The Efficacy Of Hyperbaric Oxygen Therapy For The Treatment Of Diabetic Autonomic Neuropathy

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Abstract

Objective: The aim of the present study was to examine the efficacy of hyperbaric oxygen therapy for the treatment of diabetic autonomic neuropathy. Research Design and Methods: We conducted a study of 20 consecutive eligible patients with diabetic autonomic neuropathy. All patients had been stabilized in terms of their glycemic control for 3 months before the study. The mean age of patients was 61.7±8.2 years, the mean diabetes duration 13.8±7.9 years. For the identification of autonomic diabetic neuropathy, non-invasive testing of cardiocirculatory functions were performed. All patients underwent electromyelography to obtain sympatric cutaneous responses by stimulating two different extremities.

Results: There was a significant difference in autonomic neuropathy tests after hyperbaric oxygen therapy ($p>0.001$). Before hyperbaric oxygen therapy, mean valsalva ratio was 1.1±0.1, mean heart rate variation with inspiration was 10.4±2.4 beats/min, mean heart rate response to stand up was 1.0±0.04, mean systolic blood pressure response to stand up was 33.4±2.9mmHg. After hyperbaric oxygen therapy, mean valsalva ratio was 1.2±0.1, mean heart rate variation with inspiration was 15.9±2.2 beats/min, mean heart rate response to stand up was 1.0±0.03, mean systolic blood pressure response to stand up was 14.1±6.6mmHg. There was a significant differences in symphatic cutaneous responses that were obtained by stimulation of different region during electromyelography procedure.

Conclusion: After Hyperbaric Oxygen Therapy, the autonomic neuropathy tests and electromyelographic findings were significantly improved. We supposed that hyperbaric oxygen therapy was an effective therapeutic modality for the treatment of diabetic autonomic neuropathy

introduction

Diabetes mellitus is the commonest cause of neuropathy in industrialized countries. The usual pattern is a distal symmetrical sensory polyneuropathy, associated with autonomic disturbances. Less often, diabetes is responsible for a focal or multifocal neuropathy. It is well known that diabetic autonomic neuropathy develops within a short duration of diabetes even when somatic neuropathy is not apparent. Metabolic abnormalities due to hyperglycemia and their consequences, ischemic phenomena secondary to diabetic microangiopathy account for nerve lesions. Diabetic autonomic neuropathy causes functional disorders of many organs, such as cardiovascular, gastrointestinal, genitourinary, metabolic, and pupillary dysfunctions. Among these, cardiovascular autonomic neuropathy may increase the risk of sudden death and affects the mortality of diabetic patients. Therefore, the diagnosis and treatment of autonomic neuropathy at an early stage is important for the management of diabetic patients.

Research Design And Methods

The study subjects were recruited from the patients who consecutively visit the internal medicine clinic of GOlhane Military Medical Academy, Haydarpasa Training Hospital. A total of 20 diabetic patients who have diabetic autonomic neuropathy were enrolled in the present study. Patients with any other causes of neuropathy, including severe liver renal dysfunction, malignant diseases, hypothyroidism, or excessive

alcoholic intake, were excluded. We also excluded patients with diseases interfering with cardiovascular reflexes (e.g., ischemic heart disease, heart failure, or valvular heart disease) and those receiving cardiac glycosides, anticholinergics, sympathomimetics, R-blockers, or other agents affecting the heart rate variability. All patients had been stabilized in terms of their glycemic control for 3 months before the study.

The mean age of patients was 61.7±8.2 years, the mean diabetes duration 13.8±7.9 years. After obtaining informed consent, the baseline neurological function was established, and the patients underwent hyperbaric oxygen therapy (20 days, 120 minute per day). Neurological assessments including neurological examination, nerve conduction tests, and cardiovascular autonomic function tests were performed by investigators who were blinded to study group before entry into the trial and at the end of the trial. During the study, the patients continued their antidiabetic therapy, such as diet, exercise, oral hypoglycemic agents, or insulin; no attempt was made to alter the therapy or the level of glycemic control.

For the identification of autonomic diabetic neuropathy, non invasive testing of cardiocirculatory functions (Valsalva's maneuver, variation of the RR intervals, respiratory variation of R-R intervals, blood pressure between recumbent and upright positions) were performed. After 5 minute rest on a bed in the supine position, an electrocardiograph (Cardiofax V, ECG-9320K, Nihon Kohden Cooperation, Tokyo, Japan) was used to measure the R-R interval of 100 heartbeats and calculate automatically the corrected QT time (QTc) and resting heart rate variation. The ratio of the breathing at a rate of six times per minute was calculated. Postural changes of blood pressure were obtained by measuring the blood pressure in the resting supine position on a bed and after standing up.

All patients underwent electromyelography (Amplaid EMG 14) to obtain sympatric cutaneous responses by stimulating two different extremities. By this method, we obtained 8 different sympatric cutaneous responses for every subject (table 1)

Table 1: Eight different sympatric cutaneous responses that were obtained by stimulation of different region during electromyelography procedure.

Symp·:Ada(' clitaneous Recording **to on** relp0119E•S		Stimulation ivOii
I	Right hand	Right elbow, median nerve
Ⅱ	Right hand	Left elbow, median nerve
Ⅲ	Right hand	Right ankle, peroneal nerve
IV	Right hand	Left ankle, peroneal nerve
V	Left hand	Right elbow, median nerve
VI	Left hand	Left elbow, median nerve
VII	Left hand	Right ankle, peronml nerve
VIII	Left hand	Left ankle, peroneal nerve

We evaluated two components of these recorded responses; (L1)-time duration between stimulation and first positive wave, (L2)- time duration between stimulation and first negative wave.

After obtaining basal data included sympatric cutaneous responses and cardio circulatory function tests, all patients underwent hyperbaric oxygen therapy with 2-atmosphere pressure, lasting 20 days and 120 minute per day. After hyperbaric oxygen therapy, all tests mentioned above were performed again.

Statistical Analysis

All data were presented as mean ± SD. For comparison of data that were obtained pre and post-HBO therapy, the Wilcoxon Signed Ranked test was used. Probability levels less than .05 were considered significant.

Results

Twenty consecutive eligible patients with diabetic autonomic neuropathy were enrolled to the study. The group included 13 women and 7 men, had a BMI of 27,4±3,4 kg/m2 (range 21.5-36.2) and were aged 61.7 ± 8.2 years (range 49-78).

The mean glucose level was 12.0±2.5 mmol/L, mean glycosylated hemoglobin (HbA1c) was 9.5±2.1, mean duration time of diabetes was 13.8±7.9. These results were summarized in Table 2.

Table 2: Values (mean ± sd) of some demographic, anthropometric and metabolic parameters in study patients

Variable	Study Pi-dims
n	20
Sex (woman)	65
Age (years)	61.7±8.2
Duration of diabetes(years)	13.8: ±7.9
BMI (kg/m)	27.4±3.4
Fasting Glucose	12.0±2.5
HbAlc (%)	9.5±2.1

There was a significant difference in autonomic neuropathy tests after hyperbaric oxygen therapy. Before hyperbaric oxygen therapy, mean valsalva ratio was 1.1±0.1, mean heart rate variation with inspiration was 10.4±2.4 beats/min, mean heart rate response to stand up was 1.0±0.04, mean systolic blood pressure response to stand up was 33.4±2.9mmHg. After hyperbaric oxygen therapy, mean valsalva ratio was 1.2±0.1, mean heart rate variation with inspiration was 15.9±2.2 beats/min, mean heart rate response to stand up was 1.0±0.03, mean systolic blood pressure response to stand up was 14.1±6.6mmHg. These results were summarized in table 3 and 4.

Table 3: Values (mean ± standard deviation) of autonomic neuropathy tests in study patients before and after hyperbaric oxygen therapy.

	Before HBO tlierapy	After HBO dier˙tpy
ii	20	20
Valsalva ratio	1 1+0 1	1 2+0 1
Heart rate variation with inspiration (beats/min)	10.4+2.4	15.9+12
Heart rate response to standup	1 O*0 04	1.0+0.03
Systolic blood pressure resporise to stand up (mmHg)	33.4+2.9	14.1+6,6

Table 4: Statistical differences (according to Wilcoxon ranked signed test) between autonomic neuropathy tests before and after HBO therapy.

Variable	Before HBO therapy 20	After HBO therapy 20	p values
Valsalva ratio	1,1+0.1	1.2+0.1	p<0.001
Heart late variationwith inspiration (beatsinin)	10.4+2.4	15.9+2.2	p<0 001
Heart roe response to stand up	1.0+0.04	1.0+0.03	p<0.001
Systolic blood pres.que response to stand (ion dig)	33.4+2.9	14.1+6,6	p<0.001

(NS=non-significant, p<0,05=significant)

There was a significant differences in sympatric cutaneous responses that were obtained by stimulation of different region during electromyelography procedure. These results were summarized in table 5 and 6.

Table 5: Values (mean±sd) of sympatric cutaneous responses that were obtained by electromyelography before and after HBO therapy

Stimulation region during electromyelography	LI time duration (sec) (Before HBO therapy)	LI time duration (sec) (After HBO therapy)	L2 time duration (sec) (Before therapy)	L2 time duration (sec) (After HBO therapy)
I	2.1±0.3	2.2/.1.8	2.7/0,4	2.4±0.3
	2.912.2	2.2+1.9	2.9±0.3	2.5/0.3
III	, 7*2.0	—3/1.9	2."/O.4	
IV	.612.0	2,411.9	2 610.4	510.3
V	3.0±2.2	.6/2.0	2.9±0.5	2. 7±0 .4
VI	3.0±2.2		2.9±0.3	2.610.4
VII		3.6±2,2	3.2±0	2.84:0,5
VIII	3.1/2.3	3.1±2.2	3.1+0.4	2.8A:0.5

(HBO=Hyperbaric oxygen therapy)

Table 6: Statistical differences between sympatric cutaneous responses that were obtained by electromyelography before and after HBO therapy

Stimulation region during electromyelography	LI time duration before vs. after HBO therapy	L2 time duration before vs, after HBO therapy
I	**p- .1301**	p - AI
II	**1)-11001**	p.; 0.001
III	p<0,01	0.01
IV	p<0.01	p 0.05
V	p<0,01	0,01
VI	p<001	0.01
VII		p:0.05
VIII		NS

Wilcoxon signed ranked test; p>0.05: non-significant (NS)

Discussion

Among the most common of the long-term complications of diabetes are those affecting the peripheral nervous system (1). A simple definition of diabetic neuropathy was agreed to by the International Consensus Group on neuropathy: "The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (2).

The observation that neuropathy has been described in patients with primary (typel and type 2) and secondary diabetes of varied causes suggests that a common etiologic mechanism based on chronic hyperglycemia has received support from large prospective studies such as the Diabetes Control and Complications Trial and U.K.Prospective Diabetes Study (3 , 4 , 5). The most important etiological factors that have been associated with neuropathy are poor glycemic control, diabetes duration, with possible roles for hypertension, age, smoking, hypoinsulinemia, and dyslipidemia (6).

Nerve fibers degenerate and blood vessels supplying them are grossly diseased in patients with diabetic neuropathy. Until the last 10 years, the role of vascular factors in the pathogenesis of diabetic neuropathy was denied or seriously questioned. However, the recent data from animal models provides inconvertible evidence that microangiopathy plays a crucial role in the pathogenesis of nerve damage. Furthermore, the development of a significant microangiopathy may form the critical point, which determines whether or not nerve fibers repair themselves or proceed to total degeneration and hence clinically relevant neuropathy (7).

Therapeutic intervention with a range of vasoactive drugs improves nerve function in animal models. Promising results in diabetic patients have also been achieved using a range of therapies, including large-vessel revascularization, ACE inhibitors, g-linoleic acid, and lipoic acid. The results of large clinical trials involving therapies acting via the vascular axis supported the clinical relevance of the vascular hypothesis (7, 8 , 9 , 10 , 11 , 12). Hypotheses concerning the etiology of diabetic polyneuropathy have involved a direct metabolic insult to nerve fibers, indirect consequences of neurovascular insufficiency, impaired neurotrophic support, and autoimmune damage (12, 13 , 14). Reduced nerve perfusion is an important factor in the etiology of diabetic neuropathy. Studies in streptozocin-induced diabetic rats show that nerve conduction velocity (NCV) and blood flow deficits are corrected by treatment with vasodilator drugs, with angiotensin II and endothelin-1 antagonists being particularly important. The AT1 antagonist ZD7155 also prevents diabetic deficits in regeneration following nerve damage, indicating that hypoperfusion is an important limitation for nerve repair (12, 15).

The main effects of diabetes are likely to depend on hyperglycemia. The major metabolic changes caused by hyperglycemia are increased polyol pathway flux, elevated oxygen free radical formation, and advanced glycosylation. All of these factors appear to have a negative impact on nerve blood flow and NCV in diabetic rats (7,8,9,10,12). While several hypotheses are potentially applicable, it is clear that polyol pathway involvement depends largely on vascular events. Aldose reductase inhibitors (ARIs) prevent the development of impaired NO-mediated endothelium-dependent relaxation in large vessels from diabetic rats. Further evidence linking polyol pathway effects to a vascular mechanism, comes from studies showing that NO synthase inhibitors completely block the beneficial actions of ARIs on NCV and blood flow in diabetic rats (12, 16).

Diabetes causes endothelial dysfunction, reduced nerve perfusion, and impaired nerve function. The majority of pharmacological manipulations shown to improve nerve function in diabetic rats do so via a neurovascular rather than a neurochemical mechanism. Thus, tje importance of the endoneurial microenviroment and maintenance of adequate perfusion must be considered for selecting therapeutic agents in patients with diabetic neuropathy. It is becoming clear that there are important defects in several control systems, and therefore a multiple treatment strategy could be appropriate (12).

After hyperbaric oxygen therapy, the autonomic neuropathy tests and electromyelographic findings were significantly improved. We supposed that hyperbaric oxygen therapy was an effective therapeutic modality for the treatment of diabetic autonomic neuropathy.

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