.3)	198 (36.7)	30 (54.6)	**0.009**	54 (49.1)	30 (54.6)	0.509
Source				**0.003**			0.186
Charcoal	455 (76.5)	403 (74.6)	52 (94.6)		102 (92.7)	52 (94.6)	
Gas and oil	94 (15.8)	93 (17.2)	1 (1.8)		7 (6.4)	1 (1.8)	
Fire	46 (7.7)	44 (8.2)	2 (3.6)		1 (0.9)	2 (3.6)	
No. of HBO_2 sessions within 24 hr after ED arrival				0.330			0.158
1	497 (83.5)	451 (83.5)	46 (83.6)		98 (89.1)	46 (83.6)	
2	80 (13.4)	71 (13.2)	9 (16.4)		9 (8.2)	9 (16.4)	
3	18 (3.0)	18 (3.3)	0 (0.0)		3 (2.7)	0 (0.0)	
CO exposure time (hr)	3.0 (1.0–8.0)	3.0 (1.0–8.0)	2.0 (1.0–5.0)	**0.041**	2.0 (1.0–4.0)	2.0 (1.0–5.0)	0.624
Time from rescue to HBO_2 (hr)	5.3 (3.5–8.6)	5.2 (3.4–8.2)	7.4 (4.3–10.8)	**0.004**	6.9 (3.8–11.3)	7.4 (4.3–10.8)	0.629
Drug co-ingestion	42 (7.1)	28 (5.2)	14 (25.5)	**<0.001**	21 (19.1)	14 (25.5)	0.346
GCS score	15.0 (12.0–15.0)	15.0 (12.0–15.0)	15.0 (11.0–15.0)	**0.030**	15.0 (12.0–15.0)	15.0 (11.0–15.0)	0.077
Comorbidities							
Diabetes mellitus	50 (8.4)	44 (8.2)	6 (10.9)	0.447	5 (4.6)	6 (10.9)	0.183
Hypertension	86 (14.5)	78 (14.4)	8 (14.6)	0.984	13 (11.8)	8 (14.6)	0.620
Cardiovascular disease	17 (2.9)	15 (2.8)	2 (3.6)	0.665	3 (2.7)	2 (3.6)	1.000
Psychiatric disease	74 (12.4)	64 (11.9)	10 (18.2)	0.175	26 (23.6)	10 (18.2)	0.424
Current smoking	255 (42.9)	238 (44.1)	17 (30.9)	0.060	47 (42.7)	17 (30.9)	0.142
Symptoms and signs at ED arrival							
Loss of consciousness	304 (51.1)	275 (50.9)	29 (52.7)	0.799	58 (52.7)	29 (52.7)	1.000
Shock	6 (1.0)	3 (0.6)	3 (5.5)	**0.012**	2 (1.8)	3 (5.5)	0.335
Seizure	7 (1.2)	6 (1.1)	1 (1.8)	0.495	4 (3.6)	1 (1.8)	0.666
Laboratory findings							
CO-Hb (%)	19.1 (8.6–30.2)	19.8 (8.4–30.6)	17.9 (9.7–25.2)	0.415	21.1 (9.2–30.4)	17.9 (9.7–25.2)	0.472
Bicarbonate (mmol/L)	21.6 (19.4–23.3)	21.5 (19.4–23.2)	22.8 (20.7–24.2)	**0.009**	22.5 (20.5–23.5)	22.8 (20.7–24.2)	0.605
Lactate (mmol/L)	2.0 (1.3–3.3)	2.0 (1.3–3.3)	2.2 (1.7–3.9)	0.080	2.1 (1.3–3)	2.2 (1.7–3.9)	0.070
Creatinine (mg/dL)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–0.9)	0.657	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.276
Creatine kinase (U/L)	129 (86–234)	129.5 (90.0–238.0)	124.0 (75.0–180.0)	0.204	124.5 (80.0–234.0)	124.0 (75.0–180.0)	0.676
Troponin I (ng/mL)	0.015 (0.013–0.076)	0.015 (0.015–0.073)	0.01 (0.003–0.117)	**0.042**	0.015 (0.015–0.023)	0.01 (0.003–0.117)	0.246
Intubation	48 (8.1)	39 (7.2)	9 (16.4)	**0.032**	7 (6.4)	9 (16.4)	0.041
GDS				0.238			1.000
Good (GDS 1–3)	560 (94.1)	506 (93.7)	54 (98.2)		107 (97.3)	54 (98.2)	
Poor (GDS 4–7)	35 (5.9)	34 (6.3)	1 (1.8)		3 (2.7)	1 (1.8)	

Values are presented as median (range) or frequency (%). Statistically significant results are marked in bold.
PSM: propensity score matching, ATA: atmospheres absolute, HBO_2: hyperbaric oxygen, ED: emergency department, CO: carbon monoxide, GCS: Glasgow Coma Scale, CO-Hb: carboxyhemoglobin, GDS: Global Deterioration Scale.

Table 2. Change in GDS from 1 month to 6 months before PSM

1-Month GDS vs. 6-month GDS	Total	HBO_2 pressure		*p*-value
		2.8 ATA (n=529)	3.0 ATA (n=30)	
Improved	40 (7.1)	38 (7.2)	2 (6.7)	
No change	517 (92.5)	489 (92.4)	28 (93.3)	1.000
Worsened	2 (0.4)	2 (0.4)	0	

Values are presented as number (%). The p-value was calculated using Fisher's exact test. Of the 595 patients, 36 had missing GDS stage data at 6 months.
GDS: Global Deterioration Scale, PSM: propensity score matching.

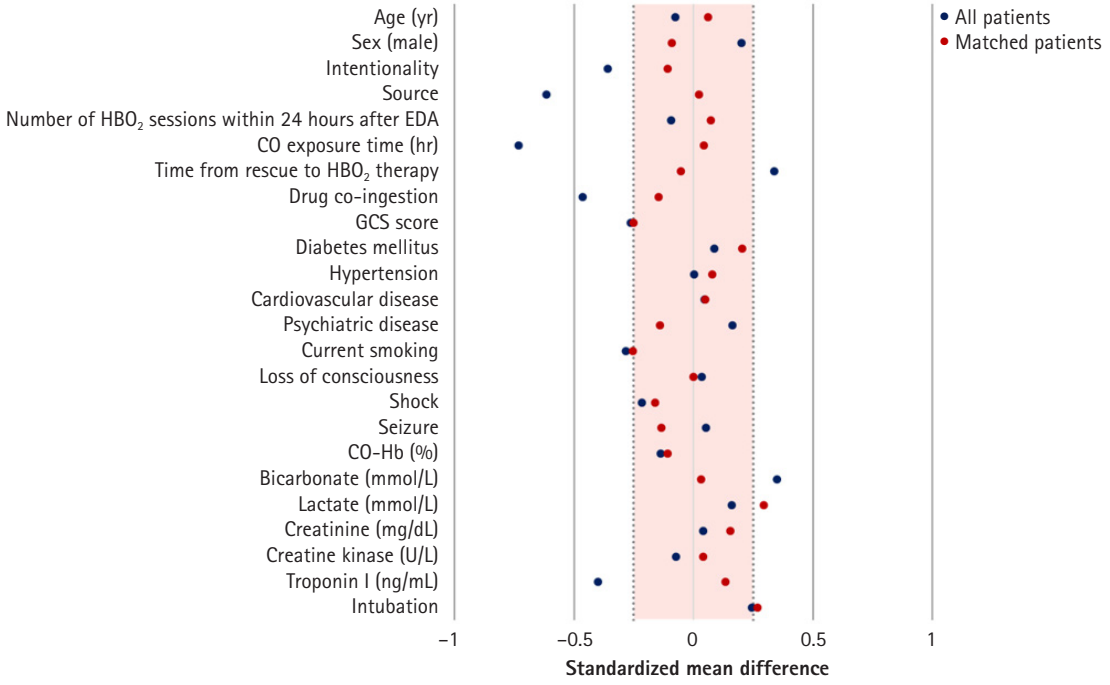

Fig. 3. Forest plot of standardized mean differences before and after matching. HBO_2: hyperbaric oxygen, EDA: emergency department arrival, CO: carbon monoxide, GCS: Glasgow Coma Scale, CO-Hb: carboxyhemoglobin.

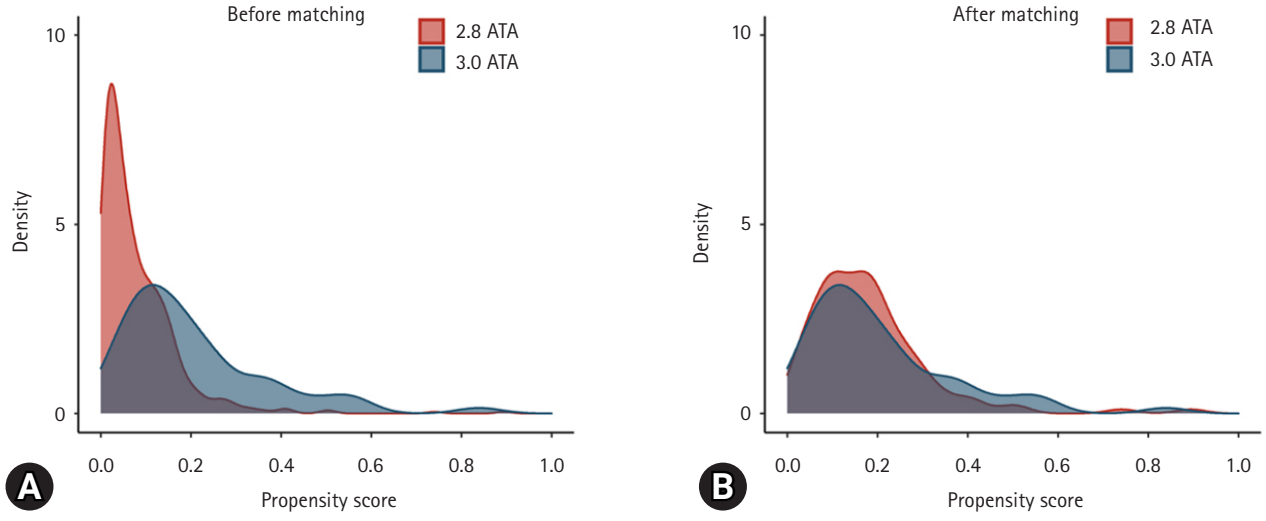

Fig. 4. Distribution of propensity score before propensity score matching (PSM) (A) and after PSM (B). ATA: atmospheres absolute.

Table 3. Baseline characteristics of patients in the non-intubated group

Variable	Before PSM	After PSM		*p*-value
	Total (n=547)	HBO_2 pressure		
		2.8 ATA (n=103)	3.0 ATA (n=46)	
Age (yr)	43.0 (33.0–54.0)	43.0 (33.0–54.0)	40.5 (33.0–55.0)	0.994
Sex (male)	80 (53.7)	52 (50.5)	28 (60.9)	0.240
Intentionality	72 (48.3)	48 (46.6)	24 (52.2)	0.530
Source				0.610
Charcoal	141 (94.6)	96 (93.2)	45 (97.8)	
Gas and oil	7 (4.7)	6 (5.8)	1 (2.2)	
Fire	1 (0.7)	1 (1.0)	0	
No. of HBO_2 sessions within 24 hr after ED arrival				0.330
1	131 (87.9)	92 (89.3)	39 (84.8)	
2	16 (10.7)	9 (8.7)	7 (15.2)	
3	2 (1.3)	2 (1.9)	0	
CO exposure time (hr)	2.0 (1.0–4.5)	2.0 (1.0–4.0)	2.1 (1.0–5.0)	0.255
Time from rescue to HBO_2 (hr)	7.0 (3.8–10.8)	6.5 (3.8–11.0)	7.8 (4.3–10.8)	0.373
Drug co-ingestion	28 (18.8)	18 (17.5)	10 (21.7)	0.538
GCS score	15.0 (12.0–15.0)	15.0 (12.0–15.0)	15.0 (12.0–15.0)	0.254
Comorbidities				
Diabetes mellitus	11 (7.4)	5 (4.9)	6 (13.0)	0.095
Hypertension	19 (12.8)	13 (12.6)	6 (13.0)	0.943
Cardiovascular disease	5 (3.4)	3 (2.9)	2 (4.4)	0.644
Psychiatric disease	28 (18.8)	23 (22.3)	5 (10.9)	0.098
Current smoking	57 (38.3)	43 (41.8)	14 (30.4)	0.189
Symptoms and signs at ED arrival				
Loss of consciousness	71 (47.7)	51 (49.5)	20 (43.5)	0.496
Shock	1 (0.7)	0	1 (2.2)	0.309
Seizure	3 (2.0)	2 (1.9)	1 (2.2)	1.000
Laboratory findings				
CO-Hb (%)	17.9 (9.6–27.0)	21.1 (9.2–29.4)	16.5 (9.7–22.5)	0.091
Bicarbonate (mmol/L)	22.7 (20.8–23.9)	22.6 (20.6–23.8)	23.1 (21.4–24.2)	0.238
Lactate (mmol/L)	2.1 (1.4–3.0)	2.1 (1.2–3.0)	2.0 (1.6–3.3)	0.329
Creatinine (mg/dL)	0.8 (0.6–0.9)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	0.267
Creatine kinase (U/L)	119.0 (75.0–178.0)	119.0 (75.0–221.0)	112.0 (73.0–156.0)	0.545
Troponin I (ng/mL)	0.015 (0.006–0.021)	0.015 (0.015–0.016)	0.006 (0.003–0.029)	0.008
GDS				0.553
Good (GDS 1–3)	146 (98.0)	100 (97.1)	46 (100.0)	
Poor (GDS 4–7)	3 (2.0)	3 (2.9)	0	

Values are presented as median (range) or frequency (%).
PSM: propensity score matching, HBO_2: hyperbaric oxygen, ATA: atmospheres absolute, ED: emergency department, CO: carbon monoxide, GCS: Glasgow Coma Scale, CO-Hb: carboxyhemoglobin, GDS: Global Deterioration Scale.

nificant difference ($p=0.495$), the 3.0 ATA group showed a higher trend in seizure rate. Therefore, a minimal pressure with an optimal therapeutic effect is needed.

The findings of this study can be understood with respect to the pathophysiology of CO poisoning and the mechanism of action of HBO_2 therapy. Acute CO poisoning causes neutrophil degranulation by activating intravascular neutrophils through platelet-neutrophil aggregates[18]. When neutrophils are stimulated, they attach to vascular endothelial cells. This process leads to oxidative stress, the transformation of xanthine dehydrogenase to xanthine oxidase in endothelial cells, lipid peroxidation, and apoptosis by causing the release of myeloperoxidase, proteases, and reactive oxygen species[18,19]. Finally, these reactions induce an adaptive immunological response through microglia activation, causing CO-mediated neurocognitive sequelae through the formation of chemically

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Table 4. Baseline characteristics of patients in the intubated group

Variable	Before PSM	After PSM		p-value
	Total (n=48)	HBO_2 pressure		
		2.8 ATA (n=7)	3.0 ATA (n=9)	
Age (yr)	46.5 (33.0–58.5)	51.0 (29.0–58.0)	42.0 (37.0–65.0)	0.640
Sex (male)	8 (50.0)	5 (71.4)	3 (33.3)	0.315
Intentionality	12 (75.0)	6 (85.7)	6 (66.7)	0.585
Source				0.475
Charcoal	13 (81.3)	6 (85.7)	7 (77.8)	
Gas and oil	1 (6.3)	1 (14.3)	0	
Fire	2 (12.5)	0	2 (22.2)	
No. of HBO_2 sessions within 24 hr after ED arrival				0.475
1	13 (81.3)	6 (85.7)	7 (77.8)	
2	2 (12.5)	0	2 (22.2)	
3	1 (6.3)	1 (14.3)	0	
CO exposure time (hr)	1.1 (0.5–3.7)	1.6 (0.5–8.0)	1.0 (0.5–1.5)	0.461
Time from rescue to HBO_2 (hr)	8.1 (4.9–14.5)	14.5 (7.3–46.6)	6.6 (4.8–8.9)	0.084
Drug co-ingestion	7 (43.8)	3 (42.9)	4 (44.4)	1.000
GCS score	8.0 (5.0–8.0)	8.0 (3.0–8.0)	8.0 (8.0–8.0)	0.180
Comorbidities				
Diabetes mellitus	0	0	0	–
Hypertension	2 (12.5)	0	2 (22.2)	0.475
Cardiovascular disease	0	0	0	–
Psychiatric disease	8 (50.0)	3 (42.9)	5 (55.6)	1.000
Current smoking	7 (43.8)	4 (57.1)	3 (33.3)	0.615
Symptoms and signs at ED arrival				
Loss of consciousness	16 (100.0)	7 (100.0)	9 (100.0)	–
Shock	4 (25.0)	2 (28.6)	2 (22.2)	1.000
Seizure	2 (12.5)	2 (28.6)	0	0.175
Laboratory findings				
CO-Hb (%)	34.9 (10.7–42.9)	14.7 (8.3–40.3)	39.3 (30.0–48.2)	0.356
Bicarbonate (mmol/L)	19.1 (16.2–21.8)	19.0 (14.5–23.2)	20.4 (18.5–21.4)	0.716
Lactate (mmol/L)	3.4 (1.9–6.0)	3.2 (1.3–4.4)	3.9 (3.1–7.5)	0.307
Creatinine (mg/dL)	0.8 (0.7–1.2)	0.8 (0.8–1.5)	0.8 (0.7–0.9)	0.307
Creatine kinase (U/L)	173.5 (127.5–1047)	244.0 (127.0–1812.0)	137.0 (128.0–298.0)	0.470
Troponin I (ng/mL)	0.377 (0.118–0.709)	0.337 (0.015–0.739)	0.418 (0.119–0.680)	0.755
GDS				1.000
Good (GDS 1–3)	15 (93.8)	7 (100.0)	8 (88.9)	
Poor (GDS 4–7)	1 (6.3)	0	1 (11.1)	

Values are presented as median (range) or frequency (%).
PSM: propensity score matching, HBO_2: hyperbaric oxygen, ATA: atmospheres absolute, ED: emergency department, CO: carbon monoxide, GCS: Glasgow Coma Scale, CO-Hb: carboxyhemoglobin, GDS: Global Deterioration Scale.

modified myelin basic protein[20]. With respect to the mechanism of action of HBO_2 therapy, Thom et al.[7,21] reported that exposure to 2.8 ATA or 3.0 ATA HBO_2 can transiently inhibit leukocyte β_2-integrin function by S-nitrosylation and cell adherence to the cerebral microvasculature, inhibiting the sequential immunological reaction, as shown in both animal and human studies. However, there was no statistically significant decrease in 2.0 ATA. Therefore, at a pressure of 2.8 ATA or higher, neutrophil adhesion, which causes neurocognitive complications of acute CO poisoning, can be inhibited.

Ducasse et al.[10] conducted an RCT comparing between normobaric oxygen therapy and HBO_2 with 2.4 ATA in non-comatose patients, and the results showed that HBO_2 therapy was associated with lower initial recovery time and number of neurological sequelae. However, their study had some limitations including no calculation of sample size, small sample size

(total 26 patients), and no description of the randomization method. Although no study has directly compared the therapeutic effects of 2.8 ATA with those of 3.0 ATA, one pilot RCT compared the therapeutic effects between 2.4 ATA (n = 18) and 3.0 ATA (n = 12)[22]. A neurocognitive screening test was performed immediately after HBO_2 therapy and repeated 14–21 days later. The results showed no significant difference in outcomes between 2.4 ATA and 3.0 ATA. However, the study had some limitations including no calculation of sample size, a small sample size (30 patients), enrollment of only fully conscious patients, and randomization method (the selection of a sealed envelope). Additional RCTs are needed with respect to the therapeutic effects of 2.4 ATA.

There are a few limitations to this study. First, this was an observational, non-randomized study. However, from an analytical perspective, PSM was used to minimize bias owing to the study design[23]. In addition, although a large number of patients were excluded for accurate comparison, to the best of our knowledge, this was the first study with a large sample size (> 500 patients). Second, the number of patients who received 3.0 ATA HBO_2 therapy was small. Third, although RCTs have conducted more than six neurocognitive tests, usually equivalent to CO batteries[4,5], we only evaluated outcomes using the GDS stage combined with neurological impairment. Our institute uses the GDS stage to evaluate neurocognitive prognosis in patients with CO poisoning because it has the advantage of recognizing neurocognitive functions (e.g., memory and concentration), as well as activities of daily living, through interviews. We have previously reported the GDS stage for the measurement of neurocognitive outcomes in a study related to CO poisoning[11,24,25]. Fourth, some patients were lost to follow-up due to their condition, distance from the hospital, or poor compliance. Fifth, although we compared intubated and non-intubated patients, further studies are needed because of the small number of these patients. Sixth, we only compared the 1-month outcomes. Studies comparing outcomes at longer time points (6 months and 1 year) may be needed. Further studies that address the study limitations will be needed.

CONCLUSION

Neurocognitive sequelae at 1 month do not differ according to the initial HBO_2 maximal pressure (2.8 ATA versus 3.0 ATA) in patients with acute CO poisoning. In addition, they also do not differ in patients with mild and severe poisoning. Therefore, we suggest the use of 2.8 ATA in HBO_2.

ORCID

Jeong Yun Kim https://orcid.org/0009-0001-4331-4806
Jihye Lim https://orcid.org/0000-0002-2972-1579
Sung Hwa Kim https://orcid.org/0000-0002-5482-1758
Sang Il Han https://orcid.org/0000-0002-8979-8367
Yong Sung Cha https://orcid.org/0000-0001-9897-4273

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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