REVIEW

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Hyperbaric Oxygen Therapy for Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic, inflammatory, and degenerative neurological illness with no cure. It has been suggested that Hyperbaric Oxygen Therapy (HBO_2T) may slow or reverse the progress of the disease. This article summarizes the clinical evidence for the use of HBO_2T in the treatment of MS. We conducted a literature review focused on the interaction of hyperbaric oxygenation and MS. In particular, we appraised the clinical data regarding treatment and performed a *meta*-analysis of the randomized evidence using the methodology of the Cochrane Collaboration. We found 12 randomized studies in the area, all of which were performed between 1983 and 1987. A *meta*-analysis of this evidence suggests there is no clinically significant benefit from the administration of HBO_2T. The great majority of randomized trials investigated a course of 20 treatments at pressures between 1.75ATA and 2.5ATA daily for 60–120 min over 4 weeks against a placebo regimen. None have tested the efficacy of HBO_2T against alternative current best practice. No plausible benefit of HBO_2T on the clinical course of MS was identified in this review. It remains possible that HBO_2T is effective in a subgroup of individuals not clearly identified in the trials to date, but any benefit is unlikely to be of great clinical significance. There is some case for further human trials in selected subgroups and for prolonged courses of HBO_2T at modest pressures, but the case is not strong. At this time, the routine treatment of MS with HBO_2T is not recommended.

Introduction

Multiple sclerosis (MS) is a chronic neurological disease in which there is patchy inflammation, demyelination, and gliosis in the central nervous system (CNS). MS occurs most widely in races of Northern European Ancestry (lifetime risk about 1 in 400) [1,2] and is the commonest cause of chronic neurological disability in such people. The disease frequently affects young adults, with a mean age at onset in the late 20s [3,4].

There is considerable variability in both presenting clinical features and the progression of disability across the spectrum of MS. Since the 1980s, clinical and laboratory criteria have been used to classify the disease and establish a diagnosis (the McDonald criteria). These have been updated by consensus several times, and most recently summarized by Polman in 2005 [5]. These new criteria allow earlier diagnosis by the addition of specific magnetic resonance imaging (MRI) findings, and therefore, early institution of therapies designed to slow the progress of the disease.

Despite many recent advances in immunology, genetics, molecular biology, and related fields, the etiology of MS remains uncertain [6]. The view that MS is an inflammatory, autoimmune demyelinating disease in genetically susceptible individuals has been challenged for some years, but remains the generally accepted model [6,7]. The prevailing hypothesis is that exposure to unknown environmental antigens in genetically susceptible individuals results in activation of certain T-cell populations toward myelin antigens, oligodendrocytes, and/or neurons. This triggers a massive inflammatory process that results in tissue destruction within the CNS.

The histological changes described in MS are remarkably constant [6]. Discrete areas of inflammation appear and evolve within the CNS, showing a marked perivenular distribution. The lesions are mainly in the white matter, but extend into the gray matter and may occur in the cerebral hemispheres, cerebellum, spinal cord, and optic nerves. 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. The area in which these series of events occur is known as a plaque. Damage to myelin sheaths, oligodendrocytes, and degeneration of axons causes the neurological deficits by which the disease becomes apparent. The presence of thinly myelinated sheaths in some chronic lesions suggests that partial remyelination may occur.

The most obvious feature of the acute lesion is a vigorous inflammatory response with abundant lymphocytes and macrophages, along with some plasma cells and eosinophils. The proinflammatory cytokines TNF-α, γ-interferon, and IL-2 can be shown on cells within the lesion. Frohman has recently published an account of the pathogenesis of the inflammatory and neurodegenerative aspects of MS that summarizes the case for MS as an immunological disease [8].

Some authors have noted that inflammation is a feature of neurodegenerative diseases of the CNS and they go on to suggest that the inflammatory changes summarized above are reactive rather than causative [9,10]. As Chaudhuri points out, immune cells are a feature of a number of neurological disorders including stroke, where a 7-fold rise in circulating and CSF myelin-antigen reactive T cells is accepted as a response to acute brain injury rather than its cause. Further, several features of MS are highly suggestive of a disorder of metabolic regulation including the protective effect of sunlight and sex steroids during pregnancy. Following histopathologic analysis of a series of very early lesions, Barnett and Prineas have proposed that all MS lesions may start with apoptosis of oligodendrocytes secondary to an ischaemic or metabolic insult yet to be identified, rather than inflammation being the primary event [11].

Multiple Sclerosis as a Vascular/ischaemic Event

The similarity noted between the diffuse neurological abnormalities associated with gas embolism and decompression illness on the one hand, and MS on the other, has led some to suggest that MS is of vascular origin. Several features of the disease support this position, including the observation of perivenular lesions [12], abnormal permeability of vessels in MS [13], and abnormal vessel reactivity [14]. The close anatomical relationship between MS plaques and venules in the CNS was first remarked upon in 1863 [15]. Acute lesions often extend along the vessels in a sleeve-like manner and both thrombosis and perivascular haemorrhages have been described [12].

In a 1982 review, James suggested a novel mechanism to explain the typical lesions [16]. Noting the sudden onset of neurological symptoms in the absence of generalized illness could be explained as an embolic phenomenon, James postulated that a subacute form of fat embolization may be responsible. Such emboli could be triggered by a number of stimuli, and in theory at least might lead to downstream hypoxia, endothelial damage and leakage of both reactive oxygen species and hydrolysed fats into the interstitium. Damage to myelin might then produce the typical plaque over time [16,17]. This mechanism is summarized in Figure 1.

More recently, a modified vascular hypothesis has been proposed, with attempts to include both immunological and vascular processes in the general pathogenesis of MS [18]. In this hypothesis, Minagar suggests that breaching of the BBB is a consequence of endothelial dysfunction, in turn mediated by leukocyte–endothelial interactions. Either leucocytes or cerebral vascular endothelial cells may act as the primary antigen-presenting cells in this process, but the result is chemotaxis between them, opening of the endothelial tight junctions (TJs) that characterize the BBB and entry of activated T cells and macrophages to the cerebral interstitium. The resulting cascade of inflammatory response damages both cellular elements and myelin. There is some experimental evidence to suggest a high incidence of TJ abnormality in MS compared to both other neuropathologies and control white matter [19]. Pharmacological agents designed to specifically target adhesion molecules along the BBB have already been introduced into clinical practice, although the first, Natalizumab, has recently been withdrawn due to reports of progressive multifocal leucoencephalopathy while on the drug [20,21].

Therapy for MS

MS is currently an incurable disease. HBO_2T has been postulated to modify disease progression and to reduce relapse rate, therefore this discussion is limited to those measures designed to produce similar treatment effects. For the most part, such measures are immunosuppressive and/or immunomodulatory. Drugs used in MS include interferon beta (IFNB), Glatiramer acetate (GA), intravenous immunoglobulin, mitoxantrone, methotrexate, and corticosteroids. The most commonly employed options have been evaluated by the American Academy of Neurology and the MS Council for Clinical Practice Guidelines [22].

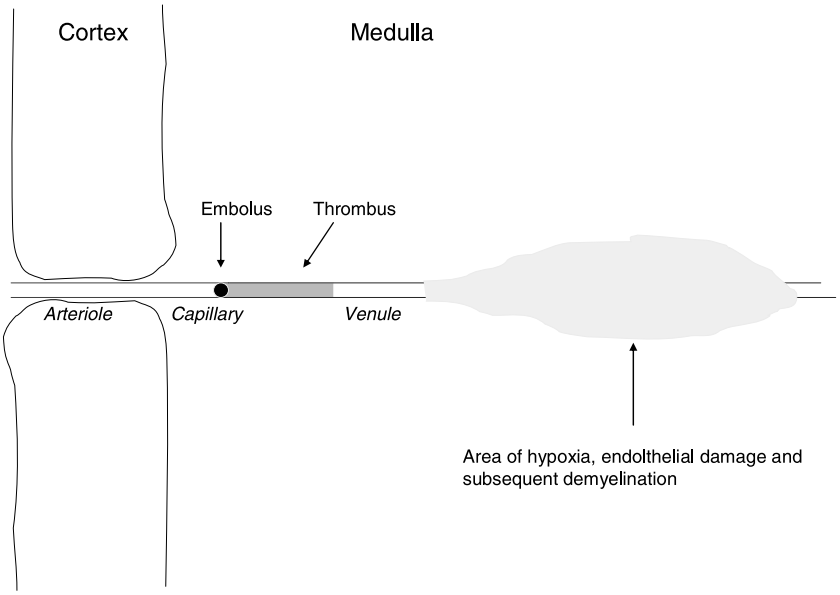

Figure 1 Theoretical pathology of plaque formation from James [16] and based on data from Dow and Berglund [17]
Fat embolus causes downstream hypoxia, thrombus formation, and endothelial damage. Leakage of reactive species into the interstitium damages myelin and promotes plaque formation.

IFNB 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 [23–30]. These trials suggest a limited benefit in relapsing–remitting and secondary progressive MS, although all the trials have methodological limitations. Benefits are achieved at high cost with the annual cost per patient in the United Kingdom estimated to be between £10,000 and £20,000 [31]. 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. The annual drug cost per patient is estimated to be about £10,000 [31].

Current best practice consists of the administration of one of these partially effective disease-modifying treatments to appropriate patients. The identification of nonresponders is problematic, and there are no absolute criteria by which to plan the timing of new or addition therapy [32]. In any case, 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 [33,34].

Outcome Assessment

While MRI findings are now widely accepted as surrogate outcomes for disease extent and progression, clinical outcomes were the standard measure by which the success or failure of therapeutic interventions were judged at least until the early 1990s. While there are several such clinical assessment schemes, by far the most popular are those developed by Kurtzke et al. The Kurtzke Extended Disability Status Score (EDSS) and the Kurtzke Functional Status Score (FSS) were intended to be used together to reproducibly describe the degree of functional impairment across seven systems (FSS) and a score for overall disability (EDSS) [35,36].

In the overall EDSS, each 0.5 of a point is given a different descriptor from zero indicating normal examination to ten indicating death. These scales are categorical and should not be treated as indicating "equal" decrements in functional ability or symptoms for each numerically equal decrement on the scale. Most of the clinical literature examining the effectiveness of HBO_2T for MS used one or both of these scales to compare functional and global impairment.

The Clinical Evidence for the use of Hyperbaric Oxygen

In his 1982 article suggesting MS was a vascular-ischaemic event, James proposed the use of HBO_2T based on the demonstrated ability of hyperbaric oxygen to produce vasoconstriction with increased oxygen delivery and some anecdotal evidence of efficacy [16,37–39]. The clinical evidence is summarised in Table 1.

Early reports had for the most part supported a role for HBO_2T in preventing progression and indeed reducing disability across a wide range of patients. Neurologists and hyperbaricists were divided into enthusiasts or

Table 1 Selected clinical evidence for the treatment of MS with HBO_2T

Level of evidence [40]	Author	Study design	Subjects	Conclusion
Level Ia	Bennett and Heard [41]	*Meta*-analysis	14 controlled trials	No net benefit shown
Level 1a*	Kleijnen et al. [42]	Semiquantitative review	14 controlled trials	Majority of trials showed no benefit
Level 1b	Fischer et al. [43]	RCT, double-blind	40 chronic severe	Positive benefit, some transient
Level 1b	Neiman et al. [44]	RCT, double-blind	24 chronic progressive	No benefit
Level 1b	Wood et al. [45]	RCT, double-blind	44 chronic progressive	No benefit
Level 1b	Slater et al. [46]	RCT, double-blind	57 chronic stable or progressive	No benefit
Level 1b	Erwin et al. Massey et al. [47,48]	RCT, double-blind, crossover	18	No benefit
Level 1b	Confavreux et al. [49]	RCT, double-blind	17 chronic progressive	No benefit
Level 1b	Wiles et al. [50]	RCT, double-blind	88 chronic progressive	No benefit
Level 1b	Harpur et al. [51]	RCT double-blind	82 definite MS	No benefit
Level 1b	Barnes et al. [52]	RCT double-blind	120 chronic stable	Transient symptomatic sphincter improvement
Level 1b	Oriani et al. [53]	RCT, double-blind	44 chronic stable	Improved symptoms and disability scores
Level 1b	L'Hermitte et al. [54]	RCT, double-blind	49 chronic	No benefit
Level 1b	Murthy et al. [55]	RCT, double-blind	40 no details	Some benefit in mild disease
Level 2b	Worthington et al. [56]	Comparative study, HBO v HBAir in crossover design, nonrandom	51 (all types)	Minor benefit from HBO_2
Level 2b	Pallotta et al. [57]	Cases compared with untreated controls	22	Reduced relapse
Level 4	Boschetty and Cernoch [37]	Case series	26	Transient symptomatic improvement (15/26)
Level 4#	No authors [58]	Case series	703 (417 chronic progressive, 43 chronic static, 167 relapsing)	Improved disability scores and symptomatology
Level 5	Gottlieb and Neubauer [7]	Qualitative review	14 trials	Poor trials, data misinterpreted

*No *meta*-analysis but some attempt to synthesise data.

#Internet publication only. No authors formally recognized, but advice of James and Perrin acknowledged.

staunch opponents of this approach, and the place of HBO_2T was controversial. In the late 1980s, Kindwall initiated a national data register for MS patients having HBO_2T [59]. One hundred and seventy neurologists across 22 institutions in the United States of America contributed to this 2 years longitudinal study and a total of 312 patients were enrolled. Kindwall described a high drop-out rate (only 76% finished the initial course of 20 treatments) and at completion of the 2 years study period, only 28 of the original 312 patients remained in treatment (9%). The mean deterioration on the Kurtzke EDSS score was 0.93 or almost a full step from the beginning of treatment until the last evaluation. These disappointing results led the Undersea and Hyperbaric Medical Society to suggest that MS should not be an approved indication.

On the other hand, an informal longitudinal case series published only on the web suggested significant benefit from the application of hyperbaric oxygen to patients with a variety of MS presentations (The experience of MS National in treating MS with prolonged courses of high dosage oxygenation. Accessed at http://www.ms-selfhelp.org/html/oxygen_3.html). In particular, those data suggested HBO_2T was associated with the prevention of long-term deterioration by regular maintenance therapy. This analysis was not attributed to any individual author and has since been removed. The results were likely to be significantly biased in favor of apparent effectiveness as the only patients for whom we had late assessments are those who continued treatment over several years. As one might speculate was the case with the Kindwall study, those dropping out are

likely to be those who found little or no benefit from HBO_2T.

The evidence from comparative trials has been far less positive. For example, Worthington, in a nonrandomized crossover trial involving 51 patients with chronic– progressive and relapsing– remitting disease, found some minor benefits after 20 hyperbaric oxygen 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 [56].

Between 1983 and 1990, there was a flurry of activity resulting in the publication of several small RCTs with mixed results. The clinical impact of these trials has subsequently been examined in three reviews. In a qualitative review, Gottlieb and Neubauer suggested many of the RCTs were methodologically flawed and suggested the authors may have misinterpreted their trial data [7]. Of particular concern was the possibility that the dose of oxygen was too high and that few trials included ongoing "top-up" treatments after the original course of HBO_2T. Neubauer recommended a starting pressure of 1.5 ATA with graduated introduction of higher pressures titrated to the patient response [60]. Of note, however, is that the only positive RCT published at that time (Fischer 1983) used 2 ATA of oxygen and showed positive results at 1 year follow-up despite not including "top-up" treatments [43]. Neubauer and Gottlieb concluded that despite generally poor results, these trials justified the use of HBO_2T when interpreted in the light of their own vascular-ischaemic pathophysiological model.

In 1995, Kleijnen and Knipschild published a semiquantitative analysis and concluded: "the majority of controlled trials could not show positive effects" [57]. 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 favour of HBO_2T. In 2004, we published a Cochrane systematic review with *meta*-analysis [41]. This review is discussed below in more detail.

Summary of the Cochrane Review

This review included any RCT, regardless of allocation concealment and blinding, where HBO_2T was part of the randomized methodology. Trials enrolling any MS patients (based on clinical criteria) irrespective of the disease state or course were considered for inclusion. The methodology conformed to that of the Collaboration, and has been described in detail elsewhere [41]. Our search strategies were repeated in July 2009 but did not locate further relevant studies.

The primary outcomes of interest were objective assessments by neurologist or hyperbaric physician, specifically: Kurtzke EDSS at completion of the intervention, 6 months and/or 1 year [35], the numbers of participants suffering at least one exacerbation and the numbers of participants suffering sideeffects or adverse events associated with treatment.

Analysis of data were performed most recently using RevMan 5.0 software (Version 5.0. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2008). In general, continuous data were analyzed using comparison of group means (difference between means across trials) and standard deviation (SD), whilst dichotomous data were presented as an odds ratio (OR). Where meaningful, the number needed to treat to achieve one extra favorable outcome was calculated and presented with 95% confidence intervals. On the basis of comments of Gottlieb and Neubauer [7], subgroup analysis was considered by individual treatment session nitrogen dose (nature of sham treatment– P_IN_2), individual treatment oxygen dose (treatment pressure), and length of therapy– (1 month [20 treatment sessions] vs. 6 months or 1 year).

Description of Studies

The search identified 36 relevant publications and initial examination suggested 19 possible comparative trials. After appraisal of the full reports, nine publications were excluded because they were not reports of RCTs or did not contain new data [7,42,46–48,55–57,59].

Ten reports of nine trials contributed to this review. In total, these trials include data on 504 participants, 260 receiving HBO_2T and 244 control or sham therapy. The lowest dose of oxygen administered was 1.75 ATA for 90 min (Harpur) [51], while the highest dose was 2.5 ATA for 90 min (Confavreux; Oriani) [49,53]. All others used 2.0 ATA for 90 min. All trials used an initial course of 20 treatment sessions over 4 weeks, while two (Harpur 1986; Oriani 1990) continued to administer "top-up" treatments [51,53]. Overall, there were 31 participants lost to final follow-up (7.7% of the total number enrolled).

Results

There were no significant improvements in mean EDSS at the completion of 20 treatments (HBO_2T 0.07 points better than sham, 95%CI –0.09 to 0.23, $P = 0.4$; Fig. 2), nor at 6 months (0.22, 95%CI –0.09 to 0.54, $P = 0.17$), however there was a statistically significant benefit at

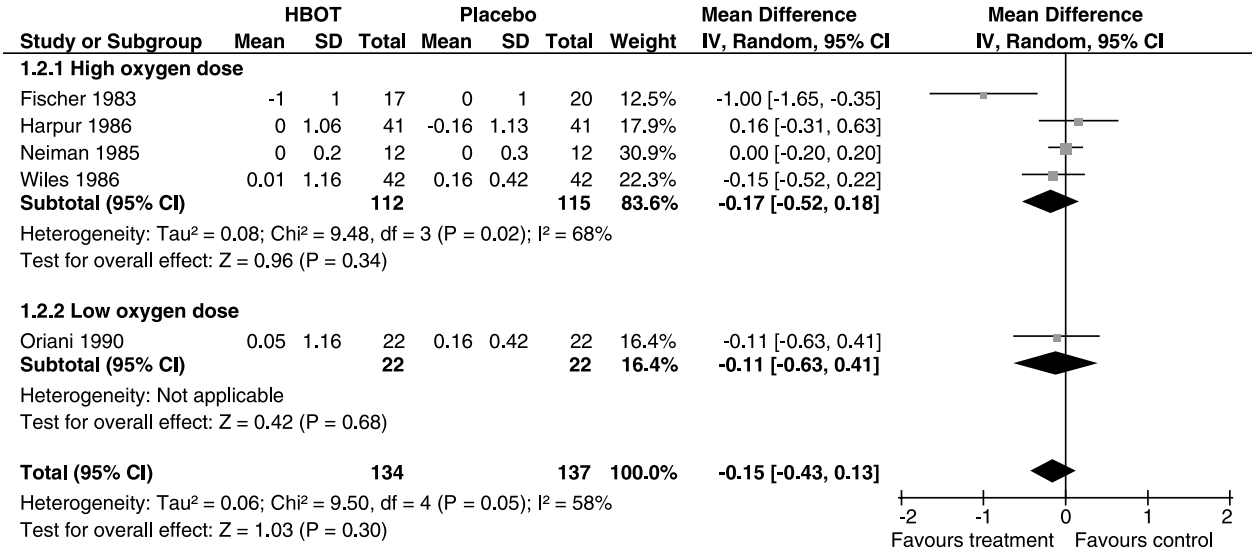

Figure 2 Forest plot for improvement in EDSS after 20 treatments– subgroup analysis by oxygen dose.

1 year after completion of initial course (0.85, 95%CI 0.42 to 1.28, $P = 0.0001$). Subgroup analysis by P_IN_2 during treatment and the oxygen dose did not explain these findings. The only two out of nine trials that reported mean EDSS at 1 year were also the only two generally positive trials.

Similarly, the proportion of participants improved by at least one point on EDSS did not differ at completion of 20 treatments. Few participants improved in either group: 11 (5%) in the HBO_2T group and 3 (1.5%) in the sham group. The OR for benefiting from sham was 0.33, 95% CI 0.09 to 1.18, $P = 0.09$, and at 6 months 0.42, 95%CI 0.16 to 1.08, $P = 0.07$. Again, there was a statistically significant benefit from HBO_2T at 1 year (OR 0.2, 95%CI 0.06 to 0.72, $P = 0.01$). Thirteen participants (14.3%) improved in the HBO_2T group and four participants (4.5%) in the sham group. This analysis largely reflects the Oriani study, to which it contributes 84.7% of the weight. This result was sensitive to the allocation of drop-outs with a loss of any significant advantage from the administration of HBO_2T with worst case assumptions (OR 1.34, 95% CI 0.08 to 21.75, $P = 0.21$). The analysis suggests we would need to treat 10 participants with HBO_2T to achieve one extra patient with an improvement in EDSS of one point at 1 year, but we may have to treat as many as 71 (NNT = 10, 95%CI 5 to 71).

There was no significant reduction in the odds of experiencing an exacerbation at completion of initial course of HBO_2T (OR 0.31, 95%CI 0.01 to 7.80, $P = 0.5$), 6 months (OR 0.74, 95%CI 0.25 to 2.22, $P = 0.6$), nor at 1 year (OR 0.38, 95%CI 0.04 to 3.22, $P = 0.4$). At the final follow-up, 25.9% of patients in the HBO_2T group had suffered an exacerbation versus 36.9% in the sham group.

On analysis of individual functional systems, there was no significant improvement or slowing of deterioration in bladder/bowel control or pyramidal signs after 20 treatments (sphincter control: OR 0.72, 95%CI 0.33 to 1.60, $P = 0.4$, pyramidal signs OR 0.30, 95%CI 0.06 to 1.47, $P = 0.14$), but at 6 months and 1 year there was a reduced chance of deterioration in pyramidal signs (at 6 months OR 0.17, 95%CI 0.07 to 0.78, $P = 0.02$, 1 year OR 0.13, 95%CI 0.03 to 0.58, $P = 0.007$). At one year, 13.2% of patients improved in the HBO_2T group compared to 4.5% in the sham group. These results largely reflect the outcome in a single trial (Oriani 1990) and suggest we would need to treat at least six patients with HBO_2T in order to improve one extra individual, but perhaps as many as 197 patients (NNT = 11, 95% CI 6 to 197).

Adverse Effects

There were significantly increased odds of deteriorating vision following the administration of HBO_2T (OR 24.87, 95% CI 1.44 to 428.50, $P = 0.03$). The analysis suggests the number need to treat with HBO_2T to get one further complaint of visual disturbance is very low (NNT = 1; 95%CI 1 to 2).

Discussion

We concluded there is little evidence of a significant effect for the administration of HBO_2T in this review. Whilst

there was a modest benefit demonstrated in mean EDSS at 12 months, this result is uncertain given that only two trials reported on this outcome at this time (16% of the total participants in this review) and they were the only trials of the nine in this review to suggest benefit. There was similarly little consistent evidence for benefit with respect to the secondary outcomes relating to improvements in function systems. No analysis indicated benefit in global FSS or the bladder/bowel sphincter function element of this scale. The benefit in the pyramidal function element at 6 months and 12 months reflected one single positive trial (Oriani 1990) [56].

Of the 20 separate outcome factors where *meta*-analysis was possible, significant benefit was only suggested in three. Where appropriate we made up to three previously planned subgroup analyses with respect to treatment length, nature of the sham, and oxygen dose per treatment session. None could explain the heterogeneity between the results of Fischer and Oriani and the other seven trials, because those two trials were in alternative subgroups in all three analyses.

We recognise this review is hampered by the modest total number of participants enrolled, variation in entry criteria and treatment length between studies and the large number of analyses where there were no individuals with the outcome of interest in either arm of the study. Nevertheless, the entry EDSS scores indicated the majority of participants had mild or moderate disabilities and the analyses are most likely to reflect outcomes in these patient groups.

The first RCT published (Fischer) [43] defined a reduction of one point on the EDSS as a "major improvement", and a similar reduction of one point on the FSS as a "minor improvement". Most subsequent authors followed this example. The reduction in mean EDSS in the HBO_2T group at 12 months was 0.84 points. This magnitude of improvement is of dubious clinical benefit. Over all these trials, only a small proportion of participants improved by a full point in either group (at 20 treatments 6.8% HBO_2T group, 3% sham).

These results should be interpreted with great caution for a number of reasons. It is possible, for example, there is bias toward later reporting in those trials showing successful outcomes compared to those in which the initial findings were unpromising. It is also biologically implausible that a benefit be absent at 6 months after treatment and present at 12 months. Proponents of HBO_2T suggest that a long course of treatment may be required to demonstrate benefit [61] and that those trials giving only 20 treatments are flawed in this regard. Others maintain that treatments over 2 ATA are toxic and unhelpful [7,60]. Both these assertions are difficult to sustain however, in that of the two trials contributing to this significant result, one gave a short course at only 2 ATA (Fischer) [43], while the other continued with "top-up" treatments to 12 months and used 2.5 ATA (Oriani) [53], and both showed benefits after 20 treatments and 6 months. Furthermore, the only other trial to administer a longer course of treatments (Harpur) [51] failed to suggest any benefit in EDSS at 20 treatment or 6 months (no data at 12 months).

Anecdotally, most improvements reported have been in sphincter function and pyramidal system function, and these trials focus particularly on these areas. There was no evidence from this review to support the improvement of bladder/bowel function following HBO_2T when compared to a sham. Pyramidal function was improved at 6 months only, and are due to the findings of a single study.

Cost-effectiveness of HBO_2T

The patient charge for providing HBO_2T is highly variable and in part dependent on the type of facility, the presence or absence of physician supervision and the healthcare system within which it is delivered. Whilst the true cost of HBO_2T is difficult to establish, a range of likely cost to benefit can be estimated from recently published data from an Australian facility [62].

These authors calculated the dollar cost of HBO sessions and the total HBO_2T costs per diagnosis treated in their unit in 2003 to 2004– defining the financial cost as the expenditure on goods and services purchased. On the basis that MS patients would be outpatients for the most part and involve a relatively low level of complexity, a reasonable estimate of the true cost of a single treatment for MS in a hospital setting was likely to be $AUD304. The first annual cost for a course of 20 sessions with "top-up" treatments of twice each month (42 treatments in total) is estimated at $AUD12,768.

On the basis of the results of the *meta*-analysis above, the likely cost for one extra individual to achieve an increase of a single point on the Kurtzke EDSS at one year is $AUD127,680, with a 95% CI of $AUD63,840 to $AUD906,528 (NNT 10, 95%CI 5 to 71).

Such estimates assume the cost of provision of HBO_2T will be similar to those of a tertiary HBO_2T facility. The actual cost of provision in centers operated and designed solely for the provision of HBO_2T to ambulatory MS patients is likely to be considerably lower. If the cost was $100/treatment, for example, the equivalent figures for an improvement in EDSS would be $AUD42,000 (95%CI $AUD21,000 to $AUD298,200).

On the other hand, on the basis of an initial course of 20 treatments and "top-up" treatments weekly, each patient would require 68 treatments in the first year rather

than the 42 estimated earlier, with a corresponding rise in the total costs.

Conclusions

There is no consistent evidence to confirm a beneficial effect of HBO_2T for the treatment of MS and routine use does not seem justified on the available evidence. The small number of analyses suggestive of benefit in the Cochrane *meta*-analysis are isolated, difficult to ascribe with biological plausibility and would need to be confirmed in future well-designed trials. The cost to achieve any benefit is likely to be high.

The published clinical evidence, and in particular the randomized clinical trials concerning HBO_2T for MS are somewhat dated and difficult to interpret compared to contemporary investigations. Whilst there is some case for further research, there is little indication that strong and clinically useful treatment effects are likely. It is possible, however, that modest treatment benefits may be present in a subset of disease severity or classification.

Any future trials would need to be carefully planned. They would need to enrol appropriate sample sizes with power to detect expected differences in carefully selected target patients. Inclusion criteria and outcome measures will both need to include MRI data and validated quality of life instruments. Finally, any future trials should assess both the safety and cost of therapy. It is our opinion that such trials are difficult to justify given the existing evidence, and it is likely that only staunch advocates would be willing to pursue such investigations.

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Contribution of Authors

The conception and design of systematic review, development of search strategy, appraisal and selection of studies for inclusion, data analysis, and drafting article (M.B.). The appraisal and selection of studies for inclusion, data extraction and entry, critical review of article (R.H.).

Conflict of Interest

The authors have no conflict of interest to declare in relation to this review.

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