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Full Length Research Paper

Comparative study of hyperbaric oxygen therapy and conventional drug treatment on spinal cord injury at different therapeutic windows

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In the present study, the curative effects of hyperbaric oxygen therapy and conventional drug treatment on spinal cord injury at different therapeutic windows were observed and compared. A total of 328 cases of spinal cord injury (SCI) were randomly divided into hyperbaric oxygen (HBO) group and medicine group. The conventional drug treatment in the medicine group consisted of mannitol, ganglion monoglyceride, rehabilitation training and acupuncture. Hyperbaric oxygen therapy on the basis of the aforementioned basic drug treatments was given in the HBO group. Before treatment and 3 months after treatment, neurological functions and activities of daily living of each patient were evaluated with ASIA neurological function scoring and Barthel index. The sensory, motor function and activities of daily living of patients who were treated within 8 h after SCI were significantly improved in two groups (P<0.01). The symptoms of the patients who were treated within 24 h after SCI were improved (P<0.01), but the efficacy was worse than patients who were treated within 8 h. Besides, the curative effects in the HBO group was better than medicine group (P<0.05). Among different therapeutic windows in the same group, treatment within 24 h could obtain satisfactory curative effects. The curative effects of treatment later than 1 w were poor in both groups (p>0.05). Both hyperbaric oxygen therapy and conventional treatment within 8 h following SCI could greatly improve the neurological functions and activities of daily living of SCI patients. Both treatments between 8 h and 1 w following SCI could also improve the neurological functions and activities of daily living of SCI patients, but the curative effects of hyperbaric oxygen therapy were better than conventional treatment. However, the curative effects of these treatments beyond 1 w were poor.

Key words: Spinal cord injury, hyperbaric oxygen, medicine, therapeutic windows, curative effects.

INTRODUCTION

Spinal cord injury (SCI) is a kind of severe trauma in the central nervous system, with a high morbidity and mortality (Divanoglou et al., 2010; Guilcher et al., 2010) and SCI brings worse impact on the quality of life and family of patients. Because the majority of SCI patients are youths or adults, SCI largely increases social burden. The mechanisms of SCI include primary mechanical injuries and multiple secondary injuries. At present, the treatments of SCI include three categories in clinical practice as follows: 1) External factors continuously injuring the spinal cord must be removed as soon as possible, and treatments should be carried out to avoid further expansion of injured areas, such as surgical decompression and dehydration (Batchelor et al., 2010; Fehlings et al., 2010; Linsenmeyer and Oakley, 2003); 2) Secondary pathologic changes should be blocked or limited in the acute phase of SCI to protect residual axons and neurons from secondary injuries, such as the

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administration of methylprednisolone, calcium channel antagonists and naloxone, local hypothermal protection and artificial high-pressure perfusion (Benzel et al., 1992; Brackett et al., 2007; Bracken, 2001; Leypold et al., 2007; Nicholas et al., 2009; Agrawal et al., 2000; Shi et al., 2005); 3) All treatments which can promote the regeneration and repair of nervous tissues should be given as soon as possible, such as the administration of neurotrophic drugs, all kinds of cell transplantation, gene therapy and HBO therapy (Asamoto et al., 2000; Fry et al., 2010; Gros et al., 2010; Kwon et al., 2010; Low et al., 2010).

For patients with indications, timely optimal surgical decompression and methylprednisolone pulse therapy can avoid the further development of SCI (Rabinowitz et al., 2008). Due to the complicated pathological changes of SCI (especially pathological changes of secondary injuries), general clinical treatments can not obtain satisfactory curative effects, and the nervous functional recovery is poor (Coleman and Geisler, 2004; Fliess-Douer et al., 2010; Wirz et al., 2010). Hyperbaric oxygen (HBO) plays import roles in the regeneration and repair of SCI, and HBO has good curative effects on SCI in clinical practice, including satisfactory recovery of sensory and motor functions, and most SCI patients re-obtain some self-care abilities. HBO can block or even reverse the pathological changes following SCI and promote the regeneration and repair of neurons, and the satisfactory recovery of nervous functions is obtained in most SCI patients (Asamoto et al., 2000).

In this study, SCI patients were randomly divided into a conventional drug treatment group and a hyperbaric oxygen therapy group to compare their curative effects at different therapeutic windows and to better guide the clinical application of HBO in the treatment of SCI.

MATERIALS AND METHODS

Clinical data and grouping

A total of 316 SCI patients hospitalized in our center from September 2007 to September 2010 were enrolled in this study. The inclusion criteria included acute SCI induced by trauma, spontaneous pain in trunk or limbs, varying degrees of sensory functional disturbance in conduction tract below injured segments, flaccid or spastic paralysis in limbs and urination and defecation dysfunction, and the diagnosis of SCI was confirmed by imaging examinations (X-ray films/CT/MRI) or operation. The exclusion criteria included SCI induced by infection or degeneration, patients with hypertension, cardiovascular diseases or diabetes, had a history of cerebral hemorrhage and infarction, the accompanied injury of brain damage, and nervous system diseases. Before treatment, SCI patients were randomly divided into two groups using a random number table.

In the HBO group, there were 80 males and 78 females with a mean age of 37.12±11.73 years (19 to 55 years), and the mean time from onset to therapeutic windows was 20.34±6.43 h (5 h~11 d), and the mean treatment duration was 35.26±8.79 d (30~50 d), and the imaging examinations revealed injured segments were cervical segment in 32 cases, thoracic segment in 50 cases, lumbar segment in 65 cases and sacrococcygeal segment in 11 cases, and SCI scoring of ASIA (American Spinal Injury Association, 2000) was grade A in 8 cases, grade B in 30 cases, grade C in 77 cases and grade D in 45 cases. The HBO group divided into four subgroups: the <8 h group, HBO treatment was performed within 8 h after SCI; <24 h group, HBO treatment was performed in the 8 to 24 h; > 24 h group, HBO treatment was performed in the 24 h to 1 week; > 1 week group, HBO treatment was performed after 1 week.

In the conventional medication group, there were 81 males and 77 females with a mean age of 37.08±12.03 years (18 to 55 years), and the mean time from onset to therapeutic windows was 21.13±5.47 h (4 h~12 d), and the mean treatment duration was 36.05±8.32 d (30~52 d), and the imaging examinations revealed injured segments were cervical segment in 30 cases, thoracic segment in 51 cases, lumbar segment in 67 cases and sacrococcygeal segment in 10 cases, and SCI scoring of ASIA (American Spinal Injury Association, 2000) was grade A in 7 cases, grade B in 33 cases , grade C in 74 cases and grade D in 44 cases. There were no significant differences in gender ratio, mean age, mean time from onset to therapeutic windows, mean treatment duration and ASIA scores between two groups (P>0.05).

Treatment methods

The patients in both groups were treated positively: patients with spinal cord compression received anterior/posterior decompression plus internal fixation; patients with unstable spine, although without compression of spinal cord, should receive internal fixation, external orthosis or skull traction to restore stability of spinal column. In the early stage of SCI, methylprednisolone pulse therapy was carried out in both groups. When the pathological conditions of SCI patients were stable in the acute phase the following treatments were given:

1) 125 ml mannitol was intravenously infused once every 8 h;
2) 100 ml normal saline containing 100 mg ganglion glycoside was intravenously infused once a day in the acute phase, and then 2 to 3 weeks later, 100 ml normal saline containing 20 to 40 mg ganglion glycoside was intravenously infused once a day for 6 weeks;
3) Psychological consultation and support was given to establish sufficient confidence in the treatment and ensure their active cooperation with relevant treatments;
4) Rehabilitation training, such as physical therapy, occupational therapy, electrical stimulation and bladder training;
5) Acupuncture or massage according to the conditions of paralyzed limbs;
6) Bladder training.

In the HBO group, based on the aforementioned basic treatments, HBO therapy was additionally added. HBO therapy was performed in a compression chamber, the pressure was gradually increased to 0.2 MPa (2 ATA) in 25 min, and then patients inspired hyperbaric oxygen with a mask for 90 min, and then inspired the air in chamber without masks, and the pressure was gradually decreased in 25 min. SCI patients received HBO therapy once a day, and a courses of HBO treatment consisted of 10 times of HBO therapy. If SCI patients continuously received several courses of HBO treatment, and there should be an intermission of two days between two courses.

HBO therapy should be given as early as possible if the effective circulation and respiration of SCI patients had been established. During HBO therapy, a rehabilitation physician should monitor the patients in the chamber.

Assessment of curative effects

Before and 3 months after treatment, neurological function and

Table 1. Comparison of neurological functional scores of spinal cord in two groups at different therapeutic windows ($x \pm s$).

Group	Therapeutic window	N	Sensory function score		Motor function score	
			Prior treatment	Post-treatment	Prior treatment	Post-treatment
HBO	<8h	42	91.23±11.48	192.68±21.37[a]	34.88±11.05	68.36±16.85[a]
	<24h	48	90.92±13.86	161.38±16.97[bc]	35.37±11.39[c]	62.11±18.74[b]
	>24h	40	91.34±14.92	135.02±17.04[bc]	35.62±11.19	55.68±19.25[bc]
	>1w	28	93.45±15.29	98.94±12.45	36.23±11.09	39.20±18.27
Medicine group	<8h	40	91.59±12.69	191.43±17.89[a]	35.80±10.48	67.90±18.86[a]
	<24h	47	92.56±15.46	138.69±21.89[b]	36.19±12.00	52.13±20.81[b]
	>24h	35	90.89±12.23	114.85±16.24[b]	35.26±11.15	45.56±20.78[b]
	>1w	41	92.14±12.02	95.94±14.78	36.85±10.69	38.33±17.54

Note: a, compared with prior treatment, P<0.01; b, compared with prior treatment, P<0.05; c, compared with post drug treatment, P<0.05.

activities of daily living of SCI patients were assessed by two neurologists who were blind to the study with ASIA assessment standards in 2000 and Barthel index, respectively. Neurological functions scoring of ASIA in 2000 includes:

1) Sensory functional assessment: 28 dermatomes (skin area was dominated by dorsal roots of spinal segment) in each side of body are examined, and sensory functional assessment in each site includes needling (with safety pin for single use) and light touch (with cotton tip). Sensory functional score includes three grades: 0 score, loss of sensory function or unable distinguish blunt and sharp stimulus; 1 score, some sensory functional impairment, including hyperaesthesia; 2 score, the sensory function is normal, and the full scores of sensory functional assessment in two sides are 224.
2) Motor functional assessment: the muscle force of 10 sarcomeres in each side of body are examined with manual muscle test (MMT) from top to down, and the score of motor function is equal to the grade of muscle force (0 to 5), and the full scores of motor functional assessment in two sides are 100.

Barthel index assessment includes 10 inspection items such as eating, dressing, urination, defecation, transfer and so on. The score of each item is divided into 3 or 4 levels based on action completion, and its full score is 100. Higher scores indicate milder dysfunction.

Statistical analyses

All statistical analyses were performed with SPSS version 13.0 statistical software. Measurement data were expressed as $x \pm s$, and comparison between two groups and comparison pre- and post-operation was performed using paired t test. Numeration data were compared with x^2 test. P<0.05 was considered significantly different.

RESULTS

Comparison of neurological functions before and after treatments

Neurological functional scores in two groups at different therapeutic windows are listed in Table 1. Before treatment, the scores of ASIA sensory function and motor function were not significantly different between both groups (P>0.05). In the subgroup of therapeutic windows within 8 h, there was significant difference in the score of neurological functions before and after treatment (P<0.01), but there was no significant difference in the score of neurological functions between both groups (P>0.05), indicating that both HBO therapy and conventional medical treatment could significantly improve the sensory function and motor function of SCI patients. In the subgroup of therapeutic windows from 24 h to 1 week, there was significant difference in the scores of neurological functions before and after treatment (P<0.05), and the scores of neurological functions between two groups was also significantly different (P<0.05), indicating that HBO therapy could better improve the sensory and motor functions compared with conventional drug treatment. However, the neurological function scores of patients who received HBO therapy or conventional drug treatment beyond 1 week following SCI were lower, and there were no significant differences in the scores of sensory and motor functions before and after treatment (P>0.05).

Comparison of activities of daily living in two groups before and after treatments

Activity scores of daily living in two groups at different therapeutic windows were listed in Table 2. Before treatment, activities of daily living were not significantly different between two groups (P>0.05). In the subgroup of therapeutic windows within 8 h, there was significant difference in activities of daily living before and after treatment (P<0.01), but there was no significant difference in activities of daily living between two groups (P>0.05), indicating that both HBO therapy and conventional medical treatment could significantly improve activities of daily living of SCI patients. In the subgroup of therapeutic windows from 24 h to 1 week, there was significant difference in activities of daily living before and after treatment (P<0.05), but its curative effects worse than the subgroup of therapeutic windows within 8 h, and

Table 2. Comparison of activity scores of daily living in two groups at different therapeutic windows ($x \pm s$).

Group	Therapeutic window	Barthel index	
		Prior treatment	Post-treatment
HBO	<8h	34.26±7.35[a]	78.99±11.65[a]
	<24h	33.57±6.99[bc]	63.52±11.37[bc]
	>24h	35.01±8.11[bc]	52.14±10.84[bc]
	>1w	33.98±7.70	37.55±10.27
Medicine	<8h	34.80±7.11[a]	77.11±13.15[a]
	<24h	34.34±8.37[b]	54.40±10.48[b]
	>24h	35.30±8.10[b]	44.88±11.58[b]
	>1w	34.57±7.90	36.66±12.92

Note: a, compared with prior treatment, P<0.01; b, compared with prior treatment, P<0.05; c, compared with post drug treatment, P<0.05.

the activities of daily living in the HBO group was better than that in the conventional drug treatment group (P<0.05), indicating that the curative effects of HBO therapy given within 24 h following SCI were satisfactory. However, activities of daily living of patients who received HBO therapy or conventional drug treatment beyond 1 week following SCI were significantly limited (P>0.05).

DISCUSSION

At present, HBO is more and more widely applied in all kinds of fields in clinical practice. A series of animal studies have shown that HBO intervention may block or even reverse the pathophysiological processes of SCI in many aspects to promote the functional recovery of injured spinal cord (Al-Waili et al., 2005; Li et al., 2007). Asamoto et al. (2000) found that HBO could rapidly reverse the hypoxia of injured myeloid tissues, and decrease the internal pressure of vertebral canal, and alleviate tissue edema, and significantly improve the motor and sensory function. There were ideal curative effects of HBO on SCI. Previous studies (Niu et al., 2007; Thom, 2009) showed that HBO played its curative roles by decreasing oxidative stress reaction, but up to now, its detailed mechanism of HBO treating on SCI is not unknown. Recent studies reveal that HBO can maintain the energy metabolism of nerve cells (Buras et al., 2001) and inhibit the apoptosis of neurons (Hardy et al., 2002) and enhance the function of sensory and motor neurons (Freiberger et al., 2006) and regulate the functions of chondriosomes (Weber et al., 2009; Dave et al., 2003) and up-regulate the levels of basic fibroblast growth factors and its mRNA, and increase the expression of nerve growth-related proteins in myeloid tissues (Uno et al., 2003) and thus HBO can play protective roles in myeloid tissues.

In this study, SCI patients who received HBO therapy at different therapeutic windows following SCI obtained different curative effects. Better recovery of neurological functions and activities of daily living of SCI patients treated within 8 h following SCI can be observed. Later the SCI patients were treated by HBO, worse curative effects were obtained. Beyond 1 week following SCI, neither conventional drug treatment nor HBO therapy can obtain satisfactory curative effects. This may be related to different targets of HBO in different pathological stages of SCI. Pathological changes of SCI include spinal cord ischemia and hypoxia caused by primary injuries, and internal environment disorders, circulatory disorders, edema, electrolyte, energy metabolism disorders and eventually apoptosis and necrosis of neurons cased by secondary injuries. HBO therapy was given within 8 h following SCI, and HBO therapy could increase arterial oxygen partial pressure, tissue oxygen reserves, oxygen diffusion distance of capillary blood, and could expand arteries, speed up blood flow rate, increase the blood supply of spinal cord, and thus the hypoxia and ischemia of injured tissues could be satisfactorily corrected.

In this phase, HBO therapy could play protective roles in the neurons of spinal cord in primary injured area, and HBO therapy could block secondary “waterfall” pathological changes to avoid the further injury of neurons, which was the important pathophysiolgoical basis of neurological functional recovery and curative effects. During this treatment period of HBO, ischemia, hypoxia and other pathological changes of neurons are still compensatory, and thus the curative effects of HBO and conventional drug treatment were better. Compared with the HBO group within 8 h following SCI, the curative effects of HBO therapy which was given between 8 to 24 h were worse. During this phase, the mechanisms of HBO might include the following aspects:

1) The production of free radical was inhibited, and free radical was rapidly removed to the injury of ischemia–reperfusion on spinal cord;
2) Leukocyte aggregation and adhesion was inhibited, and blood viscosity was reduced, and the blood supply of spinal cord tissues was increased, and thus the

microcirculation disturbance in the injured sites was improved;
3) Aerobic metabolism was enhanced, and anaerobic metabolism-local acid poisoning-increase of vascular permeability-edema in the injured area was blocked, and the vicious cycle of local environmental deterioration was thus reversed, and blood vessels of injured spinal cord tissues was contracted to increase the energy supply, improve microenvironment and reduce the edema of spinal cord.

During this stage, HBO therapy could limit the spinal cord suffering from secondary injury, but spinal cord tissues at primary injury sites had suffered from irreversible denaturation and necrosis, and the neurons in injured areas had lost conduction function. Besides, the recovery of pathological states of microenvironments must cost a longer time. Thus, the secondary injury of some spinal neurons was inevitable, and some function of neurons must be lost, and thus the curative effects of HBO were slightly poor. If HBO therapy was given from 24 h to 1 w after SCI, HBO therapy could regulate the expressions of nerve growth factors, Bcl-2 family, tumor necrosis factor-α, heat shock proteins, immediate early genes, basic fibroblast growth factor and neurotrophin-3 (Vitarbo et al., 2004; Armstead and Hecker, 2005; Michael et al., 2005; Quintana et al., 2005), and then the apoptosis of spinal neurons was inhibited, the transformation of fibroblasts and the regeneration of blood capillary in injured spinal cord was promoted, and then bypass circuit was established. Besides, HBO therapy could inhibit the immunological function of lymphocytes and decrease the formation of scar tissues due to fibrosis, which provide advantageous conditions for the regeneration of neural axons and the recovery of nerve conduction.

During this phase, neurons in primary injure sites had been necrotic and secondary injury led to the loss of transduction function of neurons. Thus, HBO therapy mainly protected non-degenerative neurons, and promoted the establishment of bypass circuit and reduced the formation of scar tissues, and thus the necessary conditions for regeneration of neurons and the formation of complete transduction pathway were provided. The curative effects of HBO therapy were better than conventional drug treatment ($P<0.05$) if treatments were given from 24 h to 1 w after SCI. This might be related that conventional drug treatment only could limit primary injury but could not effectively prevent secondary injury. Furthermore, HBO therapy could more effectively improve blood supply, establish bypass circuit, and reduce the formation of scar tissues, and thus the neurological functions and activities of daily living of SCI patients were greatly recovered.

If HBO therapy is given beyond 1 week after SCI, HBO therapy can induce proliferation of neurocytes with transduction functions to replace the necrotic spinal neurons, and eventually promote the recovery of neurological functions. HBO therapy might improve the internal environment of injured areas of spinal cord, and promote the generation and differentiation of endogenous nervous stem cells (Thom et al., 2006) inhibit the necrosis of endogenous nervous stem cells (Calvert et al., 2002) induce the migration of nervous stem cells to SCI injured areas (Goldstein et al., 2006), and replace necrotic or non-neurofunctional neurons, and eventually the neurological functions of SCI patients can be greatly improved. However, the endogenous nervous stem cells were limited, and furthermore their differentiation and migration were regulated by a lot of factors. Therefore, the curative effects of HBO therapy on SCI were poor if HBO therapy was given beyond 1 w after SCI.

In conclusion, either conventional drug treatment or HBO therapy should be given as early as possible, and the curative effects were the best if treatments were given within 8 h after SCI. If the treatments were given later than 8 h after SCI, HBO therapy should be given to promote the recovery of neurological function and activities of daily living. If HBO therapy was given beyond 1 w after SCI, neither conventional drug treatment nor HBO therapy could obtain satisfactory curative effects.

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