

# Effects of hyperbaric oxygen therapy on depression and anxiety in the patients with incomplete spinal cord injury (a STROBE-compliant article)

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## Abstract

Little research has been done on the effects of hyperbaric oxygen (HBO) on depression and anxiety after spinal cord injury (SCI). The aim of this study was to investigate the effects of HBO on psychological problems and nerve function, especially on depression and anxiety in the patients with incomplete SCI (ISCI).

Sixty patients with ISCI combined with depression and anxiety were randomly divided into HBO group (20 cases), psychotherapy group (20 cases), and conventional rehabilitation control group (20 cases). All patients received routine rehabilitation therapy. However, in HBO group and psychotherapy group, patients also received HBO and psychotherapy, respectively. These therapies lasted for a total of 8 weeks (once a day and 6 days per week). Before and after 8 weeks of treatment, depression and anxiety, nerve function, and activities of daily living were, respectively, evaluated according to Hamilton Depression (HAMD) scale, Hamilton Anxiety (HAMA) scale, American Spinal Injury Association score, and functional independence measure score in all patients.

After 8 weeks of treatment, HAMD score was significantly lower in both HBO group and psychotherapy group than in control group (all  $P < .05$ ), but there was no statistical difference in HAMD score between HBO group and psychotherapy group ( $P > .05$ ). HAMA score was significantly lower in HBO group than in control group ( $P < .05$ ), but there was no statistical difference in HAMA score between HBO group and psychotherapy group, and between psychotherapy group and control group (all  $P > .05$ ). After 8 weeks of treatment, American Spinal Injury Association and functional independence measure scores were significantly higher in HBO group than in both psychological and control groups, and also higher in psychotherapy group than in control group (all  $P < .05$ ).

The effects of HBO on depression and anxiety are similar to that of psychotherapy. HBO can significantly improve nerve function and activities of daily living in the patients with ISCI, which either psychotherapy or routine rehabilitation therapy can not substitute.

**Abbreviations:** ASIA = American Spinal Injury Association score, FIM = functional independence measure, HAMA = Hamilton Anxiety scale, HAMD = Hamilton Depression scale, HBO = hyperbaric oxygen, ISCI = incomplete spinal cord injury, SCI = spinal cord injury.

**Keywords:** activities of daily living, anxiety, depression, hyperbaric oxygen, incomplete spinal cord injury, nerve function

## 1. Introduction

Spinal cord injuries (SCIs) refer to impairment of spinal cord structure or function caused by trauma, tumor, infection, degeneration, deformity, and iatrogenic factors. Primary injury may lead to spinal cord hemorrhage, inflammation, and edema, which severely affect patients' prognosis. A few hours after SCI, the main mode of cell death is apoptosis, which leads to the death

of neurons and glial cells. The treatment for secondary spinal cord edema attracts many investigators because secondary spinal cord edema is an important pathological basis of SCI.<sup>[1]</sup> In clinical practice, early application of hormone and surgical treatment can relieve spinal cord edema. Hyperbaric oxygen (HBO), an important therapy for nervous system injuries, can improve histanoxia, relieving edema. HBO can inhibit apoptosis after SCI by down-regulation of caspase-3 expression,<sup>[2]</sup> and promote neuron regeneration by improving blood supply and oxygen supply to the injured site.<sup>[3,4]</sup> Asamoto et al<sup>[5]</sup> have reported that HBO can promote the recovery of neurological function in the patients with cervical SCI. HBO also has been used in the treatments of ischemic encephalopathy, cerebral apoplexy, traumatic brain injury, and peripheral nerve injury.

Spinal cord injuries not only can affect motor, sensory, and autonomic nerve functions, and also life quality, but can also produce severe psychological problem. Therefore, for the patients with SCIs, attention also should be paid to psychological rehabilitation. It is reported that the patients with SCIs usually have marked anxiety and depression symptoms, manifesting different levels of sleep disorders, irascibility, and poor compliance, which seriously affect rehabilitation therapy.<sup>[6]</sup>

The unified assessment criteria for SCI have important significance for communication about SCI.<sup>[7,8]</sup> The American

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Spinal Injury Association (ASIA) score, recommended by ASIA and International Spinal Cord Society (ISCoS), has been widely used in the world.<sup>[9]</sup> In this study, we also use ASIA score and functional independence measure (FIM) score,<sup>[10]</sup> apart from Hamilton Depression (HAMD) scale and Hamilton Anxiety (HAMA) scale.

However, little research has been done on the effects of HBO on depression and anxiety after SCI. In this study, we observed the effects of HBO on depression and anxiety in the patients with incomplete SCI (ISCI).

## 2. Materials and methods

All study methods were approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All the subjects enrolled into the study gave written formal consent to participate.

### 2.1. Subjects

Inclusion criteria were as follows: patients who were diagnosed with cervical, thoracic, or lumbar ISCI by computed tomography (CT) or magnetic resonance imaging (MRI) according to the diagnostic criteria made by ASIA;<sup>[11]</sup> patients who had depression and/or anxiety diagnosed by psychiatrist based on Chinese Classification and Diagnostic Criteria of Mental Disorders; patients who had mild to moderate depression (8–24 scores of HAMD scale) and/or anxiety (7–29 scores of HAMA scale); patients who received surgical treatment within 15 days after injury and had stable vital signs; SCI caused by trauma; and patients aged 18 to 50 years.

Exclusion criteria were as follows: patients with craniocerebral injury or other nervous system diseases; patients with cognitive dysfunction; patients who had a history of psychiatric disorders;

SCI caused by other causes except trauma; and patients who were not suitable for HBO, such as untreated pneumothorax, mediastinal emphysema, pulmonary bulla, active bleeding, and tuberculous cavity combined with hemoptysis.

In all, 60 patients who underwent rehabilitative treatment in the Department of Rehabilitation Medicine, the First Affiliated Hospital of Zhengzhou University, from January 2014 to December 2015, were enrolled in this study. They were divided into HBO group (20 cases), psychotherapy group (20 cases), and conventional rehabilitation control group (control group: 20 cases) by random numbers. There were no significant differences in age, sex, course of disease, and disability classification amongst the 3 groups before treatment (all  $P > .05$ ) (Table 1).

### 2.2. Treatment

In control group, patients received drugs for improving circulation (Danhong injection with essential components including Dan-Shen and safflower, which have effects of dilating blood capillary and activating blood circulation) and promoting nerve cell repair (Monosialotetrahexosylganglioside sodium injection with protective effects on injured nerve) once a day, and underwent routine rehabilitation therapy for SCI including respiratory function training, bladder training, standing exercise, and joint motion training in early stage, and muscle training, posture conversion exercise, sit-up training, and sitting balance training in stable stage, and physiotherapy once a day and 6 days per week.

In psychology group, apart from the treatments in control group, patients also received supportive psychotherapy and cognitive behavioral therapy from psychiatrists and psychologists, and comfort treatment from society and family once a day and 6 days per week.

**Table 1**

**HAMD, HAMA, ASIA, and FIM scores, and also general data in the 3 groups before treatment (n,  $\bar{x} \pm s$ ).**

Groups	HBO	Psychotherapy	Control	P
No. of cases (n)	20	20	20	
Sex (n)*				.788
Male	14	15	13	
Female	6	5	7	
Age (y, $\bar{x} \pm s$ ) <sup>†</sup>	36.1 $\pm$ 5.2	34.8 $\pm$ 4.7	33.1 $\pm$ 4.6	.154
Disability classification (n) <sup>†</sup>				.864
Grade B	12	10	10	
Grade C	5	8	7	
Grade D	3	2	3	
Injured sections (n)*				.894
Cervical	7	8	7	
Thoracic	8	6	9	
Lumbar	5	6	4	
Sensation scores <sup>†</sup>				
Light touch sense	54.2 $\pm$ 3.6	53.3 $\pm$ 3.4	52.5 $\pm$ 3.1	.288
Needling sense	55.3 $\pm$ 3.9	54.5 $\pm$ 4.1	53.7 $\pm$ 3.3	.414
Motion scores <sup>†</sup>	53.7 $\pm$ 3.3	49.3 $\pm$ 3.4	48.2 $\pm$ 3.7	.187
FIM <sup>†</sup>	58.4 $\pm$ 5.7	55.9 $\pm$ 6.2	57.3 $\pm$ 4.8	.373
HAMD <sup>†</sup>	17.8 $\pm$ 2.0	17.5 $\pm$ 2.4	17.1 $\pm$ 2.5	.632
HAMA <sup>†</sup>	17.3 $\pm$ 2.1	16.8 $\pm$ 2.5	17.1 $\pm$ 1.9	.767

Disability classification includes A, B, C, D, and E grades. Grades B, C, and D belong to incomplete injury. Grade B retains sensory function, but has no motor function in S<sub>4</sub>-S<sub>5</sub>. Grade C has motor function, but the muscle strength of more than half of key muscles is below grade 3. Grade D has motor function, and the muscle strength of more than half of key muscles is above grade 3. ASIA includes disability classification, sensation scores, and motion scores.

ASIA = American Spinal Injury Association score, FIM = functional independence measure, HAMD = Hamilton Depression scale, HAMA = Hamilton Anxiety scale, HBO = hyperbaric oxygen.

\* Indicates chi-square test.

<sup>†</sup> Indicates rank test.

The patients in control group and psychology group were also put into a HBO chamber with normal state once a day and 6 days per week.

In HBO group, apart from the treatments in control group, patients also received HBO once a day and 6 days per week. A HBO chamber for multiple individuals was used in this study. Patients were in decubitus position with oxygen mask or tracheotomy tube. The pressure in the HBO chamber reached 0.2 MPa (2.0 ATA) at a uniform speed within 20 minutes, and lasted for 30 minutes twice. There was an interval of 10 minutes between the two 30-minute HBO. And then the pressure in the HBO chamber was uniformly reduced to normal pressure within 20 minutes. Each HBO took 110 minutes.

All managements for all patients lasted for a total of 8 weeks.

### 2.3. Evaluation

The ASIA2000 standards were made by ASIA for assessment of spinal injuries.<sup>[12]</sup> It includes damage score, motor score, and sensory score. ASIA may be used to determine complete SCI and ISCI, and can provide quantitative evaluation for SCI. Motor scores are evaluated using manual muscle testing with a maximum of 50 scores on each side limb. Sensation includes light touch sense and needling sense. Each kind of sensation is a maximum of 56 scores on each side limb. Motion-injury plane, sensation-injury plane, and nerve-injury plane were determined based on the scores above. Disability classification includes A, B, C, D, and E grades. Grade A refers to complete SCI injury without any sensory and motor function in S<sub>4</sub>-S<sub>5</sub>. Grades B, C, and D belong to incomplete SCI injury. Grade B retains sensory function, but has no motor function in S<sub>4</sub>-S<sub>5</sub>. Grade C has motor function, but the muscle strength of more than half of key muscles is below grade 3. Grade D has motor function, and the muscle strength of more than half of key muscles is above grade 3. Grade E has normal sensory and motor function.

The HAMD scale contains 24 items and is suitable for the adults with depression. Each item is divided into 5 grades evaluated using 0 to 4 scores. The total scores of the HAMD scale can reflect patients' depressive condition to some extent. The total scores of less than 8 is regarded as no depression, 8 to 16 mild depression, 17 to 24 moderate depression, and more than 24 severe depression.

The HAMA scale contains 14 items and is suitable for the adults with anxiety. Each item is divided into 5 grades evaluated using 0 to 4 scores. The total scores of HAMA scale can reflect patients' anxious condition to some extent. The total scores of less than 7 is regarded as no anxiety, 7 or more possible anxiety, 14 or more definite anxiety, 21 or more marked anxiety, 29 or more severe anxiety.

Functional independence measure can accurately reflect the level of disability and evaluate rehabilitative effects. FIM contains 6 aspects with a total of 18 items including 13 motor items and 5 cognitive items.

The FIM scoring standards include complete independence (7 scores), conditional independence (6 scores), and conditional dependence (1–5 scores). Conditional dependence is divided into custodial care and preparation (5 scores), little physical contact help (4 scores), moderately physical contact help (3 scores), massively physical contact help (2 scores), and complete dependence (1 score).

Regarding FIM function level, FIM scores were between 126 and 18. FIM is divided into complete independence, basic independence, very little dependence or conditional independence, mild dependence, moderate dependence, severe dependence, very severe dependence, and complete dependence.

Before and after 8 weeks of treatment, evaluations above were performed in all patients by the same physician blind to this study. ASIA was performed by manual muscle test, whereas HAMD and HAMA were carried out by questionnaire method.

### 2.4. Statistical analysis

Statistical treatment was performed using SPSS 17.0 software. All measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). The data consistent with normal distribution and homogeneity of variance were treated by variance analysis. The data without normal distribution and homogeneity of variance were analyzed by rank test. Comparison of 2 groups was performed using Bonferroni method. Enumeration data were analyzed using chi-square test or rank test. Statistical significance was established at  $P < .05$ .

## 3. Results

Before treatment, there were no statistical differences in HAMD, HAMA, ASIA, and FIM scores amongst the 3 groups (all  $P > .05$ ; Table 1).

In HBO group, all patients had no HBO-induced complications/side effects such as barotraumas of middle ear, sinus barotraumas, pulmonary barotrauma, and numbness of fingers after HBO therapy.

After 8 weeks of treatment, HAMD score was significantly lower in both HBO group and psychotherapy group than in control group (all  $P < .05$ ), but there was no statistical difference in HAMD score between HBO group and psychotherapy group ( $P > .05$ ). HAMA score was significantly lower in HBO group than in control group ( $P < .05$ ), but there was no statistical difference in HAMA score between HBO group and psychotherapy group, and between psychotherapy group and control group (all  $P > .05$ ). After 8 weeks of treatment, ASIA and FIM scores were significantly higher in HBO group than in both psychological and control groups, and also higher in psychotherapy group than in control group (all  $P < .05$ ) (Table 2).

## 4. Discussion

### 4.1. Problems in the patients with SCI

Spinal cord injury, with a high disability rate, is a kind of extremely severe trauma occurring in the central nervous system.

**Table 2**  
HAMD, HAMA, ASIA, and FIM scores in the 3 groups after treatment (score,  $\bar{x} \pm s$ ).

Groups	HBO	Psychotherapy	Control	P
No. of cases (n)	20	20	20	
Sensation scores				
Light touch sense	90.6 $\pm$ 4.2*	85.2 $\pm$ 3.6 <sup>†</sup>	79.6 $\pm$ 2.8 <sup>‡</sup>	<.001
Needling sense	93.2 $\pm$ 4.1*	88.3 $\pm$ 3.5 <sup>†</sup>	81.5 $\pm$ 3.1 <sup>‡</sup>	<.001
Motion scores				
FIM	72.5 $\pm$ 1.9*	69.8 $\pm$ 2.1 <sup>†</sup>	67.2 $\pm$ 1.5 <sup>‡</sup>	<.001
HAMD	98.6 $\pm$ 4.3*	83.8 $\pm$ 4.1 <sup>†</sup>	75.9 $\pm$ 3.6 <sup>‡</sup>	<.001
HAMA	8.9 $\pm$ 1.8	10.4 $\pm$ 2.1 <sup>†</sup>	13.8 $\pm$ 2.3 <sup>‡</sup>	<.001
	9.2 $\pm$ 1.5	10.5 $\pm$ 1.8	11.9 $\pm$ 2.3 <sup>‡</sup>	.002

Rank test is used in Table 2.

ASIA includes sensation scores and motion scores.

ASIA = American Spinal Injury Association score, FIM = functional independence measure, HAMD = Hamilton Depression scale, HAMA = Hamilton anxiety scale, HBO = hyperbaric oxygen.

\* Indicates  $P < .017$  as compared with psychology group.

<sup>†</sup> Indicates  $P < .017$  as compared with control group.

<sup>‡</sup> Indicates  $P < .017$  as compared with HBO group.

Most SCI patients can not take care of themselves because of neurological dysfunction below injured level. Although the survival rate of SCI patients has been increased due to advances in medical technology, most SCI patients still have various degrees of disability, severely affecting their daily life, work, and learning.<sup>[13]</sup> Sudden changes in physiological status and social status, and sharp difference between therapeutic effects and patients' expectations all make SCI patients produce a great psychological pressure with a series of nonspecific psychological reactions such as depression and anxiety.<sup>[14]</sup> Kiersma et al<sup>[15]</sup> have reported that mental and psychological trauma is much severer than body trauma when SCI patients lose independent self-care ability. Different from other patients, SCI patients readily have depression and anxiety, because plegia cannot be completely cured and only little function is recovered by functional exercise. Shin et al<sup>[16]</sup> have described that depression occurs in about 63.9% of SCI patients. Depression and other psychological problems are 1 of the important issues which should be urgently resolved during rehabilitative treatment. Physical functional rehabilitation and psychological rehabilitation, especially psychological rehabilitation, have become big problems in the departments of rehabilitation medicine and neurology. A variety of therapies for psychological rehabilitation have been investigated, but little research has been done on the effects of HBO on psychological problems.

#### 4.2. HBO therapy

Hyperbaric oxygen, which has been used in many clinical fields, is an important measure for treatment of SCI with better therapeutic effect.<sup>[17]</sup> HBO can increase blood dissolved oxygen and tissue oxygen reserves,<sup>[18]</sup> effectively improving spinal microenvironment<sup>[19,20]</sup> and relieving spinal edema.<sup>[21]</sup> HBO can improve plasmalemmal antioxidant capacity by inhibiting free radical-mediated lipid peroxidation.<sup>[22,23]</sup> HBO also can relieve secondary spinal injury by reduction of the levels of excitatory amino acid and proinflammatory cytokine, and elevation of the level of anti-inflammatory cytokine.

Clinical data have indicated that in early stage of SCI, HBO can markedly promote functional rehabilitation in the patients with ISCI, but it fails to show therapeutic effects in the patients with complete SCI.<sup>[24]</sup> Therefore, in this study, all patients had ISCI. In this study, another criterion was that all patients had mild to moderate depression and/or anxiety before treatment, because better therapeutic effect requires psychotropic drugs for above moderate depression or anxiety according to clinical experience. In this study, although there were no statistical differences in HAMD and HAMA scores between HBO group and psychotherapy group, when compared with control group, both HAMD and HAMA scores were significantly decreased in HBO group (all  $P < .017$ ), whereas in psychotherapy group, only HAMD score was significantly decreased ( $P < .017$ ). These results suggested that HBO is similar to psychotherapy in improving psychological problems. In addition, ASIA and FIM scores were significantly increased in HBO group as compared with both psychotherapy group and control group (all  $P < .017$ ), which is consistent with other results.<sup>[5]</sup>

#### 4.3. Psychotherapy

Conventional rehabilitation therapy can greatly induce residual limb function, improving their activities of daily living (ADL), whereas systematic psychological intervention can relieve

patients' depression, sadness, fear, anxiety, disappointment, anger, and other negative emotions, promoting positive rehabilitation training.<sup>[25]</sup> This study indicated that after 8-week treatment, ADL was significantly improved in psychotherapy group as compared with control group, suggesting that psychotherapy is conducive to recovery of nerve function. However, ADL was significantly improved in HBO group as compared with psychotherapy group, demonstrating that psychotherapy can not substitute HBO in improving ADL.

#### 4.4. HBO is similar to psychotherapy in improving anxiety and depression

In this study, although there were no statistical differences in HAMD and HAMA scores between HBO group and psychotherapy group, when compared with control group, both HAMD and HAMA scores were significantly decreased in HBO group (all  $P < .017$ ), whereas in psychotherapy group, only HAMD score was significantly decreased ( $P < .017$ ). These results suggested that HBO is similar to psychotherapy in improving psychological problems. This may be that there is a vicious cycle between psychological factors and functional impairment in SCI patients with psychological problems, and HBO is able to break this vicious cycle. HBO can improve functional impairment; relieve depression, anxiety, and other negative emotions; strengthen patients' resolve to overcome disease; and let patients more actively participate in rehabilitation training, forming a virtuous circle.

In summary, based on conventional rehabilitation therapy, HBO can significantly relieve depression and anxiety, and improve physical function and ADL in the patients with ISCI. However, we did not calculate sample size because the sample was small, and follow-up only lasted 8 weeks in this study. Therefore, it is necessary to collect more samples and prolong follow-up time.

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