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Protective Effect of Hyperbaric Oxygen Therapy on Cognitive Function in Patients with Vascular Dementia

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Abstract

Recent studies have shown that hyperbaric oxygen (HBO) has a therapeutic effect on vascular dementia (VD); however, the exact mechanism remains unclear. This article aims to reveal the protective effects and underlying mechanisms of HBO on VD. A total of 158 patients with VD were prospectively included in the study and were randomly divided into control group and HBO group. The control group was given conventional treatment and the HBO group was treated with HBO in addition to conventional treatment. The following HBO protocol was practiced: 5 days per week, 60 min each, 100% oxygen at 2 standard atmospheric pressures for 12 weeks. The Mini-Mental State Examination (MMSE) scores and serum Humanin levels were detected before and after treatments in both groups. The baseline characteristics were not different dramatically between groups ($p > 0.05$). There was no significant difference in MMSE scores and serum Humanin levels between the two groups before treatment ($p > 0.05$). After treatment, compared with the control group, the MMSE scores and serum Humanin levels in the HBO group were significantly increased ($p < 0.05$). Spearman correlation analysis showed that the serum Humanin levels were positively correlated with MMSE scores ($r = 0.409$, $p < 0.05$) and this correlation was independent of baseline characteristics ($\beta = 0.312$, $p < 0.05$). HBO therapy can improve cognitive function in patients with VD, and its mechanism may be related to elevated serum Humanin levels.

Keywords

vascular dementia, hyperbaric oxygen, cognitive function, humanin

Introduction

According to the World Health Organization, there are currently about 36 million dementia patients worldwide, and this number will reach 66 million and 115 million by 2030 and 2050, respectively[1,2]. Vascular dementia (VD) is the second largest type of dementia in the world after Alzheimer's disease (AD), accounting for about 20% of cases of dementia[3]. Epidemiological studies have shown that the incidence of VD in the elderly over 65 years old is 5–10%[4,5]. The incidence of VD increases exponentially with age, and it is estimated that the incidence doubles every 5.3 years[6]. VD seriously affects patients' quality of life, and the cost of treatment for dementia is enormous, which places a heavy burden on society and families[7]. With the increase in human life expectancy, VD has gradually received attention as a public health problem.

Hyperbaric oxygen (HBO) therapy is the inhalation of 97–100% oxygen above a standard atmospheric pressure in

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a compression chamber, which is generally considered safe and effective between 1.5 and 3.0 standard atmospheres[8,9]. HBO was first recommended as a treatment 40 years ago, and now has been applied to treat a variety of diseases[10]. HBO has not been recommended as a treatment for VD in the available guideline until now. Interestingly, a study from China has shown that HBO is effective in treating VD[11]. A recent meta-analysis also suggested that HBO therapy can be recommended as an effective and safe complementary therapy for the treatment of VD[12]; however, the exact mechanism is still unclear.

Humanin is a 24-amino acid secreted bioactive peptide, which was first identified in the brains of patients diagnosed with AD in 2001[13,14]. Humanin is widely distributed in blood vessel walls, neurons, skeletal muscle, and peripheral blood, and has anti-apoptotic, metabolic, and anti-inflammatory effects[15]. Multiple studies have shown that Humanin is closely related to the pathogenesis of cognitive impairment[16]. Moreover, we found that Humanin played a neuroprotective role in a rat model of VD previously[17]. However, the relation between Humanin and cognitive functions in VD patients are still unclear. We predict that HBO therapy may improve cognitive function in patients with VD, and Humanin may play an important role in this. If this assumption is confirmed, it will be of great significance.

Materials and Methods

Participants

A total of 158 patients with VD who were hospitalized in Taian City Central Hospital, Taian, Shandong Province, China, from April 2016 to April 2018 were prospectively enrolled. All patients met the diagnostic criteria for VD according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[16] and National Institute for Neurological Disorders and Stroke (NINDS-AIREN)[18]. Patients suffering from other types of dementia, mental illness, brain trauma, severe systemic diseases involving organs such as heart, liver and kidney, and tumor diseases and taking drugs that affect cognitive function were excluded. Patients with VD were randomized into the control group and the HBO treatment group by the random number table method. Patients' clinical baseline data were collected including age, gender, education, body mass index (BMI), hypertension, diabetes, hyperlipidemia, drinking status, and smoking status. Both groups of patients were informed and consented to undergo relevant examinations. This study complies with the Helsinki Declaration and is approved by the Ethics Committee of Taian City Central Hospital, Shandong First Medical University & Shandong Academy of Medical Sciences.

Hyperbaric Oxygen Treatment

Patients in the control group were treated with donepezil hydrochloride (Eisai Chemicals Co., Ltd., Ibaraki, Japan), 5 mg/d, orally before bedtime. HBO treatment group patients were given HBO therapy in addition to donepezil hydrochloride. HBO treatment was carried out in a multiplane hyperbaric chamber once a day, 5 days per week. The treatment protocol consisted of 60 min periods of inhalation of 100% oxygen at a pressure of 2.0 standard atmospheric pressures, interspersed with 2 "air breaks," lasting 5 min, after each 30 min of inhalation.

Cognitive Function Testing

Cognitive function was assessed by Mini-Mental State Examination (MMSE) before the treatment and on the second day after 12 weeks of treatment. The MMSE is one of the most popular cognitive function screening tools. MMSE scores were measured before and after treatment in both groups. MMSE comprises seven sections including time orientation, location orientation, immediate memory, attention and computational power, delayed memory, language, and visual space. The MMSE scale has a total of 30 questions, with a total score of 30, and low MMSE scores indicate poor cognitive function[19]. The MMSE scale is tested under standard conditions with an average of 15 min, and a score less than 24 points is considered to reflect a decline in cognitive function[20]. Since 1988 a Chinese version of MMSE has been widely used in China, and a cutoff of 24 provided 100% sensitivity and 71.4% specificity[21]. The attending physicians were blinded to the baseline data of patients.

Testing of Serum Humanin Levels

All subjects were examined after overnight fasting for at least 8 h before and after treatment in both groups. Serum Humanin levels were detected before the treatment and on the second day after 12 weeks of treatment. A total of 5 ml of blood was drawn into an EDTA-containing tube and was centrifuged for 15 min at 3000 *g*. The serum was obtained and stored at $-80^{\circ}C$ for analysis. Humanin concentrations were measured by a commercial ELISA reagent kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) in strict accordance with the instructions, and was completed by the Central Laboratory of Taian City Central Hospital.

Statistical Analysis

Continuous variables were summarized as means $\pm$ standard deviation (SD) and categorical variables were summarized as frequency and percentages. Differences between control group and treatment group were examined using Student's *t*-test and χ^2 test for continuous variables and categorical variables, respectively. The correlation between MMSE scores and different variables was examined using Spearman correlation analysis. Logistic regression was applied to evaluate the contribution to the variables on MMSE scores. The SPSS statistical package for Windows version 20.0 (SPSS Inc. Chicago, IL, USA) was used for data analysis, and $p < 0.05$ was considered statistically significant.

Table 1. Baseline Characteristics of VD Patients.

Characteristics	Control group (n=79)	Treatment group (n=79)	p
Age, years	67.8 ± 7.1	69.2 ± 8.4	0.260
Sex, male/ female	42/37	44/35	0.873
Education, years	9.1 ± 2.6	9.3 ± 2.3	0.609
BMI, kg/m^2	24.9 ± 1.5	24.6 ± 1.7	0.241
HP, n (%)	26 (32.9%)	20 (25.3%)	0.381
HL, n (%)	19 (24.1%)	28 (35.4%)	0.164
Diabetes, n (%)	20 (25.3%)	15 (19.0%)	0.443
Smokers, n (%)	8 (10.1%)	5 (6.3%)	0.563
Alcohol, n (%)	7 (8.9%)	9 (11.4%)	0.792

BMI: body mass index; HL: hyperlipidemia; HP: hypertension.

Table 2. Patient's MMSE Scores and Serum Humanin Levels.

Variables		Control group (n=79)	Treatment group (n=79)	p
MMSE	Before treatment	18.28 ± 2.32	18.09 ± 2.58	0.627
	After treatment	20.06 ± 2.75	21.68 ± 2.36	< 0.001
Humanin (pg./ml)	Before treatment	126.3 ± 7.0	124.8 ± 6.2	0.156
	After treatment	143.1 ± 8.6	146.5 ± 9.4	0.019

Results

From April 2016 to April 2018, 158 VD patients were consecutively included in the study. VD patients were randomly divided into the control group and HBO treatment group. At baseline, the two groups were generally similar in age, sex, education, BMI, hypertension, diabetes, hyperlipidemia, and tobacco and alcohol intake. A comparison of baseline characteristics is summarized in Table 1.

The MMSE scale was used to measure patients' cognitive function. There was no significant difference in the MMSE scores between the two groups before treatment ($p > 0.05$). However, compared with the control group, the MMSE scores of the HBO treatment group were significantly higher after treatment and the difference was statistically significant ($p < 0.05$). Similarly, there was no significant difference in serum Humanin levels between the two groups before treatment ($p > 0.05$). Serum Humanin levels in the HBO treatment group were significantly higher than in the control group after treatment, and the difference was statistically significant ($p < 0.05$). The comparisons of MMSE scores and serum Humanin levels are summarized in Table 2.

The results of Spearman correlation analysis and logistic regression analysis between MMSE scores and variables in VD patients are presented in Table 3 and Table 4, respectively. Spearman correlation analysis showed a positive association between MMSE scores and serum Humanin levels in VD patients ($r = 0.409$, $p = 0.012$). The results of logistic regression analysis indicated that there was also a positive correlation between MMSE scores and serum Humanin levels after adjusting for confounding factors in VD patients ($\beta = 0.312$, $p = 0.002$). However, there was no significant correlation between MMSE scores and baseline variables including age, sex, education, BMI, hypertension, diabetes, hyperlipidemia, and tobacco and alcohol intake ($p > 0.05$).

Table 3. Spearman Correlation Analysis between MMSE Scores and Variables.

Variables	r	p-value
Age	0.132	0.116
Sex	0.157	0.208
Education	0.271	0.355
BMI	0.183	0.247
HP	0.235	0.398
HL	0.214	0.289
Diabetes	0.256	0.343
Smokers	0.281	0.336
Alcohol	0.242	0.179
Humanin	0.409	0.012

BMI: body mass index; HL: hyperlipidemia; HP: hypertension.

Table 4. Logistic Regression Between MMSE Scores and Variables.

	Standardized Coefficients		95% CI for B	
model	Beta	p	Lower Bound	Upper Bound
Age	–0.182	0.307	0.136	0.397
Gender	–0.147	0.111	0.062	0.091
Education	0.160	0.468	0.109	0.211
BMI	–0.103	0.240	0.163	0.284
HP	–0.125	0.237	0.227	0.356
HL	0.024	0.335	0.152	0.249
Diabetes	0.173	0.153	0.122	0.239
Smokers	–0.120	0.183	0.231	0.397
Alcohol	–0.135	0.126	0.184	0.408
Humanin	0.312	0.002	0.036	0.259

BMI: body mass index; HL: hyperlipidemia; HP: hypertension.

Discussion

In the current study, the differences of cognitive function and serum Humanin levels in VD patients between control group and HBO group were examined. Our results indicated that in HBO therapy group VD patients have significantly higher MMSE scores and serum Humanin levels. Our study indicated that HBO therapy might contribute to the improvement of cognitive function, and there existed a possible link between serum Humanin levels and cognitive function in VD. We further evaluated the correlation between MMSE scores and serum Humanin levels. The results indicated that

there was a positive correlation between MMSE scores and serum Humanin levels in VD patients, and the association was significant even after adjusting for baseline variables. To the best of our knowledge, there have been few reports on the correlation between serum Humanin levels and cognitive function in patients with VD.

Numerous studies have shown that HBO has a therapeutic effect on dementia[22]. In a mouse model of AD, Shapira et al. found that HBO therapy can improve cognitive function by reducing neuroinflammation[23]. In a rat model of AD, Zhao et al. showed that HBO therapy can reduce hippocampal neuronal apoptosis and thus improve cognitive function by reducing phosphorylation of the P38 MAPK signaling pathway[24]. In addition to AD, HBO therapy can also improve cognitive function in VD. One study revealed that HBO therapy can improve the blood supply and promote neurogenesis in the piriform cortex of VD rats[25]. The above studies show that HBO therapy can improve cognitive function, consistent with the conclusions of our current study. However, previous research on HBO treatment for dementia mainly focuses on animal experiments, and there are few clinical reports.

HBO can improve the cognitive function of VD; nevertheless, its underlying mechanism remains unclear[26]. Humanin is a novel neuroprotective peptide discovered in recent years, and has protective effects against various neurological diseases[14]. One study showed that Humanin can improve the cognitive function of APP/PS1 double transgenic mice by reducing insulin resistance and activating autophagy[27]. Another study reported that Humanin can attenuate the toxicity of NMDA to cortical neurons by improving mitochondrial function in vitro[28]. In addition, studies have suggested a neuroprotective role for Humanin against Aβ and some other insults[29,30]. Previously we have found that Humanin plays a neuroprotective role in a rat model of VD[17,31]. Different from previous studies, in the current study we found that HBO treatment can increase serum Humanin levels in VD, and the serum Humanin levels are positively correlated with the MMSE scores, suggesting that HBO might exert neuroprotective effects by elevating the serum Humanin levels. As far as we know, no clinical studies have been published on the correlation between Humanin and VD to date.

There are some limitations in our study. First, the number of VD patients included in our study is relatively small. Second, we did not correct the interference of recently taking medicine on cognitive function and serum Humanin levels. Third, dynamic changes in serum Humanin levels during treatment were not detected. Fourth, the course of VD was not available. Finally, we did not use a sham intervention in our current study, which also lacked allocation concealment and results over longer periods. However, our research still has important implications for the treatment of VD. This study suggests that the therapeutic effect of HBO on VD may be related to elevated serum Humanin levels. If confirmed by future well-designed controlled trials with larger sample sizes, it may present a novel therapeutic target for disease modification during the progression of VD.

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Ethical Approval

This study was approved by Ethics Committee of Taishan Medical University Affiliated Taishan Hospital, Shandong Province, China.

Statement of Human and Animal Rights

Human specimens were tested in accordance with our institutional review board guidelines [2016]2016-01-6.

Statement of Informed Consent

We obtained the patients' informed consent for this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013;9(1):63–75.e2.
2. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 2012;4(5):40.
3. O'Brien JT, Thomas A. Vascular dementia. Lancet. 2015; 386(10004):1698–1706.
4. Dichgans M, Leys D. Vascular cognitive impairment. Circ Res. 2017;120(3):573–591.
5. Yassuda MS, Grinberg LT. Vascular cognitive impairment. Dement Neuropsychol. 2017;11(4):335.
6. O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry. 2006;14(9):724–733.
7. Shah H, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, Chan KY, Joanette Y, Prince M, Rossor M, Saxena S. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol. 2016;15(12):1285–1294.
8. Yan L, Liang T, Cheng O. Hyperbaric oxygen therapy in China. Med Gas Res. 2015;5(1):3.
9. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011;127(suppl 1):131s–141s.

10. Lamm K, Lamm H, Arnold W. Effect of hyperbaric oxygen therapy in comparison to conventional or placebo therapy or no treatment in idiopathic sudden hearing loss, acoustic trauma, noise-induced hearing loss and tinnitus. A literature survey. Adv Otorhinolaryngol. 1998;54:86–99.
11. Wang SP, Tao Z, Ding SJ, Cheng JC, Yu BS, Wang YQ. Hyperbaric oxygen combined with donepezil in the treatment of vascular dementia. Chinese J Physical Med Rehabilitat. 2009, 31(7):478–480.
12. You Q, Li L, Xiong SQ, Yan YF, Li D, Yan NN, Chen HP, Liu YP. Meta-analysis on the efficacy and safety of hyperbaric oxygen as adjunctive therapy for vascular dementia. Front Aging Neurosci. 2019;11:86.
13. Zapala B, Kaczynski L, Kiec-Wilk B, Staszel T, Knapp A, Thoresen GH, Wybranska I, Dembinska-Kiec A. Humanins, the neuroprotective and cytoprotective peptides with antiapoptotic and anti-inflammatory properties. Pharmacol Rep. 2010; 62(5):767–777.
14. Lee C, Yen K, Cohen P. Humanin: a harbinger of mitochondrial-derived peptides? Trends Endocrinol Metab. 2013;24(5):222–228.
15. Matsuoka M. Protective effects of Humanin and calmodulin-like skin protein in Alzheimer's disease and broad range of abnormalities. Mol Neurobiol. 2015;51(3):1232–1239.
16. Mahboobi H, Golmirzaei J, Gan SH, Jalalian M, Kamal MA. Humanin: a possible linkage between Alzheimer's disease and type 2 diabetes. CNS Neurol Disord Drug Targets. 2014;13(3): 543–552.
17. Zhang XP, Zhang QL, Du YF. A novel rattin expression in the brain of the rat model of patients' vascular dementia. J Neurol Sci Turkish. 2013;30(2):249–256.
18. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6(8):734–746.
19. Xu Y, Wang Q, Liu Y, Cui R, Lu K, Zhao Y. Association between Helicobacter pylori infection and carotid atherosclerosis in patients with vascular dementia. J Neurol Sci. 2016;362:73–77.
20. Xu Y, Wang Q, Liu Y, Cui R, Zhao Y. Is Helicobacter pylori infection a critical risk factor for vascular dementia? Int J Neurosci. 2016;126(10):899–903.
21. Katzman R, Zhang MY, Ouang Ya Q, Wang ZY, Liu WT, Yu E, Wong SC, Salmon DP, Grant I. A Chinese version of the Mini-Mental State Examination; impact of illiteracy in a Shanghai dementia survey. J Clin Epidemiol. 1988;41(10): 971–978.
22. Carney AY. Hyperbaric oxygen therapy: an introduction. Crit Care Nurs Q. 2013;36(3):274–279.
23. Shapira R, Solomon B, Efrati S, Frenkel D, Ashery U. Hyperbaric oxygen therapy ameliorates pathophysiology of 3xTg-AD mouse model by attenuating neuroinflammation. Neurobiol Aging. 2018;62:105–119.
24. Zhao B, Pan Y, Wang Z, Xu H, Song X. Hyperbaric oxygen pretreatment improves cognition and reduces hippocampal damage via p38 mitogen-activated protein kinase in a rat model. Yonsei Med J. 2017;58(1):131–138.
25. Zhang T, Yang QW, Wang SN, Wang JZ, Wang Q, Wang Y, Luo YJ. Hyperbaric oxygen therapy improves neurogenesis and brain blood supply in piriform cortex in rats with vascular dementia. Brain Inj. 2010;24(11):1350–1357.
26. Xiao Y, Wang J, Jiang S, Luo H. Hyperbaric oxygen therapy for vascular dementia. Cochrane Database Syst Rev. 2012;7: Cd009425.
27. Han K, Jia N, Zhong Y, Shang X. S14G-humanin alleviates insulin resistance and increases autophagy in neurons of APP/PS1 transgenic mouse. J Cell Biochem. 2018;119(4): 3111–3117.
28. Cui AL, Zhang YH, Li JZ, Song T, Liu XM, Wang H, Zhang C, Ma GL, Zhang H, Li K. Humanin rescues cultured rat cortical neurons from NMDA-induced toxicity through the alleviation of mitochondrial dysfunction. Drug Des Devel Ther. 2017;11: 1243–1253.
29. Yuan L, Liu XJ, Han WN, Li QS, Wang ZJ, Wu MN, Yang W, Qi JS. [Gly14]-humanin protects against amyloid beta peptide-induced impairment of spatial learning and memory in rats. Neurosci Bull. 2016;32(4):374–382.
30. Murakami M, Nagahama M, Maruyama T, Niikura T. Humanin ameliorates diazepam-induced memory deficit in mice. Neuropeptides. 2017;62:65–70.
31. Liu W, Zhang XP, Yang DL, Song SW. Humanin attenuated the change of voltage-dependent potassium currents in hippocampal neurons induced by anoxia. CNS Neurosci Ther. 2014; 20(1):95–97.