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Original Article

The effects of combined hyperbaric oxygen therapy on patients with post-stroke depression

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Abstract. [Purpose] To observe the effect of combined hyperbaric oxygen therapy on patients with post-stroke depression. [Subjects] Ninety patients with post-stroke depression were randomly divided into 3 groups: fluoxetine treatment group (n = 30), hyperbaric oxygen therapy group (n = 30), and hyperbaric oxygen combined treatment group (n = 30). [Methods] Fluoxetine treatment group received anti-depression drugs (fluoxetine, 20 mg/day), hyperbaric oxygen therapy group received hyperbaric oxygen (once a day, 5 days/week), hyperbaric oxygen combined treatment group received fluoxetine and hyperbaric oxygen treatments as described above. All patients received routine rehabilitation therapy. Hamilton Depression Scale (HAMD), and Scandinavian Stroke Scale (SSS) scores were evaluated before and at the end of 4th week. The total effective rate of depression release between the 3 groups was also compared at the end of study. [Results] The end scores of HAMD and SSS in the 3 groups were significantly lower than those before treatment. The total effective rate of combined hyperbaric oxygen therapy group after treatment was higher than the other two groups. [Conclusions] Combined hyperbaric oxygen therapy plays an important role in the treatment of patients with post-stroke depression. The total effective rate of combined hyperbaric oxygen therapy was higher than other routine anti post-stroke depression treatments.
Key words: Hyperbaric oxygen therapy, Post-stroke depression, Fluoxetine

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INTRODUCTION

Depression is a frequent and important problem in patients after stroke. Post-stroke depression (PSD) has been estimated to occur in 33% of patients in the acute stage and in 34% of patients over long term after stroke[1)]. PSD not only aggravates the cognitive impairment in patients, but also affects their quality of life, hinders the recovery of nerve function, and markedly increases the mortality rate[2)]. Hence, post-stroke depression has a negative impact on functional recovery. At present, there are many drugs for treating depression, each with their own advantages. In the last 20 years, there has been great progress in the research on antidepressants, however 15–33% of patients with depression have been identified as insensitive to drug treatments[3)].

Hyperbaric oxygen therapy (HBOT) is valuable in treating acute carbon-monoxide (CO) poisoning and air or gas embolism. HBOT can lead to significant neurological improvement in after stroke even at chronic late stages[4)]. HBOT-induced neuroprotection enhances neuronal viability via increased tissue oxygen delivery to the area with diminished blood flow, thus reducing brain edema and improving metabolism after ischemia[5)]. It also could up-regulate the expression of glial derived neurotrophic factor (GDNF) and nerve growth factor (NGF)[6)]. A recent study has shown that HBOT is able to significantly improve the degree of depression in the convalescent stage following cerebral hemorrhage, and promote nerve function recovery[7)]. However, a more pronounced effect of combined hyperbaric oxygen therapy with anti-depression drugs on patients with post-stroke depression is not reported. The aim of the current study was to evaluate the effects of HBOT with anti-depression drugs on patients with depression after stroke.

SUBJECTS AND METHODS

Subjects

Patients were selected from inpatients consecutively admitted from January 2012 to December 2013 to the Rehabilitation Center in Hangzhou Hospital of Zhejiang CAPF. The present study was conducted in accordance with the declaration of Helsinki (1975, revised 1983) and with the approval from the Ethics Committee of the Hangzhou Hospital of Zhejiang CAPF. Written informed consent was obtained from all participants. Ninety patients (49 females and 51 males) were recruited in this study. These patients were randomly assigned with the help of a computer-generated list to either the fluoxetine treatment group, hyperbaric oxygen therapy group, or hyperbaric oxygen combined treatment group. There were 30 subjects in each group. All patients were suffering from the first occurrence of stroke within one month. Patients with disorders of consciousness and com-

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Table 1. Clinical characteristics of three groups

	Gender	Age	Diagnosis	Stroke interval	SSS	HAMD
	Male/female (n)	year	Ischaemic/ Hemorrhagic	days	score	8–17/18–24/>24(n)
Fluoxetine treatment group (n=30)	17/13	65 ± 7.9	14/16	21.5 ± 6.9	22.8 ± 5.5	7/13/10
HBO treatment group (n=30)	16/14	63 ± 8.1	18/12	29.9 ± 8.7	24.4 ± 6.7	8/12/10
Combined HBO treatment group (n=30)	18/12	66 ± 5.9	17/13	23.4 ± 8.1	23.3 ± 4.4	7/11/12

Data are presented as mean ± SD. The three groups did not differ in terms of age, gender, SSS and HAMD score (t-test and χ^2 test, $p>0.05$).

Table 2. Comparisons of the SSS and HAMD scores between the three groups

	SSS (score)		HAMD (score)	
	before	after	before	after
Fluoxetine treatment group (n=30)	22.8 ± 5.5	17 ± 4.2[a]	19.8 ± 4.5	11.1 ± 3.9[e]
HBO treatment group (n=30)	24.4 ± 6.7	19.4 ± 5.5[b]	20.1 ± 5.7	12.4 ± 3.5[f]
Combined HBO treatment group (n=30)	23.3 ± 4.4	16.1 ± 3.9[c d]	22.8 ± 3.3	10.9 ± 4.4[gh]

Data are presented as mean ± SD. [a,b,c]$p<0.05$, comparison of SSS within each group before and after treatment. [d]$p>0.05$, comparison of SSS between combined HBO treatment group and other two groups after treatment. [e,f,g]$p<0.05$, comparison of HAMD within each group before and after treatment. [h]$p<0.05$, comparison of HAMD between combined HBO treatment group and other two groups after treatment.

plete sensory aphasia were excluded. A depression assessment was conducted using the Hamilton Depression Scale (HAMD) and nerve function defect scoring was conducted using the Scandinavian Stroke Scale (SSS). The three groups did not differ in terms of age, gender, and SSS and HAMD scores (Table 1).

Treatment

In fluoxetine treatment group (n = 30), fluoxetine was administered at 20 mg once daily for 4 weeks. The patients in the HBOT group (n = 30) were treated in a multiple-person, large HBOT cabin with a pressure of 0.2 MPa (2 ATA). After entering the cabin, pure oxygen was breathed in, via a face mask or head mask twice for 35 min each time and the air in the cabin was breathed in for 10 min in between. The 4-week treatment course included one treatment each day, 5 times each week. Hyperbaric oxygen combined treatment group (n = 30) were treated with fluoxetine and HBOT as described above. All patients received routine rehabilitation therapy. This included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). The therapy combined elements of neurodevelopmental techniques and motor relearning program.

Evaluation

The evaluation of SSS and HAMD scores was performed before and after 4-week treatment. According to the HAMD score reduction rate standard, a score reduction rate of ≥ 75% represented a cure, ≥ 50% represented marked progress, ≥ 25% represented progress, and < 25% represented a fail[7].

Statistical analysis

Data are presented as mean ± SD. SPSS 21.0 software was used for the statistical analyses, with the ANOVA test and χ^2 test performed to examine the differences in the data between the groups. $P < 0.05$ indicated a statistically significant difference.

RESULTS

SSS and HAMD scores

The SSS and HAMD scores showed significant differences between the pre-treatment and post-treatment results within each group ($p < 0.05$); the HAMD scores also showed better improvement in the hyperbaric oxygen combined group than the other two groups ($p < 0.05$). There were no differences in SSS scores between the three groups at the end of the study ($p > 0.05$) (Table 2).

Clinical efficacy comparison

The efficacy to PSD disorder was observed and evaluated using HAMD score. The score reduction rates of the fluoxetine treatment group, HBO treatment group, and combined HBO treatment group were 70%, 76.7%, and 90%, respectively. The 4-week treatment demonstrated a statistically significant difference between the combined HBO treatment group and the other two groups ($p < 0.05$, Table 3).

DISCUSSION

PSD is an important disorder because it may result in long-term disability, change a patient's daily life quality, and significantly increase the social-economic costs. The present study is the first clinical report that demonstrates better clinical outcome evaluated by HAMD in patients with stroke using combined HBOT and anti-depressant drugs.

Table 3. Comparison of clinical efficacy between three groups

	Cure	Marked progress	Progress	Fail	Total efficacy (%)
Fluoxetine treatment group (n=30)	2	11	8	9	70 (%)
HBO treatment group (n=30)	3	12	8	7	76.7 (%)[a]
Combined HBO treatment group (n=30)	5	12	10	3	90 (%)[b]

[a]$p>0.05$, comparison of total efficacy between fluoxetine treatment group and HBO treatment group. [b]$p<0.05$,comparison of total efficacy between combined HBO treatment group and other two groups.

Cerebral hypoxic ischemic injury possibly affects the brainstem, thalamus, basal ganglia, frontal cortex, and other areas and causes depression[8]. Therefore, an improvement in the oxygen supply to the brain in stroke patients can not only reduce the secondary damage to the cerebral cortex and relevant nerve functions but also promote brain remodeling and functional reorganization in patients with cerebral apoplexy at the convalescent stage. HBOT increases the expression of brain-derived neurotrophic factor (BDNF), GDNF, and NGF, which nourish the cranial nerve, and promote proliferation and restoration of the neurons[9]. It is reported that HBOT could help decrease the levels of TNF-α and IL-1β, which have shown to induce depression after stroke[10]. A recently randomized, prospective trial has shown that HBOT can activate the neuroplasticity of brain tissues in post-stroke patients, even in the chronic phase[4], and 6 randomized controlled trials involving 283 participants update the former summary by Bennett et al[11]. Bennett et al used Trouillas Disability Sca to assess the otcome and found that the disability and functional performance in individual studies indicated an improvement after HBOT 6 months later.

Our results from the present study show that fluoxetine treatment, hyperbaric oxygen therapy, and hyperbaric oxygen therapy with fluoxetine could improve post-stroke depression. These findings are consistent with previous studies[12]. Moreover, we found that hyperbaric oxygen therapy combined with fluoxetine was more effective than the other two treatments. It showed lower HAMD score and higher total efficacy. We estimate that HBOT with fluoxetine has additive anti-depression effects than other traditional treatment. The Scandinavian Stroke Scale (SSS) scores were improved in all three groups after treatment. However, there were no differences between the three groups at the end because all patients received routine rehabilitation therapy.

Currently, early antidepressant treatments and timely eradication of the emotional disorder to promote the recovery of nerve functions has been researched worldwide. In addition to drug treatment alone, many drug treatments combined with psychological and electro-acupuncture therapy[13], have been reported. Post-stroke depression can be controlled by rehabilitation[14]. In our study, combined HBOT has been used to treat depression in the recovery stage following stroke with good results and no evident adverse reaction. Therefore, combined HBO treatment is worthy of further promotion and application in the clinic.

A limitation of this study was that it was an open study without a negative control group. Another limitation was the small sample size. While we were able to demonstrate significant improvement in PSD after combined HBO treatment, this effect needs to be verified with a larger sample.

In summary, the findings of the present study show that the PSD can be most improved by combined HBO treatment. Further studies are needed to investigate the long term prognosis following this treatment.

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