POSITION PAPER

Treatment of multiple sclerosis with hyperbaric oxygen therapy

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Bennett M, Heard R. Treatment of multiple sclerosis with hyperbaric oxygen therapy. Undersea Hyper Med 2001; 28(3):117–122.— Despite considerable research effort, there is little controlled evidence that a course of hyperbaric oxygen therapy (HBO_2T) results in any benefit for patients with multiple sclerosis (MS). The great majority of randomized trials involved investigating a course of 20 treatments at pressures between 1.75 and 2.5 atm abs daily for 60–120 min over 4 wk against a placebo regimen. None has tested the efficacy of HBO_2T against alternative current best practice. A systematic review of this randomized evidence suggests there is no significant benefit from the administration of HBO_2T (Improved EDSS after HBO_2T: OR = 2.02, 95%CI 0.63–6.43. Improved sphincter function: OR = 1.3, 95% CI 0.8–2.11). On average, 42 patients would need to be treated before we could expect one individual to benefit with an improved disability status score; however, we cannot be confident that the number we would need to treat is less than infinite (NNT = 42, 95% CI 15 to infinity). There is some case for further investigation of possible therapeutic effects in selected sub-groups of patients and for the response to prolonged courses of HBO_2T at more modest pressures; however, the case is not strong. At this time, we cannot recommend the routine treatment of MS with HBO_2T

multiple sclerosis, hyperbaric oxygen therapy

Multiple sclerosis (MS) is a chronic neurologic disease in which there is patchy inflammation, demyelination, and gliosis in the central nervous system (CNS). Although it exhibits marked racial and geographic variability in its prevalence, MS occurs most widely in races of Northern European ancestry (prevalence 30–50 per 100,000) (1) and is the commonest cause of chronic neurologic disability in such countries. There is also considerable variability in the clinical features and the rate of progression of disability; however, the histologic changes are remarkably constant (2). Discrete areas of inflammation appear and evolve within the CNS, showing a marked pervenular distribution. Perivascular cuffing with lymphocytes, breakdown of the blood-brain barrier (BBB) and egress of inflammatory cells from the intravascular compartment are followed by cascading inflammatory activation. Damage to myelin sheaths and to oligodendrocytes and eventually degeneration of axons causes the neurologic deficits by which the disease becomes apparent. At least in the early stages a degree of recovery is possible (3), but with successive episodes of inflammation, remyelination becomes less efficient, axonal loss accumulates and neurologic disability progresses.

Magnetic resonance imaging (MRI) data have shown that breakdown of the BBB is an extremely early event in the evolution of an inflammatory lesion in MS (4). It is widely held that this process, and subsequent stages in the development of a plaque, are immunologically mediated (5). Despite the current wide adoption and success of immunosuppressive therapy in MS (corticosteroids, beta interferons [IFNB], glatiramer acetate [GA]), the evidence for an immunologic process remains circumstantial.

The similarity noted between the diffuse neurologic abnormalities associated with gas embolism and decompression illness on the one hand and MS on the other, led some workers to re-examine the concept, first proposed in 1882, that MS was of vascular origin. Several features of the disease suggest there may be a vascular association including the observation of perivenular lesions (6), abnormal permeability of vessels in MS (7), and abnormal vessel reactivity (8). In a 1982 review, James suggested a novel mechanism to explain the typical lesions (9). He postulated that a subacute form of fat embolization similar to that following trauma may be responsible and that such emboli were triggered by a number of stimuli. The reduced vascularity of the cortex in comparison to the white matter was postulated to explain the anatomical distribution of lesions. Gottlieb et al. (10) developed this "vascular-ischemic model", further suggesting that MS may be viewed as a wound in the CNS resulting from a vascular dysfunction. They suggest that the described immunologic changes are a

result of this dysfunction rather than the primary cause of the clinical syndrome.

James (9) suggested the use of hyperbaric oxygen administration as a treatment for MS based on the demonstrated ability of HBO_2 to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy. In the subsequent 10 yr, a flurry of activity produced a number of randomized, controlled trials (RCTs) in the United Kingdom, Unitd States, Australia, and Europe, despite widespread scepticism concerning the postulated pathophysiology.

Today, many patients are treated with HBO_2T on a permanent recurrent basis, particularly in the UK (11). Many neurologists practicing in this area continue to feel such treatment is unlikely to be helpful and HBO_2T is not widely available for this indication in other countries.

It is the aim of this document to define the position of the Undersea and Hyperbaric Medical Society on the treatment of MS with HBO_2T and to outline the evidence basis for this position.

Current Alternative Practice

Multiple sclerosis is currently an incurable disease. In general, there are three approaches to treatment: prevention of disease progression and reduction of relapse rate, treatment of acute exacerbations, and treatment of chronic symptoms. HBO_2T has been postulated to modify disease progression and to reduce relapse rate, therefore this discussion will be limited to those drugs designed to produce similar treatment effects.

For the most part, measures aimed at altering disease progression and relapse are immunosuppressive or immunomodulatory or both. Drugs used in MS include azathioprine, IFNB, cladribine, cyclophosphamide, GA, intravenous immunoglobulin, methotrexate, and mitoxantrone. Current therapy consists of the administration of one or more of these partially effective disease-modifying treatments to appropriate patients. The evidence for efficacy is difficult to interpret and clinical trials in this area are fraught with difficulty, not the least of which is the design and application of instruments to evaluate clinical outcomes (12,13). Over the last decade, several clinical and MRI-based (proxy) outcome measures have been described. For this reason, direct comparison of the efficacy of modern agents and HBO_2T is problematic.

While immunosuppression and immunomodulation have become the main therapeutic strategies in MS despite continuing lack of firm evidence as to the primary pathology (14), HBO_2T is not widely advocated by professional bodies or MS societies. Interferon is the agent for which there is the best evidence of efficacy, and several large, placebo-controlled RCTs have been published over the last few years (15–19). These trials suggest a limited benefit in relapsing–remitting and secondary progressive MS, although all the trials have methodologic limitations.

The PRISMS trial (15) investigated the effect of IFNB-1a thrice weekly in 560 relapsing-remitting patients. The relapse rate was significantly lower at 1 and 2 yr with this agent (Rebif) than with placebo (mean number per patient 1.73 for 44-μg group vs. 2.56 for placebo group, risk reduction 33% [95%CI 21–44]) and the proportion of relapse-free patients was significantly increased ($P < 0.05$). A once weekly regimen may also be effective, at least in terms of MRI-detectable lesions. The OWIMS Study (16) showed T2 new lesion count/scan (mean/median) at 48 wk was 3.2/1.5 for placebo and 1.5/1.0 for 44 μg interferon weekly ($P = 0.0005$). While these MRI-detectable lesions were the primary outcomes of this study, the authors did report a significant reduction in steroid use with this agent ($P = 0.014$). The European Study Group has also described benefit for patients with secondary progressive disease. The time to confirmed progression of disability was significantly longer with IFNB1-b (Betaseron) ($P = 0.0008$) such that the trial was abandoned in favor of this agent at an interim analysis. IFNB1-b delayed progression for 9–12 mo. in a study period of 2–3 yr. The odds ratio for confirmed progression was 0.65 (95% CI 0.52–0.83) (18).

Benefits, in terms of reduced relapse rate and severity, are achieved at high cost with the annual cost per patient in the UK estimated to be between £10,000 and £20,000 (20). Side-effects are common, particularly flu-like symptoms and injection site reactions.

GA, also known as copolymer 1, has been used as an alternative to IFNB and is probably the second most commonly prescribed disease-modifying therapy. A recent meta-analysis of two RCTs suggests that patients taking GA have a lower probability of relapse at 12 mo. (OR 0.17, 95% CI 0.05–0.51, $P = 0.002$) (21). A recently published phase IV trial suggests the clinical benefits may persist for at least 6 yr of treatment, although caution should be used in interpreting results in this selected group of patients (22). The annual drug cost per patient is estimated to be about £10,000 (20). There is also some randomized evidence for the efficacy of azathioprine, cyclosporin, intravenous immunoglobulin, methotrexone, and mitoxantrone in some clinical situations; however, the place of these agents remains uncertain.

The treatment of MS can be complex and confusing. Although there is some evidence for beneficial alteration of disease progression for a number of agents, for many patients the clinical reality is a progressive trial of a

number of agents in search of an individualized prescription. Although there are a number of difficulties in performing high-quality clinical studies to define best treatment, this is clearly required. Well-conducted trials, targeted at defined sub-groups of patients, with long-term follow-up for relevant outcome measures with clinical significance are needed.

The Evidence

A formal search was undertaken and the evidence is summarized in Table 1. Levels of evidence quoted are those of the National Health and Medical Research Council (NHMRC) (23).

Search Strategy

1. MEDLINE (from January 1966), EMBASE (from 1974), CENTRAL (issue 2).
2. The MS specialized registry of the Cochrane MS Review Group
3. The Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTHIM, Bennett 1999).
4. Hand search of all hyperbaric journals, proceedings and texts since 1980.
5. References from papers identified above.

A number of case reports and an informal longitudinal case series (24), suggest significant benefit from the application of HBO_2 to patients with a variety of MS presentations. In particular, the benefit claimed is the prevention of long-term deterioration by regular maintenance therapy. The Federation of Hyperbaric Oxygen Chambers' data derives from in excess of 1,000,000 treatment occasions and suggest widespread improvements in both symptomatology and mobility. Some of the claims are summarized in Table 2. These data are likely to be significantly biased in favor of apparent effectiveness as the only patients for whom we have late assessments are those who continue treatment over several years. Many of those dropping out may be those who found no improvement. Kindwall and colleagues (25) made a similar point when collecting another large opportunistic data set. Having assembled a national data register for MS patients having HBO_2T, Kindwall et al. described a high drop-out rate (only 76% finished the initial course of 20 treatments) and at completion of the 2-yr study, only 28 of the original 312 patients remained in treatment (9%).

The evidence from comparative trials has been far less positive than that suggested by the UK experience. Worthington and associates (26), in a non-randomized crossover trial involving 51 patients with chronic-progressive and relapsing-remitting disease, found some minor benefits after 20 HBO_2 treatment sessions (peak flow and finger tapping improved), although walking and mobility were improved after the placebo sessions. Self-care activities decreased during the course of the trial for each group.

In a qualitative review of the literature, Gottlieb and Neubauer (27) suggested many of the RCTs conducted were methodologically flawed and that the authors may have misinterpreted the trial data. Of particular concern to these authors was the possibility that the dose of oxygen was too high in many studies—although the more positive studies were those of Fischer et al. (2 atm abs) (28) and Oriani and associate.sd (2.5 atm abs) (29). They felt these trials justified the use of HBO_2T when interpreted in the light of their own vascular-ischemic pathophysiologic model. Two more systematic reviews have examined the randomized evidence from controlled trials published in full text or abstract. Kleijnen and Knipschild (30) conducted a semi-quantitative analysis of 14 trials and concluded "the majority of controlled trials could not show positive effects". They considered 8 of the 14 trials to be of reasonable to high quality and of these, only one trial (Fischer) showed a result in favor of HBO_2T. Bennett and Heard (31), in an interim report of a formal systematic review and meta-analysis of 14 trials, similarly concluded there was no overall evidence of efficacy. Published interim conclusions of this study are summarized in Table 3. While there was a trend to better outcomes for both disability score and sphincter function in the HBO_2T patient arms, this was not statistically significant, and any effect is unlikely to be large. There are considerable placebo effects demonstrated in some of these trials, particularly those of Wiles and colleagues (32) and Woods et al. (33).

Many of the RCTs conducted have been criticized by the proponents of HBO_2T for poor patient selection and for administering a short-term series of treatments that may be unlikely to alter the clinical course. Only one randomized study examined the response to continued "top-up" treatments over 12 mo. (29), and shows benefit from HBO_2T in a range of outcome measures. Interestingly, this is also the only trial that shows significant benefit in the extended disability score (EDSS) immediately following the initial course of 20 exposures to HBO_2T at 2.5 atm abs for 90 min daily. It is difficult to reconcile this singular result with the other published trials.

Cost of HBO_2T

The patient charge for providing HBO_2T is highly variable and in part dependent on the type of facility, presence or absence of physician supervision, and the facility funding arrangements. While the true cost of

Table 1: Evidence Hierarchy for Treatment of MS with HBO_2T

Level of Evidence (20)	References	Study Design	Subjects	Conclusion
Level 1	(31)	meta-analysis	14 controlled trials	no net benefit shown
Level I	(30)	semi-quantitative review	14 controlled trials	majority of trials showed no benefit
Level 1	(10)	qualitative review	14 trials	poor trials, data misinterpreted
Level II	(28)	RCT double-blind	40 chronic severe	positive benefit, some transient
Level II	(42)	RCT double-blind	24 chronic progressive	no benefit
Level II	(33)	RCT double-blind	44 chronic progressive	no benefit
Level II	(34)	RCT double-blind	57 chronic stable or progressive	no benefit
Level II	(39) (40)	RCT double-blind, crossover	18	no benefit
Level II	(37)	RCT double-blind	17 chronic progressive	no benefit
Level II	(32)	RCT double-blind	88 chronic progressive	no benefit
Level II	(35)	RCT double-blind	82 definite MS	no benefit
Level II	(36)	RCT double-blind	120 chronic stable	transient symptomatic sphincter improvement
Level II	(29)	RCT double-blind	44 chronic stable	improved symptoms and disability scores
Level II	(38)	RCT double-blind	49 chronic	no benefit
Level II	(41)	RCT double-blind	40 no details	some benefit in mild disease
Level III-2	(26)	comparative study, HBO v HBAir in crossover design, non-random	51 (all types)	minor benefit from HBO_2
Level III-3?	(43)	cases compared with untreated controls?	22	reduced relapse
Level IV	(44)	case series	11	improved
Level IV	(45)	case series	26	transient symptomatic improvement (15/26)
Level IV	(24)	case series	703 (417 chronic progressive, 43 chronic static, 167 relapsing)	improved disability scores and symptomatology

Table 2: Logitudinal Data From (24)

Symptom	Improved, %	No Change, %	Worse, %
Fatigue	70	22	8
Speech	64	34	1
Balance	59	37	4
Bladder	68	30	0
Walking	77	19	4

HBO_2T is even more difficult to establish, a range of likely cost to benefit can be estimated from data available.

In the USA, reimbursement by Medicare for a single two hour HBO_2 session is approximately $300.00.

On the basis of an initial course of 20 treatments and top-up treatments weekly as recommended by the Federation of Hyperbaric Oxygen Centres, each patient

Table 3: Selected Outcomes From (31)

Outcome	Odds Ratio	95% CI	NNT	95% CI
EDSS improvement	2.02	0.63–6.43	42	15, infinity
Sphincter function improved	1.3	0.8–2.11	25	9, infinity

would require 68 treatments in the first year. Meta-analysis suggests that if there is any benefit, our best estimate is that 42 patients would need treatment to produce one improvement in disability score, giving a total cost of $856,800 per patient improved. From the 95% CI, we might expect the true cost to lie between $216,000 and an infinite cost. The cost of HBO_2 might be considerably lower in other HBO_2T settings. If the cost was $100/treatment, the equivalent figures would be $285,000 (95%CI $72,000 to infinity). These figures are highly speculative and do not necessarily relate to an appropriate outcome.

Conclusions

Synthesis of the data presented above suggests there is little evidence for the efficacy of HBO_2T from trials with a low potential for bias. Most randomized controlled trials have failed to show any clinical benefit, while a minority have suggested some benefit.

It is possible that a positive treatment effect may exist in a subgroup of patients, and/or with the administration of prolonged courses of HBO_2T at pressures particularly tailored to the individual. Any treatment effect is likely to be small and costly. While the one RCT that studied patients having regular treatment for 12 months did show a beneficial effect on the EDSS, this trial is also alone in demonstrating a large treatment effect already apparent immediately after the initial course of 20 treatments. This heterogeneity in treatment effect is difficult to explain from the details presented in the paper.

We conclude that, while there is some case for further investigation of possible therapeutic effects in selected sub-groups of patients (well-characterized and preferably early in the disease course) and for the response to prolonged courses of HBO_2T, this case is not strong. Any further investigation should be of high a methodologic standard, allow a comparison of the effect of HBO_2T with current best practice and involve experts in the assessment and treatment of MS.

At this time, the UHMS cannot recommend the routine treatment of MS with HBO_2T outside appropriate comparative research protocols.

APPENDIX

The NHMRC Levels of Evidence

- I Evidence obtained from a systematic review of all relevant randomized, controlled trials.
- II Evidence obtained from at least one properly designed, randomized controlled trial.
- III-1 Evidence obtained from well-designed, pseudo-randomized controlled trials (e.g., alternate allocations.
- III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case-control studies or interrupted time series with control group.
- III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
- IV Evidence obtained from case series, either post-test or pre-test and post-test.

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Note: This paper has been approved by the Executive Committee of the Undersea and Hyperbaric Medical Society, Inc., and is the official position of the Society.