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Full Length Research Paper

Therapeutic effect of hyperbaric oxygen treatment combined with pharmacotherapy for sudden deafness: A retrospective study

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To compare the therapeutic effect of hyperbaric oxygen (HBO) treatment and pharmacotherapy with that of pharmacotherapy alone in sudden deafness (SD) patients, and to evaluate the impact of therapeutic time window on the therapeutic effect, a total of 264 patients with SD were assigned into HBO group and control group. Patients in the HBO group received routine pharmacotherapy and HBO treatment, and those in the control group were only routinely treated with drugs. Acoustic impedance measurement and pure tone audiometry were performed before and after treatment. The hearing after treatment at different time windows was compared with that before treatment. The overall efficacy in the HBO group was significantly superior to that of the control group ($P < 0.05$). The treatment initiated within 24 h after onset of SD achieved favorable outcome ($P < 0.05$) and that initiated at 24 h to 2 weeks acquired acceptable efficacy ($P < 0.05$) in both groups. However, the efficacy in the HBO group was better than that in the control group at both time windows ($P < 0.05$). Furthermore, the treatment initiated at 2 weeks after symptom onset could not achieve satisfactory efficacy ($P > 0.05$). The results demonstrated that the efficacy of HBO combined treatment was superior to that of routine pharmacotherapy for SD patients, and HBO treatment can favorably improve the hearing of these patients. HBO treatment initiated early after symptom onset (<2 weeks) is recommended, and that initiated 2 weeks after symptom onset predicts a poor outcome.

Key words: Sudden deafness, hyperbaric oxygen, time window, therapeutic efficacy.

INTRODUCTION

Sudden deafness (SD) refers to the sensorineural hearing loss of unknown cause and is usually accompanied by other symptoms including tinnitus. SD has been an important factor affecting the quality of life and work. The etiology of SD is still unclear and the pathogenesis is complicated. The potential causes of SD eventually result in ischemia and hypoxia of inner ear and finally lead to the loss of cochlear function. Hyperbaric oxygen (HBO) has been widely applied in the treatment of SD with obvious effectiveness (Bennett et al., 2007). In the present study, we compared the efficacy of combination therapy with HBO and drugs and pharmacotherapy alone in SD patients and evaluate the effect of different therapeutic time window on the efficacy. Our results may provide evidence of HBO treatment for SD.

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PATIENTS AND METHODS

Clinical information

A total of 264 SD inpatients were recruited from July 2006 to July 2010 and were assigned into the HBO and control group. Informed consents were obtained from all patients. There were 132 patients (65 males and 67 females) in the HBO group with a mean age of 47.12 ± 16.87 years (range: 22 to 64 years). The mean time to start therapy was 7.02 ± 6.88 days (4 h to 32 days) and the mean treatment duration was15.49 ± 7.30 days (7 to 35 day). All these patients had monaural hearing loss at onset and the mean auditory threshold was 74.03 ± 17.31 dB (range: 36 5 to 86 dB). There were

6 patients with mild hearing loss (26 to 40 dB), 45 with moderate hearing loss (41 to 55 dB), 43 with moderate to severe hearing loss (56 to 70 dB), 33 with severe hearing loss (71 to 90 dB) and 5 with extreme hearing loss (>91 dB).

There were 132 patients in the control group (64 males and 68 females) with a mean age of 46.96 ± 17.31 years (20 to 66 years). The mean time to start therapy was 6.84 ± 7.01 days (3 h to 31 days). The mean treatment duration was 16.38 ± 5.26 days (14 to 36 days). All these patients had monaural hearing loss at onset and the mean auditory threshold was 76.02 ± 16.21 dB (range: 37 to 87 dB). There were 5 patients with mild hearing loss, 46 with moderate hearing loss, 41 with moderate to severe hearing loss, 34 with severe hearing loss and 6 with extreme hearing loss.

The diagnosis of SD was based on the following criteria: (1) rapid loss of hearing (from several minutes, several hours to 3 days); (2) non-fluctuating sensorineural hearing loss (mild, moderate or sever hearing loss or even anacusia), the decrease of hearing in consecutive 2 frequencies was greater than 20 dB, monaural hearing loss or successive occurrence of hearing loss; (3) the causes were unknown (the local or systemic causes were not identified); (4) in the presence or absence of sense of fullness and tinnitus; (5) in the presence of vertigo, nausea, vomiting, but not repeated occurrence; (6) except for the symptoms related to the damage of eighth cranial nerve, manifestations associated with injury of other cranial nerves were not observed. The auditory nerve tumor and brainstem injury were excluded and all patients had no deafness due to infective disease, ototoxic deafness, noise deafness or deafness due to hematological disease. Computerized tomography (CT) and/or magnetic resonance imaging (MRI) of internal auditory canal were performed in all patients. Otoacoustic emission and auditory brainstem response were done to exclude the hearing loss caused by retrocochlear lesions. Acoustic impedance testing and pure tone audiometry were carried out to monitor the changes in hearing.

Treatments

In the control group**,** vasodilator, energy mixture, neurotrophic agent, etc were administered. In the HBO group, routine pharmacotherapy and HBO treatment were performed at the same time. HBO treatment was carried out in the multi-place chamber at 0.2 MPa (2 ATA). Oxygen inhalation was conducted twice for 40 min interrupted by air inhalation for 10 min. The time spent in the compression and decompression was 20 min, and one course of HBO treatment included 10 sessions. For patients receiving HBO treatment of multiple courses, there was an interval of 2 days between two consecutive courses. Nitrate esters were administered before HBO treatment to dilate blood vessels, which can counteract vasoconstriction that is induced by HBO.

Determination of therapeutic effect

Grading of the therapeutic efficacy was as follows: recovery: the hearing was normal at 0.25 to 4 KHz; or the hearing was similar to the healthy ear; or the hearing reached the level before symptom onset; favorable effectiveness: the mean increase of hearing was greater than 30 dB; effectiveness: the mean increase of hearing was about 15 to 30 dB; ineffectiveness: the mean improvement of hearing was lower than 15 dB.

Statistical analysis

Data were expressed as means ± standard deviation (x ± s) and SPSS version 13.0 statistic software package was used for statistical analysis. Paired t test was applied to compare the differences between two groups and between before and after treatment. A value of $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics

The characteristics of these patients are presented in Table 1. There were no marked differences in the age, gender, original hearing, time to treatment and treatment duration between two groups ($P > 0.05$).

Efficacy in HBO group and control group

No HBO treatment-related complications were found in the HBO group. The efficacy after combination treatment and pharmacotherapy is displayed in Tables 1 and 2. The overall efficacy in the HBO group was markedly superior to that in the control group ($P < 0.05$). When compared with the efficacy following treatments initiated at 24 h to 2 weeks after symptom onset, the efficacy was dramatically enhanced when treatments were initiated within 24 h after symptom onset ($P > 0.05$), but no significant difference was noted between two groups ($P > 0.05$). Favorable efficacy was observed when treatments started at 24 h to 2 weeks after symptom onset ($P < 0.05$) and furthermore, the efficacy in the HBO group was superior to that in the control group ($P < 0.05$). The efficacy was insufficient when these treatments began 2 weeks after symptom onset ($P > 0.05$).

DISCUSSION

The treatments of SD mainly aimed to improve the circulation of inner ear and increase the oxygen partial pressure to promote the metabolism of inner ear cells, improve the function of Na+/K+-ATPase ion pump and the electrophysiological function recovered of the cochlea (Fattori et al., 2001). HBO treatment is a common strategy in the treatment of SD and the effectiveness of HBO in the treatment of SD and concomitant symptoms have been confirmed in animal studies and clinical trials (Yoon et al., 2009).

HBO treatment can dilate the vertebral arteries and promote the blood flow leading to increase of blood supply to the labyrinth and the lesions. In addition, HBO treatment can decrease the hematocrit, improve the erythrocyte flexibility and decrease the platelet aggregation, which then reduce the blood viscosity and leukocyte aggregation resulting in improvement of microcirculation and blood supply to the injured area. Moreover, HBO treatment may promote the transformation of fibroblasts and capillary regeneration leading to formation of collateral circulation. These effects

Table 1. Characteristics of patients in both groups.

	HBO group	Control group
Gender (n)		
Male	65	64
Female	67	68
Age (yr)		
Mean	47.12 ± 16.87	46.96 ± 17.31
Range	22 - 64	20 - 66
Original hearing (dB)		
Mean	74.03 ± 17.31	76.02 ± 16.21
Range		37 - 87
Time to therapy		
Mean	7.02 ± 6.88	6.84 ± 7.01
Range	4 h - 32 days	3 h - 31 days
Duration of treatment (days)		
Mean	15.49 ± 7.30	16.38 ± 5.26
Range	7 - 35	14 - 36

Table 2. Therapeutic efficacy in both group.

Grouping	N	Efficacy (n)				Effective rate (%)
		Recovery	Favorable effectiveness	Effectiveness	Ineffectiveness	
HBO group	132	72	30	16	14	89.39
Control group	132	61	28	16	27	79.55

of HBO treatment finally result in rapid improvement of inner ear microcirculation.

HBO treatment can elevate the arterial partial pressure of oxygen and the oxygen reserve, improve the aerobic metabolism and compromise the anaerobic glycolysis. Thus, the production of ATP is facilitated, AMP level decreased and the generation of hypoxanthine reduced, accompanied by decreased activity of xanthine oxidase. Under this condition, the free radicals produced in the oxidation of hypoxanthine are reduced which then attenuates the ischemia-reperfusion injury. In addition, HBO treatment may promote the formation of hydroperoxides which can transform into stable compound through dismutation reaction. Thus, the production of free radical via chain reaction is disrupted and the amount of free radical reduced. Studies also show that HBO treatment can also activate some antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) which then scavenge the free radicals and attenuate the free radical mediated reperfusion injury leading to the protection of cochlea.

Our results showed that the efficacy of HBO treatment was superior to that of routine pharmacotherapy which may be attributed to the combined effects of HBO treatment on a variety of organs. The potential causes of SD include infection, trauma, tumors, immune diseases, toxicity, circulatory disturbance, neuropathy, metabolic diseases and others (such as stress) (Castro et al., 2007; Sun et al., 2007a; Sun, 2007b). Among these causes, circulatory disturbance of inner ear, virus infection, immune diseases and perilymph leak are widely acceptable causes. Some physicians also speculate the occurrence of SD is as a result of combined effects of the aforementioned multiple factors. HBO treatment can improve the blood system, immune system, nervous system and endocrine system of the sudden hearing loss patients and counteract with the pathological cascade leading to improvement of the SD.

In the clinical treatment of SD with HBO, HBO is frequently applied with routine pharmacotherapy. The efficacy of this combination therapy is superior to that of HBO treatment alone and pharmacotherapy alone. This may be explained by the bidirectional effects of HBO

Table 3. Impact of therapeutic time window on the efficacy.

Efficacy	HBO group			Control group		
	< 24 h	< 2 weeks	> 2 weeks	< 24 h	< 2 weeks	> 2 weeks
Recovery	69	44	19	70	42	20
Favorable	52	17	3	44	14	3
Effectiveness	11	15	4	17	8	3
Effectiveness	2	7	7	3	9	4
Ineffectiveness	4	5	6	6	11	10
Effective rate (%)	91.30	72.73	36.84	87.14	52.38	30.00

treatment. Under specific conditions, HBO treatment may elevate the lipid peroxidation and the improvement of microcirculation may be related to the frequency of treatment. When compared with HBO treatment, pharmacotherapy only improves the circulation but has limited effect on the pathological changes of cochlea of SD patients. Furthermore, increase of the dose or the type of drugs may lead to increase of side effects or even toxicity, which finally compromises the efficacy.

Our study revealed that the treatment initiated with 24 h after symptom onset could achieve excellent efficacy and that started 2 weeks after symptom onset had insufficient efficacy. The treatment of SD should be based on that recommended in the treatment of emergencies, and active and early interventions are necessary (Breuer et al., 2006). Early treatment of SD may achieve favorable outcome (Jadczak et al., 2007; Tiong, 2007). Our results revealed that both HBO treatment and pharmacotherapy acquired excellent efficacy when they were initiated within 24 h after symptom onset. Especially, combination therapy with HBO treatment and routine pharmacotherapy may recover these patients from SD regardless of the disease severity. When the treatment started within 24 h after symptom onset, the efficacy was significantly compromised, and patients initially treated 2 weeks after symptoms had poor outcome. The therapeutic efficacy of SD is closely associated with the therapeutic time window, which may be attributed to the high oxygen consumption of cochlea and its low resistance to ischemia and hypoxia (Table 3). Study showed that hypoxia of cochlea for 30 min affected the functions of hair cells, cochlear ganglion cells and spiral ligament accompanied by loss of neurons, mild changes in the tectorial membrane and irreversible destruction of action potential; ischemia for 1 h resulted in irreversible damage to cochlea function (Tabuchi et al., 2002). Treatment within 24 h after symptom onset could achieve favorable outcome, which suggests that the blood supply to the cochlea is not completely interrupted in SD and there is residual blood and oxygen supply. Due to the small sample size, we did not subgroup the patients treated within 24 h after symptom onset to explore the optimal time window of HBO treatment.

The therapeutic efficacy of HBO is relevant with the dose of treatment, which is calculated as follow: $D_{HBOT} = PO_2 \times Ts \times Nt$ (where PO_2: partial pressure of oxygen in the chamber; Ts: duration of each treatment; Nt: number of sessions). Under reasonable conditions, the therapeutic efficacy of HBO is positively related to the dose of treatment (Sata et al., 2006). In clinical treatment of SD with HBO, our experience reveals that the treatment at 2.0 ATA for 2 to 3 courses is a good regimen. Once the efficacy is not obvious after 3 courses of HBO treatment, the increase of treatment course will not further improve the outcome. This may be explained that the improvement of microcirculation disturbance in the inner ear will last for a long time and HBO treatment for longer than 20 days may cause evident lipid peroxidation and significant decrease of RBC-SOD and GSH-PX, compromising the therapeutic efficacy.

Taken together, as a strategy for the treatment of SD, HBO treatment should be initiated as early as possible. Treatment starting within 24 h after symptom onset can achieve excellent efficacy and physicians should try their best to initiate the HBO treatment within 2 weeks. In addition, for patients having poor response to initial HBO treatment, 2 or more courses of HBO treatment is recommended. For patients non-responding to HBO treatment for 3 or more courses, increasing the treatment course will not further improve the outcome and in the contrast increase the medical cost.

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