PRELIMINARY COMMUNICATION

Hyperbaric Oxygen for Treatment of Stroke and Traumatic Brain Injuries

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Abstract

Fifty stable, chronic stroke and traumatic brain injured (TBI) patients (mean age 62, mean duration post stroke 29 months) were treated with a combination of hyperbaric oxygen, physical therapy and EEG biofeedback for two months. Surveys given to patients or their family members showed that 96.7% of the patients improved one or more of their lost or diminished functions. Pre- and post-treatment physical therapy evaluations indicated that 100% of the patients experienced improvements in one or more functions. These results indicate that hyperbaric oxygen therapy in combination with other modalities is a safe and effective treatment for stroke or TBI related disabilities.

Introduction

Health care practitioners have tried a variety of different methods to improve the quality of daily life for post-stroke patients but in general, the results have not been satisfactory. Although stroke is a leading cause of death and disability, its long term management is often marked by feelings of hopelessness on the part of both patients and professionals. Any treatment that provides increased functional abilities and helps these people live more independently and economically, should be made available to this large population of suffering individuals as soon as possible for both humanitarian and economic reasons.

Hyperbaric oxygen therapy (HBO) is one such method. HBO is the use of daily treatments of oxygen under pressure and was first described as being beneficial for treatment of stroke patients in 1965. Since then many studies have demonstrated its safety and efficacy for the treatment of acute and chronic stroke and the traumatically brain injured (1,2,16-20).

The dominant theory of stroke and TBI for more than 100 years has been that the lost functions that are observed in these cases are caused by the death of brain cells due to the interruption of blood flow and the resulting lack of oxygen to part(s) of the brain. This traditional concept of infarction as the cause of all brain injury disabilities is being challenged by a theory which has been slowly evolving over the past 25 years. This theory states that the death of brain cells occurs only when the flow of blood falls below a certain level (approximately 8-10 ml/100 gr./min.), while at slightly higher levels of blood flow the tissue remains alive but not able to function. Thus in the acute stroke the affected central core of brain tissue dies while the more peripheral tissues may remain alive for many years after the initial insult, depending on the amount of blood the brain tissue receives (3,7).

Brain areas that are injured and are not receiving enough blood flow as a result of the stroke or trauma are now referred to as the "ischemic penumbra." This is the area that surrounds the central core of infarcted (dead) tissue. These "rim" tissues do not receive enough oxygen to function but do receive enough to stay alive. These brain cells have been described as "sleeping beauties," "sleeping neurons," or "dormant," or "idling neurons." These neurons are non-functional but anatomically intact and can be revived (3,8-10).

It is widely recognized that damaged blood vessels are thought to produce the ischemic penumbra in stroke or TBI. In the acute phase of stroke or TBI, damaged, dying and dead brain cells develop leaky plasma membranes allowing calcium and sodium into these cells which is followed by the accumulation of water which produces extensive and damaging edema. This swelling, if severe, may kill the person within the first 24 to 72 hours. If the person doesn't die, it may take up to 9 to 12 months for

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the edema to resolve during which time the swelling compresses the involved brain blood vessels, limiting the flow of blood to the damaged tissues. As the swelling goes away, some of the blood vessels will regain their original diameters and normal blood flow will resume (9) but other vessels will remain permanently narrowed, spastic or obliterated. HBO has been shown to be effective at reducing the amount of edematous tissue of the brain significantly (12-14).

The outermost portions of the ischemic penumbra (those portions closest to normal brain tissue) are able to metabolize but at a reduced rate compared to normal tissues; however, they are receiving more blood and oxygen than the centrally located ischemic tissues. Adenosine, a metabolite of ATP, is released from ischemic "rim" tissues when cells metabolise and repair. Adenosine is a vasodilator that stimulates new capillaries to grow into the ischemic penumbra (neovascularization). Neovascularization is defined as "new blood vessel formation in abnormal tissue or in abnormal positions" (21), while angiogenesis is defined as "the formation of blood vessels" (21). Neovascularization is thus the correct term for the process of forming new capillaries which extend from the surrounding healthy brain tissue into the areas of the ischemic penumbra. During the first year after a stroke or TBI, new blood vessels have been shown to be stimulated to move into the ischemic penumbra to re-supply it with a new blood supply (9).

Unfortunately, the ischemic penumbral tissues closer to the infarct area usually are not receiving enough oxygen or nutrients to generate adequate amounts of ATP, either from aerobic or anaerobic metabolism, for neovascularization to occur. Due to the lack of ATP formation, adenosine is not produced and the formation of new capillaries does not occur. Thus the ischemic penumbra remains ischemic and static since the process of neovascularization is not able to be completed. This often results in a substantial amount of brain tissue that remains ischemic and non-functioning in the chronic stroke and TBI patients. This failure of natural healing processes is due ultimately to damaged blood vessels and their inability to provide oxygen and nutrients to those portions of the brain that are damaged (11).

Hyperbaric oxygen works to improve chronic stroke and TBI patients by regenerating, repairing and generating new blood vessels to the injured parts of the brain. In the ischemic penumbra, the blood vessels are often constricted to the point that red blood cells can not pass through them. This creates the situation where only plasma is able to pass slowly to part or most of the ischemic area. Since plasma has nutrients, the tissues of the ischemic penumbra are able to remain alive by using anaerobic glycolysis (metabolism without oxygen) also known as fermentation. Anaerobic glycolysis only produces 2 moles of ATP per mole of glucose metabolized instead of the 36 moles of ATP formed when oxygen is present. Thus the tissues suffer from a chronic shortage of ATP and its subsequent metabolite, adenosine. Hyperbaric oxygen forces oxygen into the plasma to such a degree that as the plasma passes into the ischemic penumbra, the ischemic tissue begins to receive enough oxygen for aerobic glycolysis (metabolism that uses oxygen) to occur once more. This creates a surge of ATP production in the ischemic tissue which continues to be produced as long as the patient is within the hyperbaric oxygen chamber. When the patient is taken out of the chamber, blood and tissue levels of oxygen fall back to pre-treatment levels within 4 hours. As the tissue oxygen level falls, the newly generated ATP is used by the ischemic tissues and adenosine is released into the surrounding tissues in an effort by the tissues to continue receiving oxygen. As a part of this survival mechanism, adenosine and other chemical mediators are released into the surrounding tissues stimulating neovascularization. Done daily over many days, the HBO stimulates new blood vessels to grow into the ischemic tissues returning them back to normal in terms of their oxygen supply. Recovery of function is associated with recovery of local perfusion and metabolism (11).

Once the ischemic penumbral tissues are no longer suffering from a lack of oxygen, they are able to begin to repair their injured neurons, glial cells and extracellular matrix. These neurons not only have to repair their own cell bodies, dendrites, axons and synapses but also have to grow out and extend to the many lost connections that occurred at the time of the stroke or TBI. Due to these events, patients experience positive results during the 60 days of daily hyperbaric oxygen because of the renewed oxygen supply (neovascularization). In addition, most patients continue to see improvements for another six or more months after the completion of the course of hyperbaric oxygen due to continuing cellular repair and reconnections.

METHODS

A. PATIENTS

50 patients (male 21 and female 29) voluntarily enrolled in this study. Patients' ages ranged from 31-89 years with a mean age of 61.8 years. The duration from onset of stroke to entry into our rehabilitation program varied from 1 month to 10 years. The average duration since stroke onset was 29 months. Three of the patients suffered from the results of a stroke more than 8 years before entering our program.

TABLE 1
PATIENTS' PRE-TREATMENT CONDITION

Number	Diagnosis
9	brain hemorrhage
4	embolic infarction
3	stroke after brain surgery
1	a car accident
33	ischemic infarction (thrombosis)

B. TREATMENT

1. HBO treatment: Patients received hyperbaric oxygen therapy (HBO) at a pressure of 1.5 to 2.0 atmospheres absolute (ATA) in a sealed single person chamber (Hyox, Aberdeen, Scotland). Oxygen (100% medical grade) was inhaled through a plastic face mask.

The therapy was carried out for 90 minutes per day and 6 times per week in most patients. A few patients received HBO treatment twice a day. The average number of HBO treatments completed was 55.

Hyperbaric oxygen therapy feels much like going for a ride in a modern day jet - the chamber even looks like the cockpit of a jet fighter plane! As patients start their treatment they are sitting upright at a comfortable angle inside of this cockpit-like chamber. Patients have an oxygen mask over their mouth and nose,

the door is shut and they feel a slight movement of air as the chamber begins to be filled with more air. As the air enters the chamber they may notice a slight discomfort in one or both ears just like that experienced while flying in the large commercial jets. Patients may choose to swallow, chew gum or hold their nose and blow outward to help equalize the pressure in their ears.

2. Physical therapy treatment. Physical therapy procedures included various physical activities and modalities as assessed by a registered physical therapist. The modalities used were electrical stimulation, hot or cold packs, ultrasound, short wave diathermy and paraffin bath therapy. Each patient's condition was evaluated to determine the appropriate modality, dosage, placement and methods of application.

Physical therapy techniques were provided and adjusted as the patient's condition warranted. These included strengthening, range of motion, endurance exercise, neurodevelopmental techniques, joint mobilization, kinetic activities, myofascial release and detailed gait or orthotic training.

Initial evaluation assessed range of motion, strength grades, bed mobility, transfer status, balance, neurological findings, posture and ambulatory status. Periodic re-evaluations were performed to assess each patient's progress, and treatment plans were changed as needed. Upon discharge, a discharge evaluation was performed to assess progress and determine the patient's long term therapy program.

The number of therapies varied from 13 to 85 treatments with a mean of 40. Patients came to physical therapy 5 times per week.

3. Bio feedback treatment. Patients came to biofeedback therapy 5 times per week and received a minimum of 21 (mean 35) one-half hour daily sessions of EEG biofeedback. Sessions consisted of inhibiting and rewarding various selected EEG frequencies through audio and visual displays to encourage flexibility in brain activity. Each session's threshold levels were automatically calibrated by the instrument (American Biotech Capscan 80) and a frequency spectral display summarized EEG amplitudes over 0 to 32 Hertz.

C. Treatment Evaluation

The effects of treatment were evaluated by a patient's questionnaire and a licensed physical therapist's evaluation given both at the beginning of the program and again at the end.

In the patient questionnaire, 16 different functions ranging from motor ability and mental situations were analyzed. Patient's functions were self-graded as follows:

- : negative change
0: no improvement at all;
Slight improvement: 1-10 % of the function improved;
Mild improvement: 10- 25% of the function improved;
Moderate improvement: 20-50% of the function improved;
Significant improvement: 50 -75% of the function improved;
Back to normal: 100% of the function improved.

In the physical therapist's evaluation, 33 different functions ranging from motor ability to cognitive functioning were analyzed. For statistical purposes we assigned the therapist's evaluation of each parameter as either being no improvement or improvement.

Range of movement: NA stands for "not available" because the patient's function was within normal limits before the treatment. "No improvement" means the increased range of movement is less than 10 degrees. "Improvement" stands for when the range of movement increased 10 degrees or more. No matter how much more than 10 degrees of increased range of motion occurred, all positive results were grouped simply as "improvement."

Extremities strength evaluation: Grading was on a 0-5 degree scale with 0 indicating no strength and 5 indicating normal as compared to the non-involved extremity. NA stands for "not available" because the patient's function of that extremity was normal before the treatment. No improvement means the increased strength was less than one degree of improvement, e.g., from 3- to 3+ (minus three to plus three) was considered as no improvement. Improvement would be indicated when the strength increased at least one degree, such as from 2 to 3. No matter how much more than one degree of improvement occurred in a particular patient, it was still only graded as "improvement."

Other functions such as bed mobility, transfer (supine to sit, sit to stand, bed to chair) balance (sitting, standing, ambulatory) were graded as:

#1, independent
#2, good
#3, good with care
#4, with minimal assistance
#5, with maximal assistance
#6, unable

Improvement was defined to occur when the patient's functional evaluation score decreased by at least 1 (#6 being unable to perform the task and #1 being able to do the task independently).

Results

A. Patient Questionnaire

Patient questionnaires were collected prior to and after the series of treatments.

Patients' general comments for this program are shown in Table 2.

Table 2
Patient Ratings of Program Quality

Consider this program poor	0.0%
No improvement (received 22 HBO treatments only)	3.3%
Consider this program good	30.0%
Consider this program excellent	46.7%
Consider this program "stupendous"	20.0%
Total improvement in at least one of the functions is	96.7 %

Only insignificant problems were encountered with the combination of therapies for treating chronic stroke patients. The summary of the patients' self-evaluations are in Table 3 and Graphs 1-4.

B. Physical Therapist's Evaluation

Physical therapist's evaluations were performed prior to and at the end of the program. Thirty three (33) different functions including range of motion, strength and balance function were analyzed. From the paired evaluations, all the patients showed one or more improvements among the 33 functions.

The general findings from the physical therapist's evaluations are listed in Table 4.

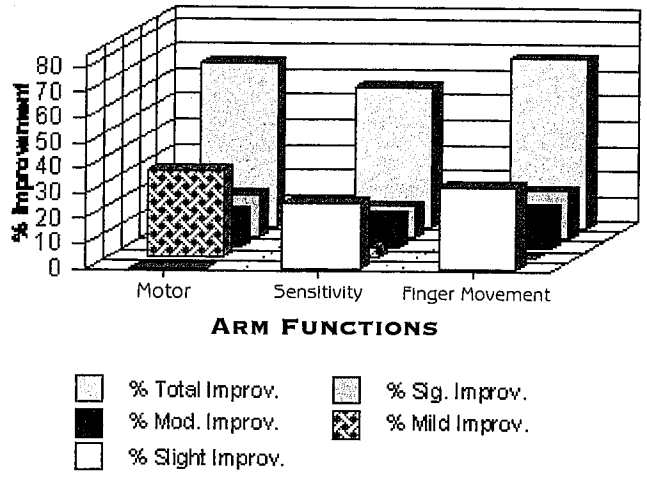
TABLE 3 IMPROVEMENT LEVEL AS EVALUATED BY PATIENTS/CARETAKER

Function	Improvement					
	%No	%Slight	%Mild	%Mod.	%Significant.	%Total
Arm's motor ability	34.29	0.00	34.29	14.29	17.14	65.72
Arm's sensitivities	43.48	26.09	4.35	13.04	13.04	56.52
Finger's movement	32.26	32.26	0.00	16.13	19.35	67.74
Leg's motor ability	13.16	13.16	34.21	21.05	18.42	86.84
Walking	13.51	0.00	24.32	35.14	27.03	86.49
Sit down ability	30.00	0.00	13.33	33.33	23.33	70.00
Stand up	33.33	0.00	10.00	40.00	16.67	66.67
Foot	53.57	21.43	0.00	14.29	10.71	46.43
Speech	26.09	4.35	30.43	21.74	17.39	73.91
Memory	20.83	0.00	29.17	25.00	25.00	79.17
Thinking	16.67	0.00	20.83	37.50	25.00	83.33
Understanding	13.64	0.00	27.27	31.82	27.27	86.36
Urine control	31.35	0.00	21.05	21.05	26.32	68.42
Bowel Control	17.65	17.65	11.76	11.76	41.18	82.35
Vision	47.37	0.00	15.79	10.53	26.32	52.63
Hearing	46.67	0.00	13.33	6.67	33.33	53.33

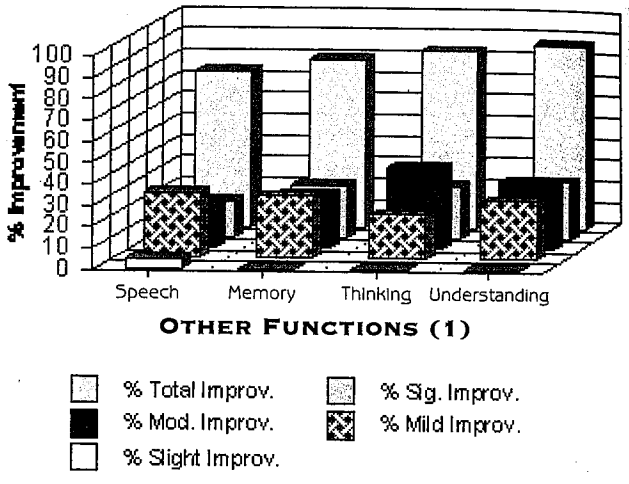
TABLE 4

% patient	general functional improvement levels
10 %	minimal gains
7 %	mild gains
48 %	good gains
34 %	excellent gains
Total 100%	show improvement

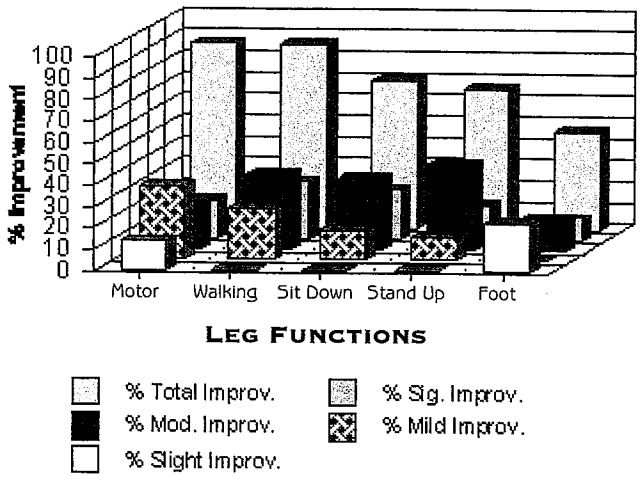
GRAPH 1
PATIENT'S IMPROVEMENT LEVEL



GRAPH 3
PATIENT'S IMPROVEMENT LEVEL



GRAPH 2
PATIENT'S IMPROVEMENT LEVEL



GRAPH 4
PATIENT'S IMPROVEMENT LEVEL

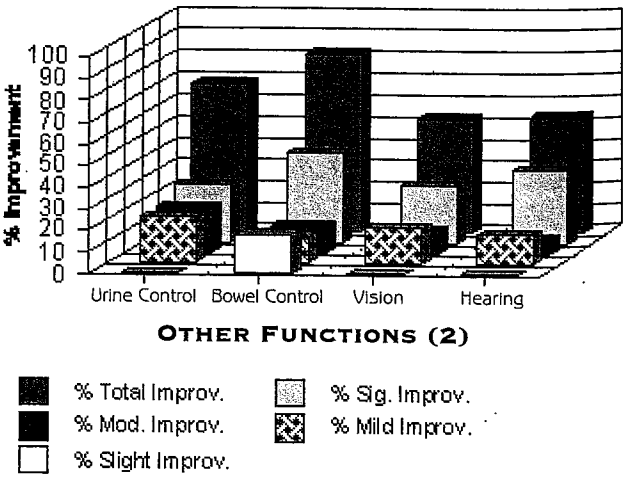


TABLE 5
PHYSICAL THERAPIST'S EVALUATION OF EXTREMITIES

	Improvement in Range of Motion		Improvement in Strength	
	No %	Yes %	No %	Yes %
Shoulder				
Extension	0.00	100.00	34.48	65.52
Flexion	0.00	100.00	48.15	51.85
Abduction	18.75	81.25	48.15	51.85
Adduction	0.00	100.00	48.15	51.85
Internal Rot	50.00	50.00	50.00	50.00
External Rot	42.86	57.14	50.00	50.00
Elbows				
Flexion	0.00	100.00	50.00	50.00
Extension	50.00	50.00	29.63	70.37
Forearm/Wrist				
Supination	33.33	66.67	55.56	44.44
Pronation	N/A	N/A	51.85	48.15
Flexion	N/A	N/A	40.74	59.26
Extension	28.57	71.43	51.85	48.15
Hip				
Flexion	N/A	N/A	41.38	58.62
Extension	N/A	N/A	42.86	57.14
Abduction	N/A	N/A	46.63	53.57
Adduction	N/A	N/A	29.63	70.37
Internal Rot	N/A	N/A	50.00	50.00
External Rot	N/A	N/A	53.57	46.43
Knee				
Flexion	50.00	50.00	62.96	37.04
Extension	100.00	0.00	35.71	64.29
Plantar Flexion	0.00	100.00	57.69	42.31
Dorsiflexion	83.33	16.67	55.56	44.44
Inversion	100.00	0.00	73.08	26.92
Eversion	N/A	N/A	68.00	32.00

TABLE 6
PHYSICAL THERAPIST'S EVALUATION

	% No improvement	% Showed improvement
Bed Mobility		
Rolling right	20.00	80.00
Rolling left	44.44	55.56
Transfer		
Supine to sit	0.00	100.00
Sit to stand	7.14	92.86
Bed to chair	7.14	92.86
Balance		
Sitting	42.86	57.14
Standing	21.05	78.95
Ambulatory	30.43	69.57

From Table 4, 100% of patients were shown to have made some improvement by the physical therapist's evaluation.

No side effects or problems were encountered with the combination of therapies for treating chronic stroke patients. The results of paired analysis are shown in Tables 5 and 6.

DISCUSSION

The results from this study demonstrate that combined use of HBO, physical therapy and EEG biofeedback benefited patients suffering from the chronic effects of a stroke. The improvements were similar among patients suffering from cerebral hemorrhage, and cerebral ischemia/thrombosis/embolism. Improvement also occurred in the 3 patients who had suffered from a stroke more than 8 years before beginning our combined therapy program.

Other improvements were also reported by the patients. For example, patients reported that their affected arm and leg felt chronically cold but changed to warm during the therapy. Fingernails and hair, which had stopped growing normally for several years, began to grow normally again. The chronic fatigue experienced by the patients prior to their therapy was generally relieved by the program.

The number of treatments required varied for each individual but experience has demonstrated that the best results occurred when at least 60 daily, consecutive treatments were done. If only 20 to 30 treatments were done, the patient would often experience "backsliding" and would often lose some of the improvement they gained from the hyperbaric oxygen treatments especially when later exposed to life stresses. In addition, some patients would not even begin to improve until they had more than thirty, forty or even more treatments. The reason for the "backsliding" that could occur with less than 30 treatments has not been studied scientifically but since it occurs at times of stress, it would seem to be due to the effects of excessive corticosteroids and catecholamines produced at these times. Stress hormones have anti-angiogenic properties and accelerate the production of free radicals and lipid peroxidation in blood vessels, all of which will have a detrimental effect on newly growing and fragile capillaries.

In the acute stroke situation, as much as 85% of the brain injury may be due to the ischemic penumbra. The newly approved "clot busting" drugs (tPA-tissue plasminogen activators) have been found to be effective in restoring the vitality of the ischemic penumbra if given within the first three hours of the onset of an ischemic type of stroke. Hyperbaric oxygen is being considered as a treatment in conjunction with tPA in the acute stroke setting since it is thought that it will extend the period of time during which the tPA can be given safely and effectively (4-6, 10).

When used according to standard protocols, with oxygen pressures not exceeding 2 atmospheres and treatment sessions limited to a maximum of 120 minutes, hyperbaric oxygen is safe (15).

In terms of overall side-effects we have had three out of more than 500 patients who had enough pain and discomfort in their ears to require an ear specialist insertion of a small tube through the ear drum (tympanostomy tube). In these cases, this cured the problem and the person was able to continue with the program without further pain and with no problems with their hearing.

Severe, advanced emphysema may be a contraindication if the person has large lung bullae (large air filled sacks within the lung). The bullae may trap the oxygen and rupture while the person is decompressing. The presence of large bullae can be checked by ordering a CT exam of the chest.

Patients who have had a seizure worry about having another episode while in the chamber. Doctor K.K. Jain (1) the MD neurosurgeon who wrote the *Textbook of Hyperbaric Medicine* states, "Seizures are extremely rare and no more than a chance occurrence during HBO sessions at pressures between 1.5 and 2 ATA (2 ATA gauge pressure= 14.7 psi=760 mmHg) even in patients with a history of epilepsy." Our experience is similar.

Claustrophobia is an often voiced fear but once the person begins to work with our technicians, he or she is generally able to overcome their fears without a problem.

Muscle, bone and peripheral nerve dysfunction and atrophy are also major factors that are present in most chronic stroke or TBI patients. This is due to inactivity, loss of weight bearing, hormonal deficiencies, mineral deficiencies and a variety of different disease states. These dysfunctions and atrophy require aggressive, daily rehabilitative efforts for a minimum of two months to produce significant, long term beneficial results.

From a practical point of view, the patient who is being considered for hyperbaric oxygen therapy can be tested to determine if he/she is a candidate. A 3-D SPECT scan (3-dimensional, three headed, single photon computerized tomogram) for determining cerebral blood flow is available at most larger hospitals in the USA. If this test is done and shows focal diminished brain blood flow, the patient has a good chance for significant improvement with a course of hyperbaric oxygen treatments.

Hyperbaric oxygen produces the best overall results when the therapy is given in combination with other treatments such as physical, occupational and biofeedback therapy. Patients come to us on average about 2½ years after their stroke or TBI. They usually have gone through all of the standard therapies and have not improved over the past year despite continuing physical therapy and an active exercise program. They or their family members recognize their lack of improvement and come to us as "the last hope." Due to the severity of their disabilities and their failure to improve with conventional therapies, most patients and family hope that the use of hyperbaric oxygen will produce gratifying results. However, even with 60 days of hyperbaric oxygen treatments, the results may not reach their expectations, especially if only hyperbaric oxygen is used. Most patients would like to maximize their chances of improving while they are attending our clinic. In view of their desires and the fact that the combination of hyperbaric oxygen and other therapies produces improved overall results, we recommend daily physical, occupational, speech, vision, biofeedback, nutritional, vitamin, hormonal and growth factor therapies as needed to help our patients reach their maximum recovery potential.

In addition to the use of the above mentioned therapies I have also found that many patients have other disease processes which must be treated to maximize their recovery. Many patients when entering our program suffer from chronic urinary tract or other infections, have autoimmune disorders such as vasculitis, suffer from diabetes and diabetic neuropathy, have osteoporosis of the paralyzed limb(s), have serious atherosclerosis, hypertension, heart disease or have hormonal deficiencies and/or combinations of all or some of these chronic conditions. All pathologic conditions and problems must be diagnosed and corrected as much as possible to maximize the patient's healing.

Conclusion

Chronic stroke and TBI patients, who are stable and have not improved their functioning abilities for months to years, can achieve significant benefits from the combined administration of HBO, physical therapy and bio-feedback. This therapy program has been demonstrated to have insignificant side effects and in our experience is safe and effective.

Biography

David Steenblock, BS, MS, DO, received his BS from Iowa State University (1964) and his MS in Biochemistry (1967) and Doctor of Osteopathy (1970) from the College of Osteopathic Medicine and Surgery in Des Moines, Iowa. His post-doctoral training included three years at Case Western Reserve University, one year at the University of Oregon Health Sciences Center and a Rotating Internship at Providence Hospital in Seattle, Washington.

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