

## Multiple Sclerosis and Hyperbaric Oxygen Therapy: Looking Back to move Ahead (1969-2013)

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### Abstract

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. The disease is characterized initially by episodes of reversible neurologic deficits. These episodes are followed by progressive neurologic deterioration over time. To study the effects of HBOT on cases of MS by retrospective analysis of all MS cases that were administered HBOT in the Dept of High Altitude Physiology and Hyperbaric Medicine (HAP & HM) at Institute of Aerospace Medicine (IAM), Indian Air Force (IAF). Case records of twenty three patients with MS who underwent HBOT at IAM, Bangalore between January 1969 to January 2013 were studied in detail. Special emphasis was placed on the type and duration of presentation of MS. All the cases were studied for follow up and compliance with HBOT. A total of 23 patients record were studied. Of these only 20 patients were selected for the study, because of the inclusion and exclusion criteria laid down. Of these 20 patients 12 cases were lost to follow up and could not be contacted with the details available at the Institute. Thus for follow up and for evaluation only 8 MS patients were available for the study. Among these, a marked improvement in bladder functions and locomotion was seen in 6 of the 8 patients. It was seen that HBOT does not have any effect on cerebellar symptoms. With details of this limited number of subjects, it was found we can conclude to some extent that HBOT for MS has had no response in active modification of the disease per se, but the beneficial effects which are seen with long term HBOT should be assessed so as to understand the efficacy of this modality of treatment. The results of this literature review are in tune with the studies in the rest of the world. The study mirrors the earlier works of Neubauer, Fischer and Barnes on the same subject. The study highlights the need for a larger sample size and a long term prospective study involving a concurrent effort by a Neurologist and a practitioner of Hyperbaric Medicine.

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### Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees (1,2,3,4). The disease is characterized initially by episodes of reversible neurologic deficits. In most patients, these episodes are followed by progressive neurologic deterioration over time. The cause of the disease is not known, but it involves a combination of genetic susceptibility and a non-genetic trigger, such as low vitamin D levels (5), a virus (6), chronic cerebrospinal insufficiency (7), or environmental factors (5), that together result in a self-sustaining inflammatory, demyelinating disease of the CNS

(1,2,3,4). Anecdotal references in literature have discussed the efficacy of Hyperbaric Oxygen therapy (HBOT) in the disease progression and improvement in quality of life for the patients of MS. This paper focusses on the cases that were administered HBOT at Department of High Altitude Physiology (Dept of HAP & HM) Institute of Aerospace Medicine (IAM) and the effects there off.

### Aim of the Study

To study the effect of HBOT on cases of MS

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vis-a vis disease modification, relapse reduction and improvement in quality of life by a retrospective analysis of all the cases of MS who were given HBOT in the Dept of HAP & HM at IAM.

## **Materials and Methods**

Case records of twenty three patients with MS undergoing HBOT at Institute of Aerospace Medicine, Bangalore, between January 1969 to January 2013 were studied in detail. All the 23 patients were civilians or dependent's of military personnel's, referred from various civil hospitals in and around Bangalore. The inclusion and exclusion criteria for the study were:-

### ***Inclusion Criteria***

1. All patients fitting the diagnosis of Multiple Sclerosis.
2. Patients who were administered atleast 10 sittings of HBOT.

### ***Exclusion Criteria***

1. Patients of MS who were administered less than 10 sittings of HBOT.
2. Patients of MS who could not be given HBOT due to co-morbidities and were not suitable for the therapy.

The above criteria were laid down to get results pertaining to MS and that to see their improvement in quantifiable terms after every few sittings of HBOT. Prior to exposure all the patients were evaluated as per laid down guidelines at IAM, IAF.

### ***Chamber Run Protocol***

All patients were subjected to HBOT runs at 1.75 ATA for 90 minutes per day. The runs were given for 5 days every week. Improvement in symptoms was taken as criteria for evaluation. All patients were contacted by means of their address and phone numbers available at this Institute. Their

responses were recorded as per the questionnaire form placed at the end of this paper.

## **Results**

A total of 23 patients record were studied. Of these 23, only 20 patients were selected for the study, because of the inclusion and exclusion criteria laid down, as one patient had left before completion of even 10 runs and 02 cases were found unfit during evaluation for HBOT. Out of the 20 patients, 13 (65%) were males and 7 (35%) were females. Of these 20 patients 12 cases were lost to follow up and could not be contacted with the details available at the Institute. Thus for follow up and for evaluation only 8 MS patients were available for the study. Of these 8 patients 4 patients had undergone treatment in the last 2 years. From the 08 patients 05 (62.5%) were males and 03 (37.5%) females.

Out of the remaining 8 cases the diagnoses was based upon McDonalds criteria 2010 (Table 1) (8).

As seen from the above results, HBOT gives good results especially with regards to symptoms for bladder functions and locomotion. Subjective feeling of fatigue is also reduced and patients report an improvement in his/her fitness or quality of life. Patients who presented with bladder symptoms were 5(62.5%) out of 8 cases. These patients reported the greatest improvement in their symptomatology. At the end of 10 sessions the patients who reported an improvement were 2 (40%) out of 5 who initially had bladder symptoms. At the end of 20 sessions almost all had marked relief in the bladder symptoms associated with MS. 04 cases that were followed up for six months to 2 yrs had marked and sustained relief from bladder symptoms for up to an year.

Patients who presented initially with cerebellar symptoms were relatively worse off with only 1

**MC Donalds Criteria Table**

<b>Clinical Attacks</b>	<b>Lesions</b>	<b>Additional criteria required to diagnose</b>
2 or More	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS.
2 or More	Objective clinical evidence of 1 lesion	Dissemination in space demonstrated by-> 1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); <b>OR</b> Await further clinical attack implicating a different CNS site
1	Objective clinical evidence of 2 or more lesions	Dissemination in time demonstrated by – Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time ; <b>OR</b> A new T2 and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing; <b>OR</b> Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by-> 1 T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); <b>OR</b> Await further clinical attack implicating a different CNS site <b>AND</b> Dissemination in time, demonstrated by Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time <b>OR</b> A new T2 and/or contrast-enhancing lesion(s) on follow-up MRI, irrespective of its timing <b>OR</b> Await a second clinical attack
0 (progression from onset)		One year of disease progression (retrospective or prospective) <b>AND</b> at least 2 out of 3 criteria: Dissemination in space in the brain based on >1 T2 lesion in periventricular, juxtacortical or infratentorial regions Dissemination in space in the spinal cord based on 2 T2 lesions <b>OR</b> Positive CSF (Oligoclonal IgG bands in CSF , not serum or elevated IgG index )

The subtype distribution of MS in our test group was as follows:-

- 1) Relapsing - Remitting MS : 6 cases
- 2) Secondary – Progressive MS : 1 case
- 3) Progressive – Relapsing MS : 1 case
- 4) Primary – Progressive MS : Nil

case out 2 who reported cerebellar symptom's benefitting from the HBOT sessions at 10 and 20 weeks. The long term follow up case did not have any cerebellar signs to begin with and hence no comment can be made upon the effects of HBOT on cerebellar symptoms of MS.

Six patients complained of symptoms like fatigue and impaired heat tolerance (Uhtoff's phenomenon). At the end of 10 sessions the number of patients reporting fatigue alleviation was as 2 out of 6 (33.33%), this figure changed to 5 (83.33%) out of 6 at the end of 20 sessions. The long term

**Presenting symptoms of these 8 patients was as follows:-**

Symptoms	Number of cases	EDSS Score
Sensory loss	1	1.5
Spinal Symptoms (Loss of bladder control predominant)	5	1.5
Cerebellar Symptoms	2	3.5/4
Constitutional Symptoms	6	1
Psychiatric Symptoms	Nil	
Pain	3	2.5
Myokymia	Nil	
Optic Neuritis	Nil	

**Response to Therapy**

No of sessions	Symptom	Positive Response(Subjective)
10	Spinal Symptoms	2
	Cerebellar Symptoms	1
	Constitutional Symptoms	2
	Sensory loss	Nil
	Pain	2
20	Spinal Symptoms	5
	Cerebellar signs	1
	Constitutional symptoms	4
	Sensory loss	Nil
	Pain	2

follow up case reported subjective improvement in fatigue even at the end of 6 months of irregular follow up. Malaise, vague aches and pains were reported by 3 patients and relief from the same were reported in 2 cases at 10 and 20 sessions .

There was no resolution of lesions as seen in the MRI in any of the cases. The relapse rate could not be commented upon, as beside one patient, all the remaining patients were given maximum only 20 sessions and long term follow up of 10 years or more was not possible.

**Discussion**

Treatment of MS using HBOT was merely speculative in earlier times. However, its role as an adjuvant in the treatment of MS was discovered by Dr Neubauer while administering HBOT to a patient of osteomyelitis who also had MS (9,10). Since then this modality has been used by various physicians with success and also been the subject of various claims and counter claims.

A controlled clinical trial conducted between 1980 and 1982 by Dr. B. H. Fischer, Dr. M. Marks,

and Dr. T. Reich at New York University Medical Center found that 17 out of 20 patients give HBOT reported improvement in their symptoms as compared to 20 equally matched MS patients who were not subjected to HBOT (11).

A study of the trial in the Cochrane database by Bennet & Heard (nine trials) showed two trials produced generally positive results, while the remaining seven reported generally no evidence of a treatment effect (12). Total numbers of participants analysed in this study were 504. Besides the study by BH Fischer alluded to above Oriani (13) also reported positive outcomes in the above series.

The pioneer Dr R A Neubauer himself completed a study of 262 patients (10) and concluded that

- 1) HBOT was not curative for MS.
- 2) Response was dose related.
- 3) Long term therapy was needed
- 4) HBOT favourably altered the natural course of the disease

Other studies especially by Barnes and Bates although initially refuted was re-analysed and found to be positive (14). Dr Barnes later established the Action for Research in Multiple Sclerosis (ARMS) in the UK. A large study conducted by the ARMS centre (now called the Federation of Multiple

**The following is a tabulated form of the results of the erstwhile ARMS centres:-**

Symptom	Better	No change	Worse
Fatigue	70	22	8
Speech	64	34	1
Balance	59	37	4
Bladder	68	30	0
Locomotion	77	19	4

Sclerosis Treatment Centres) followed up 703 patients in detail since first receiving treatment, and have 10-14 year follow up data on 447 patients. HBOT centres report symptomatic relief in the majority of these patients (10,13,14).

Possible modes of action of HBOT in MS are as follows:-

From these studies and our own experience it is felt that HBOT improves condition of MS patients by the following actions:-

1. Increased oxygenation may help by:-
  - a) Reduce tissue anoxia in chronic cerebrospinal venous insufficiency.
  - b) Increase tissue repair especially in peri-venular areas to reduce the plaques associated with the disease.
  - c) May reduce the effects of deleterious pathogens though till date none has been found in the plaques of MS.
2. Effect of HBOT on the immune system:-
  - a) HBOT reduces the activity of the host B & T lymphocytes most cases were combined with a decrease in delayed hypersensitivity and lymphocyte proliferation (15).
  - b) Reduction of activity of host macrophages are seen with reduced adhesion, chemotaxis and phagocytosis being evident (16).

There is enough evidence to suggest that HBOT is a viable and useful adjunct in MS with the possibility of preserving quality of life in MS patients (9,10,11,13,14).

We can see from these studies that around 70 % of patients who receive HBOT report an improvement in their symptoms. The above very closely tallies with our study and improvement

reports averaging around 70 % are noted depending on the symptom complex. Bladder function, Locomotion and subjective reduction of fatigue show the most improvement.

Regarding the deterioration occurring in cases of MS when subject beside medical treatment were undergoing HBOT, our study only had 04 cases of long term follow up which was followed up for a 6 month period to 2 yrs, not more. Only five patients were given 20 sittings of HBOT initially and only one followed up with a quarterly 10 session. The slowed rate of EDSS progression cannot be commented upon when using a single case although the patient remained symptom free despite his irregular therapy.

The regime used in the study was a relatively conservative one utilising 1.75 ATA as this was correlated with good efficacy and low patient risk.

The relapse rates being reduced/ increased could not be commented by the study because of the limited sessions given to the patients. It will require long term studies with constant follow up and repeated sessions to understand the disease progression with HBOT. Even if disease progression is altered or patients show better quality of life with symptomatic improvements, the type of treatment should be considered. . It is debatable to suggest such a costly mode of treatment which to some extent improves patient's quality of life, but with no effect on the disease per se, but then living with a better quality of life adds more sense than living from worsening from one relapse to another. UHMS (Undersea & Hyperbaric Medicine Society) as of now does not suggest such a modality of treatment to patients of MS, but till two years back the same was for idiopathic sudden sensorineural hearing loss (ISSHNL), which later in 2011 cleared HBOT for as a definitive treatment to ISSHNL. Lot needs to be understood about the

beneficial effects of HBOT and more studies especially long term alone can conclusively help us with this therapy and its various usages.

### **Limitations**

Apart from being a retrospective study, the study group was too small and with no long term follow up. The improvement rates are entirely subjective. A direct cause-effect relationship could not be established.

### **Conclusion**

The above study is just a foray into the emotionally charged field of MS and HBOT ridden with dogma on both sides. The study mirrors the earlier works of Neubauer, Fischer and Barnes. As per this limited study, we can conclude that HBOT for MS has had no response in active modification of the disease per se, but the beneficial effects which are seen with long term HBOT should be assessed so as to understand the efficacy of this modality of treatment. The sample size was small and follow up restricted due to various logistic and administrative reasons. The study mainly highlights the need for a larger sample size and a long term prospective study, most probably involving a concurrent effort by a Neurologist and a practitioner of Hyperbaric Medicine. The above is needed in light of the multi modal causation of MS and the need to understand differences in causation and response to therapy in Indians as opposed to western population.

### **Recommendation**

In light of the findings of this review, it is recommended that a Long term prospective study involving a hyperbaric physician and a neurologist be conducted to assess the true benefits of HBOT on MS.



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## **Questionnaire for MS Patients undergoing HBOT**

Name:

Age:

Ethnicity:

Occupation:

Diagnosis

- a) Based on :
- b) Diagnosed on:
- c) Clinical type of MS:
- d) Presenting complaints/ symptoms

Referred by:

Number of sessions

Recommended:

Completed:

Contraindications:

Concurrent Medications:

Regime of HBOT used:

MRI findings:

Whether Gd contrast used or not- Y/N

- 1) Prior to HBOT
- 2) After HBOT
  - a) 10 Sessions
  - b) Completion of planned sessions
  - c) During follow Up
  - d) Plaque resolution- Y/N

Uthoffs Phenomenon - Y/N

Neuro-myelitis Optica – Y/N

Presence of Cognitive dysfunction- Y/N

Whether Human T Lymphocytic virus associated Paraparesis ruled out in patients presenting with paresis- Y/N

Screened for JC virus – Y/N

HLA typing (if done)-

- 1) Did you face any discomfort while undergoing HBOT?
- 2) Improvement noted by treating physician with respect to improved EDSS or FSS?
- 3) Subjective improvement noted by patient?



- 4) Improvements noted in
  - a) Bladder symptoms
  - b) Locomotion
  - c) Speech
  - d) Balance
  - e) Fatigue
- 5) Any relapse while undergoing HBOT?
- 6) Any worsening of EDSS / FSS score noted by the treating physician?
- 7) Sparing effect of HBOT on use of disease modifying agents noted by treating physicians?
- 8) Whether number of planned sessions completed or not?
- 9) Reasons for inability to complete requisite sessions?
- 10) Whether likely to complete further sessions or not?
- 11) If not then reason for the same?

## **Disability Progression of MS Krutzke Expanded Disability Status Scale (EDSS)**

The most widely accepted of these is the 10-point Krutzke Expanded Disability Status Scale (EDSS), which was developed originally in 1955 as the Disability Status Scale and has been revised over the years (21). The EDSS assigns a severity score to the patient's clinical status that ranges from 0-10 in increments of 0.5. The scores from grades 0-4 are determined using functional systems (FS) scales that evaluate dysfunction in 8 neurologic systems, including pyramidal, cerebellar, brainstem, sensory, bladder and bowel, vision, cerebral, and "other." EDSS grades are as follows:-

- **0 - Normal neurologic examination**

(All grade 0 in functional systems [FS], cerebral grade 1 acceptable)

- **1.0 - No disability, minimal signs in 1 FS**

(That is grade 1 excluding cerebral grade 1)

- **1.5 - No disability, minimal signs in more than 1 FS**

(More than 1 grade 1 excluding cerebral grade 1)

- **2.0 - Minimal disability in 1 FS**

(1 FS grade 2, others 0 or 1)

- **2.5 - Minimal disability in 2 FS**

(2 FS grade 2, others 0 or 1)

- **3.0 - Moderate disability in 1 FS**

[(1 FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3/4 FS grade 2, others 0 or 1) though fully ambulatory]

- **3.5 - Fully ambulatory but with moderate disability in 1 FS**

[(1 grade 3) and 1 or 2 FS grade 2, or 2 FS grade 3, or 5 FS grade 2 (others 0 or 1)]

- **4.0 - Fully ambulatory without aid; self-sufficient; up and about some 12 h/d despite relatively severe disability**

[Consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest approximately 500 m]

- **4.5 - Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity or require minimal assistance**

[Characterized by relatively severe disability, usually consisting of 1 FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest for approximately 300 m]

- **5.0 - Ambulatory without aid or rest for approximately 200 m**

[Disability severe enough to impair full daily activities (e.g., to work full day without special provisions; usual FS equivalents are 1 grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)]

• **5.5 - Ambulatory without aid or rest for approximately 100 m**

[Disability severe enough to preclude full daily activities (usual FS equivalents are 1 grade 5 alone; others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0)]

• **6.0 - Intermittent or unilateral constant assistance**

(Cane, crutch, or brace) required to walk approximately 100 m with or without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)

• **6.5 - Constant bilateral assistance**

[(canes, crutches, or braces) required to walk approximately 20 m without resting (usual FS equivalents are combinations with more than 2 FS grade 3+)]

• **7.0 - Unable to walk beyond approximately 5 m even with aid**

[Essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about approximately 12 h/d (usual FS equivalents are combinations with more than 1 FS grade 4+; very rarely, pyramidal grade 5 alone)]

• **7.5 - Unable to take more than a few steps**

[Restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair (usual FS equivalents are combinations with more than 1 FS grade 4+)]

• **8.0 - Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms**

(Usual FS equivalents are combinations, generally grade 4+ in several systems)

• **8.5 - Essentially restricted to bed much of the day**

[Has some effective use of arms; retains some self-care functions (usual FS equivalents are combinations, generally 4+ in several systems)]

• **9.0 - Helpless bed patient; can communicate and eat**

(Usual FS equivalents are combinations, mostly grade 4+)

• **9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow**

(Usual FS equivalents are combinations, almost all grade 4+)

• **10.0 - Death due to MS**

Krutzke EDSS scale was graded by a Neurologist or by the OIC HAP in consultation with a Neurologist.

Rating based on above scale:-

- 1) Prior to initiating HBOT:
- 2) After 20 sessions of HBOT:
- 3) Six months after completion of planned sessions:
- 4) One year after stopping HBOT:

## **MS DISSEMINATION IN TIME AND SPACE**

### **Evidence for Dissemination in Space.**

> 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord

Gadolinium enhancement of lesions is not required for DIS

If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count.

Ref Swanton KL et al. *Lancet Neurology* 2007;6:677-686 / Swanton KL et al. *J Neurol Neurosurg Psychiatry* 2006;77:830-833.

### **MRI Evidence of Dissemination in Time**

A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

OR

Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

Ref Montalban X, et al. *Neurology* 2010;74:427-434.

### **Answer Keys:**

1. (b) 2. (b) 3. (b) 4. (c) 5. (d) 6. (a) 7. (b) 8. (d) 9. (a) 10. (d) 11. (c) 12. (b) 13. (b) 14. (c) 15. (b) 16. (a) 17. (d) 18. (b) 19. (a) 20. (a)