Effect of hyperbaric oxygen therapy on patients with herpes zoster

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ABSTRACT

Background: The purpose of this study was to observe the effect of hyperbaric oxygen (HBO_2) therapy on patients with herpes zoster.

Methods: A total of 68 cases with herpes zoster were randomly divided into HBO_2 and control groups. The patients in the control group were treated with drugs, while the patients in the HBO_2 group were treated with both drugs and HBO_2. Parameters of therapeutic efficacy including period of blister resolution, scar formation time and percentage of patients developing post-herpetic neuralgia (PHN) were determined for the patients in both groups. Numeric Pain Rating Scale (NPRS) and Hamilton Depression Rating Scale (HAMD) were also scored for the patients before and after treatment.

Results: The therapeutic efficacy in the control group was 81.25%, which was significantly lower than that (97.22%) in the HBO_2 group ($p<0.05$). The percentage of patients developing PHN, scar formation time and NPRS score in the HBO_2 groups were significantly lower than those in the control group ($p<0.05$). HAMD score in the HBO_2 group was significantly lower than that in the control group ($p<0.05$).

Conclusion: HBO_2 can significantly enhance therapeutic efficacy, relieve pain, accelerate herpes blister healing and lesion resolution, reduce the percentage of patients developing PHN and improve depression in patients with herpes zoster.

INTRODUCTION

Herpes zoster is an infectious disease of ganglia and nerve stems caused by varicella zoster virus [1]. Herpes zoster is characterized by skin flushing, distribution of clustering blisters along a dermatomal nerve distribution, skin burning, extension of pain outside of the skin lesions and persistent neuralgia in some patients after the associated rash has disappeared [2]. Post-herpetic neuralgia (PHN) refers to the persistent pain (one to six months) after the herpetic lesions are healed [3].

Manifesting primarily as persistent irritation, intermittent boring pain, allodynia and itching, PHN is difficult to treat and represents the most common complication of herpes zoster [4]. Typically the trigeminal or intercostal nerves are involved.

Overall, 15% of patients with herpes zoster will develop PHN, with that incidence increasing to 75% in patients over 70 years old [5]. Because of its complex pathogenesis and poor response to treatment, PHN has received extensive attention in the medical literature [6].

Skin burning and excruciating nerve pain in patients with herpes zoster often result in insomnia, irritability, anxiety and depression [7]. Herpes zoster is one of the more stubborn diseases of the middle-aged and elderly populations. Currently, there is no effective clinical treatment for this disease [8].

Hyperbaric oxygen (HBO_2) therapy treatment has been widely applied in clinics. HBO_2 therapy is a treatment by which patients are placed in a sealed, high-pressure environment while breathing high concentrations of oxygen [9]. However, the therapeutic efficacy of HBO_2 treatment on herpes zoster has not been studied. The purpose of this study was to investigate the effect of HBO_2 treatment on the duration and severity of herpes zoster signs and symptoms.

Methods

Subjects

A total of 68 cases with herpes zoster were enrolled from January 2008 to December 2010. Prior to enrollment, the disease course of these patients was less than two weeks. The diagnosis was based on the criteria of acute herpes zoster described in the literature [10,11]. Patients who were excluded from this study included

TABLE 1 – *Comparison of demographic information*

GROUPS	GENDER male	GENDER female	DISEASE course (days)	AGE (years)	TYPE mild	TYPE medium	TYPE severe
control group	14	18	7.72 ± 6.75	58.47 ± 15.86	10	16	6
HBO_2 group	20	16	9.39 ± 6.77	55.69 ±17.51	9	19	8
p	$X^2 = 0.944$	$p = 0.331$	t = -1.017 $p = 0.313$	t = 0.682 $p = 0.498$		$X^2 = 0.361$ $p = 0.835$	

women who were pregnant, breast-feeding or attempting to conceive; patients with severe heart, liver, lung and kidney dysfunction or systemic failure; those with autoimmune disease (*e.g.*, systemic lupus erythmatosus/SLE) or long-term use of corticosteroids or immunosuppressive agents; patients with malignant tumors; patients with contraindications on HBO_2 treatment; and patients with primary diseases that affect pain and depression.

These 68 cases were randomized using a computer-generated randomization scheme into the control group (n=32) and the HBO_2 treatment group (n=36). The patients were classified into three different grades of herpetic disease manifestation severity: mild, medium and severe [12,13]. Mild-grade patients had one to several patches (≤5 patches) of rash with a medium degree of pain, but without systemic symptoms. Medium-grade patients had more rash (>5 patches), obvious inflammation and pain, but still no systemic symptoms. The rash in severe-grade patients was associated with bleeding, ulcers, dissemination and obvious complications (*e.g.*, paresthesias, nerve palsies, ocular involvement or other appropriate examples) [14]. The severe-grade patients had poor general condition. There was no significant difference between the age, gender, disease course and disease grade in the HBO_2 group and those in the control group (p>0.05) *(Table 1, above)*.

HBO_2 treatment

The patients in the control group were treated with conventional drugs, while the patients in the HBO_2 group were treated with both conventional drugs and HBO_2. Pharmacotherapy included antiviral (acyclovir, 0.5g, intravenous drip, twice a day), nerve nutritive (mecobalamin, 0.5mg, intramuscular injection, once a day), pain relief (tramadol hydrochloride, 50mg, orally, once a day) and antidepressive drugs (nortriptyline, 10mg, orally, three times a day). An air-pressurized chamber (Model: YCQ34230/0.3/0.7 (-0.1) -50 VIII W; Origin: Yantai, Shandong Province, China) was used for HBO_2 treatment. For each treatment, the chamber was pressurized over a period of 15 minutes to 0.22MPa. Subjects then breathed either 100% oxygen by mask or chamber air according to the following schedule: mask oxygen 30 minutes; chamber air five minutes; mask oxygen 20 minutes; chamber air five minutes; mask oxygen 30 minutes The chamber was subsequently decompressed to ambient pressure over a period of 15 minutes. The total duration of each treatment was 120 minutes. Each subject received two HBO2 treatments daily, five days per week, for a total of 30 HBO_2 sessions.

Parameters detected for the patients before and after treatments

NPRS 15 (Numeric Pain Rating Scale: 0~10) and HAMD 16 (Hamilton Depression Rating Scale: 17 item; total score: 28.45±7.16) were scored the day prior to the first treatment and the day after completing the 30th HBO_2 treatment. Patients with a total HAMD score of less than 7 were considered to be reporting no depressive symptoms. Patients with a total HAMD score of 7-17 were considered to have mild depression. Patients with a total HAMD score of 17-24 were considered to have moderate depression. Patients with a total HAMD score of greater than 24 were considered to be suffering from severe depression.

The period of blister resolution (*i.e.*, the time between onset of the disease to the disappearance of the herpes blisters) and scar formation time (*i.e.*, the time between onset of the disease and the formation of scars) were recorded for the patients in both groups. All patients were followed for three to six months after completion of HBO_2 treatment and the number of patients developing PHN recorded. The percentage of subjects with PHN was calculated by the following formula:

PHN percentage = number of cases with PHN/ total case number in each group × 100.

TABLE 2 – *Comparison of therapeutic efficacy*

Groups	Case #	Healed	Improved	Ineffective	Efficacy rate %
control group	32	17	9	6	81.25%
HBO_2 group	36	22	13	1	97.22%

Evaluation of therapeutic efficacy

Therapeutic efficacy was evaluated on the day after completing the 30th HBO_2 treatment. The evaluation was conducted according to the criteria described previously [12,13]. The criteria for "healed" were complete subsidence of pain and rash with temporary pigmentation. The criteria for "improved" were significant pain relief and rash subsidence. The criteria for "ineffective" included no significant pain relief and no rash subsidence. Therapeutic efficacy was calculated by the following formula:

therapeutic efficacy = (number of cases with healing + number of cases with improvement)/ total case number in each group×100.

Statistical analysis

All the parameters were expressed as mean ± standard deviation (X ± S). Statistical analysis was conducted using SPSS11.0 statistical software package and Excel 7.0. Chi square analysis was used for comparison of therapeutic efficacy and PHN percentage between the two groups. Paired student t-test was used for comparison of the period of blister resolution, scar formation time, NPRS score and HAMD score between the two groups. Analysis of variance was used for comparison among multiple groups. $p<0.05$ was considered as statistically significant.

RESULTS

Comparison of therapeutic efficacy between the two groups

The calculated therapeutic efficacy in the HBO_2 group (97.22%) was significantly higher than that in the control group (81.55%) ($p<0.05$) *(Table 2, above)*.

Comparison of PHN, herpes stopping and scar formation time between the two groups

The percentage of subjects developing PHN in the HBO_2 group was 11.11%, which was significantly lower than that in the control group (31.25%) ($p<0.05$). There was no significant difference between the period of blister resolution in the HBO_2 group and that in the control group ($p>0.05$). The scar formation time in the HBO_2 group was significantly shorter than that in the control group ($p<0.05$) *(Table 3, above)*.

TABLE 3 – *Comparison of HN percentage, period of blister resolution and scar formation time*

Groups	Case #	PHN case # and %	Period of blister resolution (days)	Scar formation time (days)
control group	32	10 (31.25%)	3.25 ± 1.39	13.94 ± 4.26
HBO_2 group	36	4 (11.11%)	2.81 ± 1.45	11.08 ± 3.97

TABLE 4 – *Comparison of NPRS scores*

Groups	Case #	Before treatment	After treatment	*p*
control group	32	8.13 ± 1.68	3.53 ± 4.10	$p = 0.000$
HBO_2 group	36	7.97 ± 1.80	1.83 ± 2.72	$p = 0.000$
p		$p = 0.719$	$p = 0.046$	

Comparison of NPRS score between the two groups

Before treatment, there was no significant difference of NPRS score between the two groups ($p>0.05$). NPRS score was decreased after treatment in both groups ($p<0.01$). In addition, after treatment, NPRS score in the HBO_2 group was significantly lower than that in the control group ($p<0.05$) *(Table 4)*.

TABLE 5 – *Comparison of HAMD scores*

Groups	Case #	Before treatment	After treatment	*p*
control group	32	22.06 ± 13.55	10.94 ± 9.73	$p < 0.01$
HBO_2 group	36	19.92 ± 12.77	16.53 ± 12.04	$p < 0.05$
p		$p = 0.504$	$p = 0.041$	

Comparison of HAMD score between the two groups

Before treatment, there was no significant difference of HAMD score between the two groups ($p>0.05$). HAMD score was decreased after treatment in both groups ($p<0.01$). However, after completion of HBO_2 treatment, HAMD score in the HBO_2 group was significantly lower than in the control group ($p<0.05$) *(Table 5)*.

Comparison of adverse reactions and side effects between the two groups

Because of excessive anxiety (*i.e.*, claustrophobia prevented completion of HBO_2 treatment), assessment could not be completed in one patient in the HBO_2 group. Thus, this patient was excluded from analysis. One patient in the control group had allergic reactions (skin rash) and was also excluded. All the other patients finished examinations successfully. The percentage of cases that did not finish the study was not significantly different between the two groups ($p>0.05$). Adverse side effects secondary to HBO_2 treatment (*e.g.*, barotrauma, oxygen toxicity, decompression sickness, pulmonary atelectasis, metabolic disorders and acid-base imbalance) did not occur.

DISCUSSION

Herpes zoster is a disease characterized by the presence of pain and herpetic skin lesions in the areas innervated by nerves infected with herpes virus. Under conditions where the human immune function is suppressed, herpes zoster virus spreads to the skin via sensory nerve fibers, which results in inflammation and necrosis of the involved ganglion and nerve pain [17,18]. Consequently, clusters of blisters are formed on the corresponding skin, and inflammation occurs [19]. Clinical and laboratory studies have confirmed that HBO_2 can improve aerobic metabolism in nerve tissues, inhibit nerve tissue inflammatory edema, alleviate pain in the nerves and accelerate skin wound healing [20,21,22].

In this study, we found that the therapeutic efficacy in the HBO_2 group was significantly higher than in the control group *(Table 2)*, indicating that the combination of HBO_2 and conventional drug treatment is more effective than drug treatment alone. We also found that the NPRS score was significantly decreased after treatment in both groups, indicating that both drug treatment and combination of drug and HBO_2 can alleviate pain.

More importantly, after completion of HBO_2 treatment, the NPRS score in the HBO_2 group is significantly lower than that in control group, demonstrating that HBO_2 plays an additional role in easing and alleviating herpetic nerve pain. These results are consistent with previous studies showing that HBO_2 can alleviate chronic constrictive injury (CCI) induced neuropathic pain [23]. Our study also showed that scar formation time in the HBO_2 group was significantly shorter than that in the control group *(Table 3)*, indicating that HBO_2 enhances the alleviation of inflammation, growth of granulation tissue and healing of skin scars [24]. However, the period of blister resolution was not significantly different between the two groups, suggesting that HBO_2 does not play a role in resolution of active herpes infection.

We found in this study that PHN percentage in the HBO_2 group was significantly lower than that in control group, indicating that combination of HBO_2 and drug treatment is more effective in reducing PHN occurrence than drug treatment alone. It also suggests that HBO_2 can inhibit inflammation in nerve tissue, promote healing of nerve injury and reduce the nerve pain occurrence [23].

Skin burning and unbearable nerve pain caused by herpes zoster result in insomnia, irritability, anxiety, long-term psychological burden and depression [25]. We investigated the depression state of patients by determining the HAMD score in both groups. Our results showed that pre-treatment HAMD scores in patients with herpes zoster were significantly increased compared to the score in normal population, demonstrating that PHN induces depression. After completion of 30 HBO_2 treatments, HAMD scores were significantly reduced in both groups. More importantly, HAMD score in the HBO_2 group was significantly lower than that in the control group, indicating that HBO_2 plays an additional role in reversing the associated depression. Our results are consistent with previous reports showing that HBO_2 treatment has an antidepressantlike effect in forced-swimming tests in rats [26].

In summary, herpes zoster virus can invade nerves and cause long-term nerve pain and skin herpes. In this study, relative to management with medications alone, the addition of a course of HBO_2 treatment was associated with improvements in calculated therapeutic efficacy, a reduction in scar formation time, pain scores, severity of associated depression and a decrease in the percentage of subjects developing post-herpetic neuralgia.

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Conflict of interest statement

The authors have no conflict of interest to declare. ■

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