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Original Article

Huperzine A combined with hyperbaric oxygen on the effect on cognitive function and serum hypoxia-inducible factor-1α Level in elderly patients with vascular dementia

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Abstract: Objective: To explore the clinical effect of huperzine A combined with hyperbaric oxygen on cognitive function and serum hypoxia-inducible factor-1α (HIF-1α) level in elderly patients with vascular dementia (VD). Methods: 120 elderly VD patients admitted to our hospital from February 2018 to March 2020 were selected and divided into two groups according to the treatment method (n = 60 each). They were administered for huperzine A and huperzine A combined with hyperbaric oxygen, respectively. The comparison of disease control rate (DCR), mini-mental state examination (MMSE) score, revised hasegawa's dementia scale (HDS-R) score and serum index were conducted. Results: At 2 and 4 weeks after treatment, the HDS-R and MMSE scores were reported to be higher in the observation group than those in the control group ($P < 0.05$), and the vascular endothelial growth factor (VEGF), anti-apoptotic factor (Livin), and HIF-1α showed a higher level of improvement as compared with the control group ($P < 0.05$). Moreover, the DCR in the observation group was much higher than that in the control group ($P < 0.05$). Conclusion: Huperzine A combined with hyperbaric oxygen is remarkably effective in the treatment of elderly VD patients. It can improve the serum HIF-1α level and speed up the recovery of cognitive function.

Keywords: Vascular dementia, huperzine A, hyperbaric oxygen, cognitive function, hypoxia inducible factor-1α

Introduction

Vascular dementia (VD) is a chronic progressive disease, prominently manifests as the cognitive and intellectual impairment syndrome induced by cerebrovascular lesions [1]. The incidence is on a rise with the aging population. It is primarily exhibited as personality, emotion, language, memory, cognition and other mental disorders, severely endangering the social and daily life of patients. Consequently, it is required to carry out treatment as early as possible [1]. Huperzine A, a new alkaloid isolated from the plant Melaleuca tower, is a highly potent cholinesterase inhibitor with cholinergic activity. Although it has been documented to enhance patients' memory yet show a minimal effect in improving regional cerebral blood flow, especially in elderly patients with large infarct areas or repeated illnesses. Hence it is generally used as an adjunctive medication [2]. Hyperbaric oxygen becomes an emerging treatment option in recent years. It plays a crucial role in the treatment of patients with cognitive dysfunction due to cerebrovascular disease, facilitating the recovery of cerebral function and the improvement of cerebral metabolism [3, 4]. The desirable outcome yielded by huperzine A (A reversible cholinesterase inhibitor with selective inhibitory effect on true cholinesterase, and extensively used for middle-aged and elderly benign memory disorders and various types of dementia, memory cognitive function and emotional behavior disorders) and hyperbaric oxygen alone is currently reported, but there is a paucity of evidence demonstrating the combination of these two therapies, and the relevant mechanism of action remains

poorly understood. We thus hypothesized that the huperzine A plus hyperbaric oxygen plays a pivotal role in elderly VD in terms of Hasegawa Dementia Scale-Revised (HDS-R) score, mini-mental state examination (MMSE) score, disease control rate (DCR), serum HIF-1α and other indicators. This study is being undertaken to testify its value.

Materials and methods

Subjects

Patients who met the clinical diagnostic criteria for vascular dementia as specified in the 2018 Chinese Guidelines for the Diagnosis and Management of Dementia and Cognitive Impairment [5] jointly developed by the Cognitive Impairment Committee and the Writing Group of Dementia and Cognitive Impairment in China, aged ≥ 60 years, had a history of ischemic stroke and experienced dementia within 5 months of onset and had complete data were included in this study. Patients with a history of depression or schizophrenia, a history of allergy to choline drugs, the presence of cognitive impairment or dementia attributable to traumatic brain injury, Parkinson's disease, Alzheimer's disease, etc. and with severe organ dysfunction were excluded from the present study.

A retrospective analysis was conducted on 120 elderly VD patients. There were 68 males and 52 females, aged 60-78 years (mean: 67.58± 5.35 years) and the disease course was 5-23 months (mean: 13.84±5.27 months), and their lesion involving thalamus reported in 13 cases, hemispheric white matter in 19 cases, internal capsule and basal ganglia in 29 cases, cortex in 40 cases, multiple cavity cerebral infarction in 19 cases; the severity was classified as severe in 16 cases, moderate in 37 cases, and mild in 67 cases. The trial was conducted in the time frame of February 2018 and March 2020. These patients were assigned into two groups (each with 60 cases) according to treatment methods. The baseline information was homogenous in the two groups (**Table 1**) ($P > 0.05$). This study has obtained the approval form the ethic committee prior to initiation, and the written informed consent was provided by the participants.

Methods

Patients in the two groups underwent conventional treatment with respect to trophic nerve, anti-platelet aggregation, cerebral circulation, blood pressure and blood glucose.

The control group was administered orally with huperzine A, 0.1 mg/time, 2 times/day (SFDA approval number: H20094206; manufacturer: Zhejiang Qianjin Pharmaceuticals). These patients in the observation group were treated with huperzine A (the mode of administration was identical to that of the control group) combined with hyperbaric oxygen. The medical air pressurized chamber was provided by Yantai Hongyuan Oxygen Industrial Co., Ltd., with the decompression time of 20-25 min, the pressurization time of 15-20 min, the pressure of 0.2 MPa, and the stable pressure oxygen inhalation time of 60 min, and it was maintained for 30 min once a day. Both groups were continuously treated for four weeks.

Observation indicators

① HDS-R scores [6] was assessed before treatment and at 2 and 4 weeks after treatment, and < 10 points was defined as dementia, 10.5-21.5 points as pre-dementia, 22-30.5 points as subnormal, and 31 points as normal.

② MMSE scores [7] were compared with respect to five dimensions (memory and attention, memory, recall, orientation, language ability). 0-30 points was considered normal. Higher scores indicate better cognitive function status.

③ Vascular endothelial growth factor (VEGF), anti-apoptotic factor (Livin) and hypoxia-inducible factor-1α (HIF-1α) were compared. 3 ml of peripheral cubital venous blood was drawn from the subjects before and 2 and 4 weeks after treatment. Next, and the serum was separated and then centrifuged for 10 min at 2500 r/min with a radius of 12 cm. VEGF, Livin, and HIF-1α levels were measured by the enzyme-linked immunosorbent assay using an automatic biochemical analyzer provided by Tainuo Science and Technology Trading Co., Ltd.

④ DCR was compared. Patients who were able to engage in general social activities, responsive, and conscious, and all symptoms disappeared were considered well-controlled.

Table 1. Comparison of general data [n; %]

Indicator		Observation group (n = 60)	Control group (n = 60)	X^2/t	*P* value
Age (year)		67.67±5.13	67.29±5.26	0.401	0.689
Disease duration (M)		13.69±5.46	13.55±5.33	0.142	0.887
Gender	Male	35 (58.33)	33 (55.00)	0.136	0.713
	Female	25 (41.67)	28 (46.67)		
Lesions	Thalamus	6 (10.00)	7 (11.67)	0.217	0.642
	Hemispheric white matter	10 (16.67)	9 (15.00)		
	Internal capsule and basal ganglia	15 (25.00)	14 (23.33)		
	Cortex	20 (33.33)	20 (33.33)		
	Multiple cavity cerebral infarction	9 (15.00)	10 (16.67)		
Severity	Severe	9 (15.00)	7 (11.67)	0.508	0.476
	Moderate	17 (28.33)	20 (33.33)		
	Mild	34 (56.67)	33 (55.00)		

Table 2. Comparison of HDS-R scores (points)

Group	n	Before treatment	2 weeks after treatment	4 weeks after treatment	$F_{time\text{-}point}$	$F_{interaction}$	$F_{intergroups}$
Observation group	60	9.35±1.45	19.86±2.39*	25.44±2.74*,#	5243.155	114.298	73.185
Control group	60	9.42±1.32	15.43±2.15*	21.37±2.52*,#			
t value		0.277	10.674	8.469			
P value		0.783	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Notes: Compared with that before treatment, *$P < 0.05$; compared with that at 2 weeks after treatment, #$P < 0.05$.

Statistical methods

The statistical analysis was done using SPSS 22.0 software. Enumeration data were represented as (n, %), and χ^2 test or generalized estimating equation (GEE) analysis was performed. Measurement data were represented as ($\bar{x} \pm s$), and independent sample t-test was conducted. Repeated measures analysis of variance was used to examine the difference in various time points and groups. LSD-t test was employed for pairwise comparison. A *P*-value of < 0.05 was considered for statistical significance. HDS-R score and MMSE score were plotted using the GraghpadPrism8.0 software.

Results

Comparison of HDS-R scores between the two groups

Repeated measures analysis observed statistical differences in HDS-R scores between groups, different time points, and interactions. No statistical difference was observed in HDS-R score before treatment (P > 0.05), while the HDS-R score increased after treatment in both groups, and the observation group showed comparatively higher HDS-R score at various time points after treatment (P < 0.05) (**Table 2**; **Figure 1**).

Comparison of MMSE scores between the two groups

We observed no statistical difference in MMSE score before treatment (P > 0.05). The MMSE score increased after treatment when compared to that before treatment in both groups, and the observation group showed a more significant increase when compared against the control group (P < 0.05) (**Table 3** and **Figure 2**).

Comparison of serum indicators between the two groups

VEGF, Livin, and HIF-1α levels before treatment were basically the same in the two groups (P > 0.05). All serum indicators improved after treatment in both groups, and VEGF, Livin, and HIF-1α at 2 and 4 weeks after treatment in the observation group showed a significant impro-

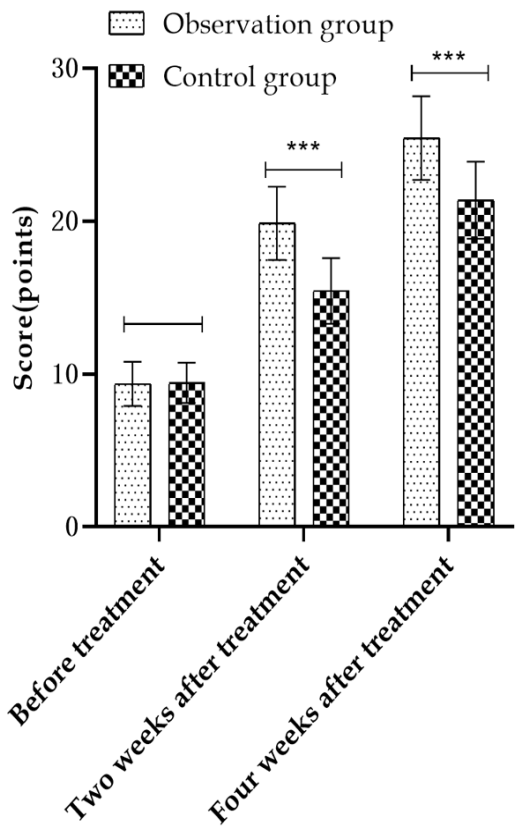

Figure 1. Comparison of HDS-R scores at different times. Note: ***P < 0.001.

vement as compared with the control group (P < 0.05) (**Table 4**).

Comparison of DCR between the two groups

Repeated variance measure showed that Wald χ^2 = 7.730, P = 0.005, with statistical difference (P < 0.05), OR = e0.976 = 2.653, 95% confidence interval (CI) (e0.288, e1.664) = (0.783, 4.523), suggesting that DCR at 1, 2 and 4 weeks after treatment in the observation group was remarkably higher (X^2 = 4.062, P = 0.044), (X^2 = 4.728, P = 0.030) and (X^2 = 8.107, P = 0.004); in addition, Wald χ^2 = 58.405, P = 0.000 was observed in terms of time points (P < 0.05), suggesting that DCR at various time points was statistically different (**Tables 5** and **6**).

Discussion

VD can lead to massive destruction of brain tissue due to insufficient synthesis and release of acetylcholine, which in turn results in acute ischemia and hypoxia, often manifested as a decline in cognitive function, memory, language, and emotional ability. It is thus urgent to stabilize and improve the metabolic function of the acetylcholine system in the brain tissue [8]. Huperzine A is a reversible cholinesterase inhibitor, and characterized by easy penetration of blood-brain barrier, high lipid solubility and high biological activity. After entering the center, it spreads across brain regions (frontal lobe, temporal lobe and hippocampus) which are closely related to memory and learning by facilitating the enhancement of neuronal excitation and conduction, increasing the content of acetylcholine. However, some scholars pointed out that this drug performs poorly on the elderly population and is not beneficial for prognosis [9]. Hyperbaric oxygen is a breakthrough in the area of medical therapy. It plays a positive role in improving the clinical symptoms caused by hypoxia, rapidly eliminating hypoxia, protecting cranial nerves and reducing hypoxic-ischemic injury of brain tissue, inhibiting thrombosis and promoting the recovery of zymogen system function [10].

HDS-R score and MMSE score are commonly used to assess the prognosis of VD patients, and may reflect the current recovery of neurological and cognitive function. In this study, the HDS-R score and MMSE score after treatment increased compared with those before treatment, indicating that huperzine A could strengthen brain memory and cognitive function to a certain extent and improve brain nerve function. Moreover, we found that the observation group had higher HDS-R score and MMSE score compared against the control group at 2 and 4 weeks after treatment. It can be assumed that the addition of hyperbaric oxygen to huperzine A was in favor of the recovery of neurological function. It is presumably due to the fact that hyperbaric oxygen can reduce the damage to the body owing to hypoxia, facilitate the improvement of neurological function, and intensify the cognitive function and memory of the brain and speed up the recovery of neurological function of the brain by acting on multiple key neurological function areas. Hyperbaric oxygen plus huperzine A is speculated to raise the concentration of cholinergic transmitters in the synaptic cleft, inhibit acetylcholine activity, and promote the excitation and conduction of cholinergic neurons, taken together, cognitive

Table 3. Comparison of MMSE scores (points)

Group	n	Before treatment	2 weeks after treatment	4 weeks after treatment	$F_{time\text{-}point}$	$F_{interaction}$	$F_{intergroups}$
Observation group	60	13.68±1.27	18.95±2.34*	25.15±1.63*,#	6392.277	84.060	43.304
Control group	60	13.52±1.31	16.68±2.12*	22.63±1.74*,#			
t value		0.679	5.569	8.187			
P value		0.498	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Notes: Compared with that before treatment, *P < 0.05; compared with that at 2 weeks post-treatment, #P < 0.05.

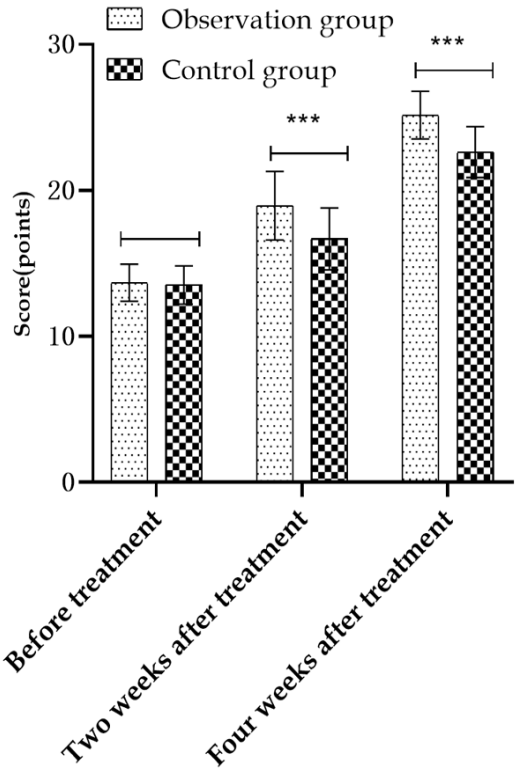

Figure 2. Comparison of MMSE scores at various time points. Note: ***P < 0.001.

function would be promoted [11]. Furthermore, we found that the DCR in the observation group was much higher than that in the control group at 1, 2 and 4 weeks after treatment, which suggested that hyperbaric oxygen combined with huperzine A contributed to the recovery of the disease. The following factors may explain the findings: (1) hyperbaric oxygen could accelerate the recovery of vasomotor function, improve tissue hypoxia-ischemia, and better reduce the toxic effect of hypoxic free radicals on neurological function; (2) hyperbaric oxygen could heighten tissue oxygen supply and neuroglobin levels, speed up glucose metabolism, ensure adequate oxygen supply to the brain, and improve cranial nerve injury caused by ischemia; (3) hyperbaric oxygen could prevent thrombosis, advance the recovery of the fibrinolytic system, and help nerve recovery and regeneration. Hyperbaric oxygen plus huperzine A was shown to penetrate the blood-brain barrier, distribute in the hippocampus, temporal lobe and other parts, and upgrade self-care ability [12].

In recent years, hyperbaric oxygen therapy has been widely used in clinics, ushering a broad medical space for the treatment of diseases. Through oxygen supply, the blood oxygen content of the human body can reach ten times that of normal conditions, which is beneficial to quickly eliminate body deficiency to improve the clinical symptoms caused by hypoxia [13]. Clinical trials have shown that the protective effect of hyperbaric oxygen on cranial nerves is mainly accomplished through the following mechanisms: (1) Restore vasomotor function. Cerebral hypoxia caused by cerebrovascular disease disrupts the dynamic balance between vasoconstriction and diastolic function, resulting in paralytic expansion of microvasculature in brain tissue. Hyperbaric oxygen treatment can increase the expression of carbon monoxide and neuropeptide Y1236 in the tissue, which can then be used to a certain extent improve the hypoxic-ischemic state of tissues and promote the recovery of vasomotor function [14]; (2) Inhibit inflammation and reduce the toxic effects of oxygen free radicals on nerves; (3) Increase oxygen supply and increase glucose metabolism rate. Animal experiments found that hyperbaric oxygen can increase the expression of brain globin, which has the ability to carry oxygen, so it can increase tissue oxygen supply and help reduce the damage of hypoxia-ischemia to brain neurons [15]; (4) Inhibit cells apoptosis, promote nerve regeneration and recovery; (5) Promote the recovery of fibrinolytic system and inhibit thrombosis. In

Table 4. Comparison of serum indicators

Indicator	Group	n	Before treatment	2 weeks after treatment	4 weeks after treatment	$F_{time\text{-}point}$	$F_{interaction}$	$F_{intergroups}$
VEGF (pg/mL)	Observation group	60	586.45±24.15	708.95±31.57*	934.54±35.21*,#	12140.222	517.733	163.586
	Control group	60	586.31±24.68	654.28±28.94*	815.24±29.55*,#			
	t value		0.031	9.888	20.104			
	P value		0.975	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Livin (μmol/L)	Observation group	60	6.12±1.38	10.38±1.86*	13.54±1.57*,#	2369.534	82.198	23.180
	Control group	60	6.23±1.41	8.95±1.54*	11.32±1.62*,#			
	t value		0.432	4.587	7.623			
	P value		0.667	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
HIF-1α (pg/mL)	Observation group	60	385.45±26.95	314.22±19.84*	285.65±15.22*,#	1298.147	64.405	65.732
	Control group	60	385.62±26.43	356.77±21.19*	322.18±19.86*,#			
	t value		0.035	11.354	11.309			
	P value		0.972	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Notes: Compared with that pre-treatment, *P < 0.05; compared with that at 2 weeks post-treatment, #P < 0.05.

Table 5. Comparison of disease control rate after treatment between the two groups [n; %]

Group	n	DCR		
		1 week after treatment	2 weeks after treatment	4 weeks after treatment
Observation group	60	38 (63.33)	47 (78.33)	59 (98.33)
Control group	60	27 (45.00)	36 (60.00)	50 (83.33)
χ^2 value	-	Wald χ^2_{group} = 7.730, Wald $\chi^2_{time\text{-}point}$ = 58.405		
P value	-	P_{group} = 0.005, $P_{time\text{-}point}$ < 0.001		

Table 6. GEE of DCR after treatment in the two groups

Parameters	B	Standard error	95% Wald CI		Hypothesis test		
			Lower limit	Upper limit	Wald x^2 value	variance	P
(Intercept)	1.901	0.3658	1.184	2.618	26.993	1	< 0.001
Observation group	0.976	0.3511	0.288	1.664	7.730	1	0.005
Control group	0[a]	.	.	.	.	.	.
1 week after treatment	-2.212	0.2988	-2.797	-1.626	54.779	1	< 0.001
2 weeks after treatment	-1.535	0.2797	-2.083	-0.987	30.115	1	< 0.001
4 week after treatment	0[a]	.	.	.	.	.	.

Notes: dependent variable: blood glucose compliance rate; model: (intercept), group, time point; [a]indicates that it is set as zero, because this parameter is redundant.

the treatment of human endothelial cells with hyperbaric oxygen, it is found that hyperbaric oxygen can increase the expression of tissue plasminogen activator gene, thereby restoring the function of the plasminogen system, which is beneficial to inhibit thrombosis and reduce hypoxic-ischemic damage of brain tissue. At present, hyperbaric oxygen has been widely used in the treatment of VD, and studies have confirmed that the combination of hyperbaric oxygen on the basis of Huperzine A therapy can make VD patients more benefit [16].

Over the years, multiple studies have found that acute ischemic state of the brain is associated with the increase in risk of dementia, and VEGF serves as a mirror of the blood supply of brain tissue after injury. To our best knowledge, livin is strongly connected to the incidence of dementia and is involved in vascular injury. Additionally, HIF-1α could participate in the ischemic and hypoxic response of brain tissue and is a sensitive factor of hypoxic response [17]. In this study, the authors found that VEGF, Livin, and HIF-1α levels in the observation

group were superior to that in the control group at different time points after treatment, showing that hyperbaric oxygen combined with huperzine A has numerous benefits regarding neuronal regeneration, protecting and nourishing nerves, and ameliorating cognitive function. It might be contributed to the mechanism of action of these two treatment modalities. It is important to note that hyperbaric oxygen was found to enhance the tolerance of the brain to local hypoxia and ischemia, improve the state of ischemia and hypoxia, restore normal cerebral blood flow, and then regulate VEGF and HIF-1α expression. Importantly, hyperbaric oxygen combined with huperzine A was documented to reduce the damage to neurons resulting from hypoxia-ischemia, increase tissue oxygen supply, and promote nerve recovery and regeneration [18-21].

In summary, we recommend huperzine A combined with hyperbaric oxygen a preferable option for elderly VD patients. However, due to the limited sample size in this study, there might be bias in the data which need be further investigated.

Disclosure of conflict of interest

None.

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