

## Original Research Article

# Effect of hyperbaric oxygen therapy on cognitive impairment after aneurysm subarachnoid hemorrhage

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### Abstract

**Purpose:** To evaluate the effect of hyperbaric oxygen therapy (HBOT) on cognitive impairment after aneurysm subarachnoid hemorrhage (aSAH).

**Methods:** The current study was carried out in a regional neurosurgical center in Taiyuan, Shanxi Province of China from January 2019 to September 2020. A total of 150 patients with persistent cognitive dysfunction at 3 months after aSAH onset were enrolled, which were randomly classified into group A (HBOT) and group B (control) via the random number table method. The outcome was evaluated by Montreal cognitive assessment (MoCA).

**Results:** There were no significant differences between group A and group B with regard to MoCA score and proportions of normal MoCA patients at 3 months after HBOT ( $p > 0.05$ ). Both groups showed no significant differences in proportions of normal MoCA patients at 6 months after HBOT ( $p > 0.05$ ). However, there were significant differences between group A and group B with MoCA score of patients at 6 months after HBOT ( $p < 0.05$ ). There were also significant differences in MoCA score and proportions of normal MoCA patients at 9 months after HBOT.

**Conclusion:** HBOT alleviates cognitive impairment after aSAH, and thus may be used to manage cognitive impairment in patients after aSAH. However, further clinical trials are required prior to application in clinical practice.

**Keywords:** Aneurysm subarachnoid hemorrhage (aSAH), Hyperbaric oxygen therapy (HBOT), Cognitive impairment

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## INTRODUCTION

Both in-hospital survival and functional recovery of patients with aneurysm subarachnoid hemorrhage (aSAH) have been markedly improved in the past decades [1]. However, many patients develop cognitive impairment after

aSAH. After aSAH, an estimated proportion of patients who can perform independent daily living activities is 36 - 60 % [2, 3], which show cognitive dysfunction to various degrees [4,5]. A number of patients experience poor functional outcomes, such as executive disorder, anxiety and depression, with their living, social activities

and working damaged after aSAH (even up to 10 years after) [6].

The mean age of patients with aSAH is approximately 50 years, and aSAH brings a heavy burden to both their family and the society [7]. Cognitive impairment is harmful, and the patients can not return to work and/or full-work and live (shopping, location and transportation) independently. According to the literature, other than indirect treatment of hydrocephalus and prevention of secondary hemorrhage as well as treatment and/or prevention of cerebral vasospasm, a few medical treatments for cognitive impairment after aSAH have been previously investigated, and the results are similar to a previous study. [5]. A pilot study was performed using rivastigmine, and it was found that it was effective for the cases who developed persistent cognitive impairment (PCI) after spontaneous aSAH [8]. However, the efficacy and clinical use of rivastigmine for cases with PCI after aSAH remain to be further verified by prospective double-blinded placebo-controlled trials.

It is imperative to find an effective method or drug to manage poor functional outcomes. In recent years, some drugs, such as simvastatin, curcumin and dimethylfumarate, have been investigated in some animal experiments and few pilot clinical trials, but they have not been validated in well-designed clinical studies. Therefore, the safety of these drugs for the treatment of cognitive impairment after aSAH is still unclear [8,9]. It has been shown that hyperbaric oxygen therapy (HBOT) can alleviate cognitive dysfunction after cerebral trauma, with good safety [10,11]. HBOT is considered one of the safest medical treatments available if it is used appropriately [12].

The aim of the current study was to determine whether HBOT is a potential adjuvant therapy for cognitive dysfunction following aSAH.

## METHODS

### Patients

A prospective observational study was carried out in The People's Hospital of Shanxi Province, Shanxi Province of China over a 2-year period from January 2019 to September 2020. Patients with persistent cognitive dysfunction at least 3 months after primary aSAH were included. The protocol was approved by the Ethical Committee of Shanxi Provincial People's Hospital, Shanxi Province, China (approval no. 17-SPPH-03), and written informed consent was obtained from all

participants and their relatives. The study also followed the guidelines of Declaration of Helsinki.

### Inclusion criteria

1) Spontaneous aSAH, with intracranial aneurysms confirmed by angiography; 2) aged 18 - 65 years; 3) persistent cognitive dysfunction at least 3 months after aSAH onset; 4) Chinese speaker; 5) completing Montreal cognitive assessment (MoCA); 6) unable to return to full-work or pursue independent living activities (such as shopping, playing cards and cooking, etc.); 7) MoCA scores < 26 [13,14].

### Exclusion criteria

1) a history of cerebrovascular or neurological disease other than unruptured intracranial aneurysms; 2) a history of neurosurgery before aSAH onset; 3) unable to cooperate with cognitive assessment; 4) hydrocephalus and functional cerebral infarction caused by aSAH.

150 cases in total were enrolled, which were classified into two groups, namely, group A (HBOT) and group B (control) using the random number table method. Patients were given HBOT in a hyperbaric chamber. With 1 - 2 pound per square inch upon 100 % oxygen, the pressure was 152 kpa. The total dive time was 60 min. HBOT was given once per day, 5 days per session in one week, with a two-day interval between two sessions. The goal was 12 HBOT sessions. The patients in control group were observed without HBOT.

### MoCA

MoCA is a short test with 30 points, which is usually completed within 15 min, and six items are evaluated as follows: orientation, naming, recall, executive/visuospatial functions, abstraction, and attention. For subjects who are educated for < 12 years, one point is given. MoCA scores < 26 are the diagnostic criteria of cognitive impairment. MoCA score changes  $\geq 2$  or  $\leq 2$  were considered significant [15]. Assessments were conducted at 3, 6, 9 months, respectively, after the beginning of HBOT by a qualified doctor.

### Statistical analysis

Mean, standard deviation and frequency were used to express the data. To analyze the significant difference between HBOT group and control group, MoCA score changes ( $\geq 2$  or  $\leq 2$ ) at 3, 6 and 9 months after beginning of HBOT were analyzed using Wilcoxon rank test for two

independent samples. Chi-square test was used to analyze the proportions of normal MoCA at the same time points.  $P < 0.05$  indicated statistically significant difference. Statistical analysis was performed using SPSS software 25.0 program (IBM Corp, Armonk, New York, USA).

## RESULTS

A total of 150 patients were enrolled in the present study. In HBOT group, 1 patient died due to other diseases and 17 patients didn't accomplish the specified HBOT and Montreal cognitive assessment during the study period. In control group, 1 patient developed chronic hydrocephalus and accepted ventriculoperitoneal

shunt surgery, and 12 patients did not accomplish the Montreal cognitive assessment during the study period. Thus, 31 patients were not included in the data processing.

There were no significant differences in the demographic data between HBOT group and control group ( $p > 0.05$ ; Table 1). Both groups showed no significant differences in changes of MoCA scores and the proportion of normal MoCA at 3 months after HBOT ( $p > 0.05$ ; Table 2 and 3), and there was also no significant difference in proportions of normal MoCA at 6 months after HBOT between the two groups ( $p > 0.05$ ; Table 4).

**Table 1:** Patients' characteristics in HBOT and control groups

Patient characteristics	HBOT (57)	Control (62)	P-value
Age (mean $\pm$ SD)	52 $\pm$ 10	51 $\pm$ 8	0.409*
Female (%)	32 (56.1)	29 (46.8)	0.307#
Hypertension (%)	20 (35.1)	18 (29.0)	0.479#
Smoker (%)	18 (31.6)	20 (32.3)	0.937#
Location of aneurysm			0.610#
Anterior circulation (%)	48 (84.2)	50 (80.6)	
Posterior circulation	9 (15.8)	12 (19.4)	
Aneurysm treatment			0.194#
Coiling (%)	(61.4)	45 (72.6)	
Clipping (%)	22 (38.6)	17 (27.4)	
Education			0.985#
More than 12 years (%)	24 (42.1)	26 (41.9)	
Less than 12 years (%)	33 (57.9)	36 (58.0)	

Data are presented as mean  $\pm$  standard deviation, or n (%); \*Student's t test; # $\chi^2$  test

**Table 2:** MoCA score changes of patients at 3 months after HBOT

MoCA score changes	Number of patients			Rank range	Mean rank	Total rank		P-value
	HBOT	Control	Total			HBOT	Control	
(1)	(2)	(3)	(4)	(5)	(6)	(7) = (2) * (6)	(8) = (3)*(6)	
PC2 $\geq$ 2	15	13	28	1-28	14.5	217.5	188.5	
PONC $\leq$ 1	41	48	89	29-117	73	2,993	3,504	
NC $\leq$ 2	1	1	2	118-119	118.5	118.5	118.5	
Total	57	62	119			T1 = 3,329	T2 = 3,811	0.521

PC= positive change; PONC = positive or negative change; NC = negative change; Control: no HBOT

**Table 3:** Proportion of normal MoCA of patients at 3 months after HBOT

Treatment	Normal MoCA		Total	P-value
	Yes	No		
HBOT	10	47	57	
Control	9	53	62	
Total	19	100		0.652

**Table 4:** The proportion of normal MoCA of patients at 6 months after HBOT

Treatment	Normal MoCA		Total	P-value
	Yes	No		
HBOT	16	41	57	
Control	13	49	62	
Total	29	90	119	0.367

**Table 5:** Changes in MoCA scores of patients at 6 months after HBOT

MoCA score change	No. of patients			Rank range	Mean rank	Total rank		P-value
	HBOT	Control	Total			HBOT	Control	
(1)	(2)	(3)	(4)	(5)	(6)	(7) = (2) * (6)	(8) = (3) * (6)	
PC2 ≥ 2	28	18	46	1-46	23.5	658	423	
PONC ≤ 1	28	43	71	47-117	82	2,296	3,526	
NC ≤ 2	1	1	2	118-119	118.5	118.5	118.5	
<b>Total</b>	<b>57</b>	<b>62</b>	<b>119</b>			<b>T1 = 3,072.5</b>	<b>T2=4,067.5</b>	<b>0.03</b>

PC = positive change; PONC = positive or negative change; NC - negative change

**Table 6:** Changes in MoCA scores of patients at 9 months after HBOT

MoCA score change	No. of patients			Rank range	Mean rank	Total rank		P-value
	HBOT	Control	Total			HBOT	Control	
(1)	(2)	(3)	(4)	(5)	(6)	(7) = (2)*(6)	(8)=(3)*(6)	
PC2 ≥ 2	34	25	59	1-59	30	1020	750	
PONC ≤ 1	22	36	58	60-117	88.5	1947	3186	
NC ≤ 2	1	1	2	118-119	118	118.5	118.5	
<b>Total</b>	<b>57</b>	<b>62</b>	<b>119</b>			<b>3,085.5</b>	<b>4,054.5</b>	<b>0.042</b>

PC = positive change; PONC = positive or negative change; NC = negative change

**Table 7:** Proportion of normal MoCA of patients at 9 months after HBOT

Treatment	Normal MoCA		Total	P-value
	Yes	No		
HBOT	27	30	57	
Control	18	44	62	
<b>Total</b>	<b>45</b>	<b>74</b>	<b>119</b>	<b>0.039</b>

However, there were significant differences between group A and group B in changes of MoCA scores at 6 months after HBOT ( $p < 0.05$ ; Table 5), and there were significant differences between the two groups in changes of MoCA scores and proportions of normal MoCA at 9 months after HBOT (Table 6 and Table 7).

## DISCUSSION

The results of this study demonstrated that 9 or 12 months of HBOT improved cognitive impairment after onset of aSAH. Although it is well known that cognitive impairment is a consequence of aSAH, the mechanism is largely unclear. There have been a variety of hypotheses proposed for cognitive dysfunction following aSAH, such as neurotoxic consequence of blood breakdown products in the subarachnoid space, diffuse neural injury induced by cerebral hypoperfusion during aneurysmal rupture and inefficient neuronal communication. Elevated intracranial pressure, delayed cerebral ischemia, and cerebral vasospasm, which frequently occur after aSAH, are also postulated to contribute to neurocognitive dysfunction. The onset of aSAH has been known to elicit inflammatory responses in the central nervous system [16]. Neuroinflammation may be correlated with post-aSAH cognitive dysfunction [17]. Evidence from the previous study demonstrates that

apolipoprotein is a known "injury" factor in the central nervous system, and the proposed mechanisms cover immunomodulatory, oxidative and neurotoxic effects (isoform-specific) [18].

In normal cognitive function. While an increased level of cytokines is related to poor neuropsychological outcomes after aSAH onset. It is indicated that the specific role of cytokines in cognition is dependent on the physiologic environment. Some therapies, which inhibit immune responses to aSAH in experiments, seem to improve cognitive outcomes. However, their clinical efficacy and the prognostic role of inflammatory cytokines remain to be verified.

The functional changes in patients with aSAH may be caused by synaptic / microscopic changes, as observed in animal models. The subsequent depression of cortical spreading may further result in ischemia, causing excitatory neurotoxicity, which may be correlated with poor outcomes of animals after aSAH. The tendency of perforator infarcts, which may affect cognitive dysfunction, might be caused by injury to functional connectivity and white matter tracts. In addition, although the neuronal damage is minimal after aSAH, long-term potentiation of hippocampus is disrupted. It is indicated that the injury is the consequence of functional changes other than cell death.

Cognitive function may be related to underlying neural pathophysiologic disorder which results from neural injury. Humanin is a new peptide found in recent years, which is neuroprotective and fights against a variety of diseases related to the nervous system [19]. After HBOT, serum humanin levels in patients with vascular dementia are increased, and they are positively correlated with the Mini-Mental State Examination scores, indicating HBOT may protect nervous system through increasing levels of serum Humanin [20]. From this study, the mechanism by which HBOT improved cognitive impairment after aSAH is not clear and it may be related to changes in the cerebral neural pathophysiologic process mentioned above.

Cognitive dysfunction is present in about 40 % of patients who even return to their communities. Given the fact above, multiple trials are ongoing, which aim to improve eventual functional outcomes. The potential treatment modalities include intravenous magnesium sulfate infusion, statins, endothelin antagonist. There are few clinical reports on the effect of HBOT on cognitive impairment after aSAH.

### Limitations of the study

Some limitations can be found in this study. First, the study sample is relatively small. Second, a sham intervention was not used in the study. Third, the follow-up time was just nine months and so a longer follow-up is required in a future study. However, the findings of this study throw some insight into the management of cognitive impairment after aSAH. The findings of this study need to be further confirmed in a prospective well-designed controlled trials with a larger sample size. The mechanism of HBOT also needs to be investigated.

### CONCLUSION

This study shows that hyperbaric oxygen treatment alleviates cognitive impairment after aSAH. However, this should be further investigated before application in clinical practice.

### DECLARATIONS

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#### Funding

None provided.

### Ethical approval

The protocol was approved by the Ethical Committee of Shanxi Provincial People's Hospital, Shanxi Province, China (approval no. 17-SPPH-03).

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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