NORMOBARIC AND HYPERBARIC OXYGEN THERAPY FOR MIGRAINE AND CLUSTER HEADACHE

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A B S T R A C T

Background

Migraine and cluster headaches are severe and disabling. Migraine affects up to 18% of women, while cluster headaches are much less common (0.2% of the population). A number of acute and prophylactic therapies are available. Hyperbaric oxygen therapy (HBOT) is the therapeutic administration of 100% oxygen at environmental pressures greater than one atmosphere, while normobaric oxygen therapy (NBOT) is oxygen administered at one atmosphere.

Objective

To assess the safety and effectiveness of HBOT and NBOT for treating and preventing migraine and cluster headaches.

Criteria for considering studies for this review

We searched the following in May 2008: CENTRAL, MEDLINE, EMBASE, CINAHL, DORCTIHM and reference lists from relevant articles. Relevant journals were hand searched and researchers contacted.

Selection criteria

Randomised trials comparing HBOT or NBOT with one another, other active therapies, placebo (sham) interventions or no treatment in patients with migraine or cluster headache.

Data collection and analysis

Three reviewers independently evaluated study quality and extracted data.

Main results

Nine small trials involving 201 participants were included. Five trials compared HBOT versus sham therapy for acute migraine, two compared HBOT to sham therapy for cluster headache and two evaluated NBOT for cluster headache.

Authors' conclusions

There was some evidence that HBOT was effective for the termination of acute migraine in an unselected population, and weak evidence that NBOT was similarly effective in cluster headache. Given the cost and poor availability of HBOT, more research should be done on patients unresponsive to standard therapy. NBOT is cheap, safe and easy to apply, so will probably continue to be used despite the limited evidence in this review.

P L A I N   L A N G U A G E   S U M M A R Y

Migraine and cluster headaches are severe and disabling. Both hyperbaric oxygen therapy (HBOT) and normal pressure oxygen therapy (NBOT) have been suggested as effective treatments to end acute attacks and prevent future attacks. HBOT involves people breathing pure oxygen in a specially designed chamber. In our review, we found some weak evidence to suggest that HBOT helps people with acute migraine headaches and possibly cluster headaches, and that NBOT may

help people with cluster headache. We found no evidence that either can prevent future attacks. Because many migraines can be treated simply with appropriate drug therapy, further research is needed to help choose the most appropriate patients (if any) to receive HBOT.

W H A T ' S   N E W

What's new
Last assessed as up-to-date: 6 May 2008.

Date	Event	Description
10 August 2009	Amended	Contact details updated.

B A C K G R O U N D

Migraine and cluster headache are disabling health problems among adults. Both types of headache are frequently severe and associated with features other than pain (IHS 2004). While the classification of headaches is complex, migraine and cluster headaches are generally distinguished by the nature of associated symptoms (nausea, vomiting and photophobia occur commonly with migraine, while cluster headaches are typically accompanied by tearing and nasal congestion), the pattern in which they occur (cluster headaches typically occur daily for up to several weeks before resolving, often for lengthy periods) and their location and character (cluster headaches are periorbital and unilateral, while migraines may be bilateral and are often described as throbbing). Migraine may be preceded by an aura - most often a visual disturbance - in some people.

Migraine is the more common of the two: surveys from the U.S. and elsewhere suggest that 6% to 7% of men and 15% to 18% of women experience migraine headaches, while about 0.2% of the population suffer with cluster headache (Mathew 2001; Russell 2004). First-degree relatives of those with cluster headaches are 5 to 18 times more likely to have such headaches than individuals in the general population. The mechanisms involved in both types of headache continue to be active areas of research (Hamel 1999; Leone 2004). Migraine results in significant disability and work loss (Burton 2002; Edmeads 2002; Lipton 2001); estimated aggregate indirect costs to employers in the U.S. for reduced productivity due to migraine range from U.S.$5.6 billion to U.S.$17.2 billion annually (Hu 1999; Osterhaus 1992). The social and economic impact of cluster headache is less clear.

Therapy for headache falls into two categories: acute and preventive. Acute therapy aims at the symptomatic treatment of the head pain and other symptoms associated with an acute attack or cluster. The goal of preventive therapy is to reduce the frequency and/or intensity of attacks and thereby improve patient functioning and quality of life. Preventive therapy is especially well-suited to patients with very frequent or severe attacks, significant headache-related disability or resistance to acute therapy.

There are many accepted drug therapies for acute migraine, including non-specific analgesics such as non-steroidal anti-inflammatory drugs, and specific agents such as sumatriptan, ergotamine and dihydroergotamine (DHE) (Geraud 2004). These drugs are effective in the majority of cases, although it is not uncommon for headache to recur within 48 hours (Bateman 1993). Most people with migraine are able to manage even these recurrent headaches successfully at home with self-administered medication. Thus, while migraine is a common problem, the number of cases unresponsive to accepted therapeutic approaches may be quite small. It is these patients who may benefit from a therapy delivered at a health facility, such as intravenous DHE, parenteral analgesics or antinauseants or, potentially, hyperbaric oxygen therapy.

Pharmacological and non-pharmacological therapies used for the prevention of migraine include various beta-blockers, amitriptyline, sodium valproate, gabapentin, relaxation, biofeedback and cognitive-behavioural therapy (Geraud 2004). Again, while most patients respond to such therapies, they are not always effective. Refractory patients may be offered preventive drug treatments with potentially serious toxicities, such as methysergide; these patients may also be candidates for other resource-intensive treatments such as hyperbaric oxygen therapy.

The standard acute treatment for cluster headache is sumatriptan and inhalation of 100% oxygen, while a number of agents have been used for prophylaxis including ergotamine, verapamil, lithium and steroids (Ekbom 2002). Again, most patients respond well to the administration of specific acute therapy. For example, in one randomised study, 74% of attacks responded to subcutaneous

sumatriptan within 15 minutes (Ekbom 1993). Only a subset of cluster headache patients would therefore be candidates for the administration of therapies such as hyperbaric oxygen where hospital attendance is required. Most recently, there have been promising advances in the search for a more permanent cure, particularly with deep hypothalamic stimulation techniques and subsequent surgical procedures (May 2003).

This review considers the evidence for the effectiveness and safety of oxygen administration for migraine or cluster headache. It includes both the use of oxygen at high percentage of normal atmospheric pressure (normobaric oxygen therapy (NBOT)) and the use of 100% oxygen at pressures above one atmosphere (hyperbaric oxygen therapy (HBOT)). We will consider oxygen both as an acute therapy for terminating individual attacks and as a preventive therapy for reducing the frequency of headache episodes. NBOT has been used with some success to treat both migraine and cluster headaches for many years (Alvarez 1939; Kudrow 1981), presumably through the ability of oxygen to constrict distal cerebral resistance vessels (Drummond 1985; Iversen 1990). The observation that oxygen administered at higher pressures produced even further vasoconstriction (with preservation of tissue oxygenation) led directly to the suggestion that HBOT might favourably influence vascular headache resistant to conventional drug therapy (Fife 1994). More recently, it has been suggested that HBOT may also exert therapeutic effects through the action of oxygen as a serotonergic agonist and an immunomodulator of response to substance P (a short chain neuropeptide involved in pain signal transmission) (Di Sabato 1996; Di Sabato 1997). Indeed, while acknowledging that vascular mechanisms are involved, it has been suggested that inflammation plays a critical role in the genesis of a migraine episode (Goadsby 1997; Hamel 1999). If this is correct, then the well-described moderation of inflammatory pathways by HBOT may both influence acute attacks and provide useful prophylaxis (Slotman 1998; Sumen 2001).

Clinically, HBOT has been reported as a successful treatment for headache since at least 1989 (Fife 1989; Weiss 1989), and sporadic reports have followed since that time, including some comparative trials. On the other hand, oxygen in high doses may increase oxidative stress through oxygen free radical species and is potentially toxic (Yusa 1987). Indeed, the brain is particularly at risk (Clark 2003). For this reason, it is appropriate to postulate that in some migraine or cluster headache patients, HBOT may do more harm than good.

Precautions against fire are required and standard practice in areas where oxygen is in use. Prolonged administration to premature neonates may be implicated in the development of retinopathy of prematurity, and oxygen has produced respiratory arrest in chronically hypercarbic patients relying on an hypoxic drive for respiration. Neither of these groups of individuals is likely to be relevant in this review. Regardless of the particular pathology being treated, HBOT is associated with some risk of adverse effects, including damage to the ears, sinuses, and lungs from the effects of pressure; temporary worsening of shortsightedness; claustrophobia; and oxygen poisoning. Although serious adverse effects are rare, HBOT cannot be regarded as an entirely benign intervention.

OBJECTIVES

The objective of the review was to examine the effectiveness and safety of normobaric oxygen therapy (NBOT) and hyperbaric oxygen therapy (HBOT) in the treatment and prevention of migraine and cluster headache. Effectiveness was assessed using a number of clinically important outcomes including pain, as detailed below.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials that evaluate the effectiveness of NBOT or HBOT for migraine or cluster headache were included.

Types of participants

We sought to identify trials that included patients of any age and either sex with migraine (with or without aura) or cluster headache. Headache classification followed the guidelines of the International Headache Society where possible (IHS 2004).

Types of intervention

We considered interventions that included NBOT at any concentration above ambient air (whether administered in a health facility or at home) or HBOT administered in a compression chamber. We included trials where NBOT was compared to HBOT, or where either was compared to a standard therapy or no treatment. The comparator groups included any standard treatment regimen designed to prevent or terminate headache or prevent recurrence, including combined therapies, as well as placebo (sham) interventions and no treatment. We included regimens where adjunctive NBOT or HBOT was compared against similar regimens excluding NBOT or HBOT. Where regimens differed significantly between studies, we have stated this clearly and discussed the implications.

Types of outcome measures

We anticipated that short-term response would be of greatest clinical importance. Primary outcome assessments were generally made during or immediately following therapy.

For outcomes relating to headache intensity, we preferred those that measure headache relief or change in headache intensity, since these are more comparable among patients with different baseline scores. There were no data available for recurrent migraine or cost-effectiveness. The outcomes considered eligible for inclusion in this review were:

Primary effectiveness outcomes

Treatment of acute attack

Proportion of patients with pain-free response (complete resolution of headache pain). Assessment times preferred were 1 and 2 hours for migraine, 15 and 30 minutes for cluster headache.

Proportion of patients with headache pain reduction from moderate/severe to mild or none (timing as for 1, above).

Proportion of patients with sustained relief for 24 hours.

Prevention

Frequency of attacks.

Number of headache days.

Days lost to work.

Secondary effectiveness outcomes

Treatment of acute attack

Degree of headache relief or headache intensity.

Functional status or disability.

Pain-free response at 4 hours for migraine and 2 hours for cluster headache.

Proportion of patients requiring rescue medication.

Proportion of patients with sustained relief at 48 hours.

Proportion of patients with photophobia or phonophobia (migraine only).

Proportion of patients with nausea and/or vomiting (migraine only).

Prevention

Self-reported assessment of treatment success.

Frequency of attacks rated by patient as 'severe'.

Quality of life.

Functional status or disability.

Headache index (nature and calculation discussed).

Adverse effects/safety

Adverse effects related to HBOT, such as the proportion of patients with visual disturbance (short- and long-term), barotrauma (aural, sinus, pulmonary in the short and long term) and oxygen toxicity (short-term).

Any other recorded adverse effects were reported and discussed.

S E A R C H   M E T H O D S   F O R   I D E N T I F I C A T I O N   O F   S T U D I E S

Search methods for identification of studies

We intended to capture both published and unpublished trials. Relevant trials were identified in the Cochrane Central Register of Controlled Trials (CENTRAL, May 2008), MEDLINE (1966 to May 2008), EMBASE (1980 to May 2008), CINAHL (1982 to May 2008), and an additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine (Bennett 2004)).

The following search strategy was used for MEDLINE and adapted for the other databases:

1 Headache/
2 exp Headache Disorders/
3 (headache$ OR migrain$ OR cephalgi$ OR cephalalgi$ OR cluster).tw.
4 or/1-3
5 Hyperbaric Oxygenation/
6 Oxygen Inhalation Therapy/
7 Oxygen/ae, tu, to [Adverse Effects, Therapeutic Use, Toxicity]
8 Hyperoxia/
9 Atmosphere Exposure Chambers/
10 (hyperbar$ or HBO$).tw.
11 (high pressure oxygen or 100% oxygen).tw.
12 ((monoplace or multiplace) adj5 chamber$).tw.
13 or/5-12
14 4 and 13
15 limit 14 to human

In addition we made a systematic search for relevant controlled trials by other means available. We contacted experts in the field of headache and leading hyperbaric therapy centres and asked authors of relevant studies for details of any unpublished or ongoing investigations, and hand searched relevant hyperbaric textbooks (Jain 1999; Kindwall 1999; Oriani 1996), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society Journal, European Journal of Hyperbaric Medicine and Aviation, Space and Environmental Medicine Journal) and conference proceedings (Undersea and Hyperbaric Medical Society, South Pacific Underwater Medicine Society, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) from first editions to 2006. Finally, we checked the reference lists of the trials and reviews identified by the above strategies.

D A T A   C O L L E C T I O N   A N D   A N A L Y S I S

Data collection and analysis

Trial identification

Records retrieved by the initial search were scanned by MB and JW to exclude obviously irrelevant studies, then two authors (MB and AS) identified trials that may have met the inclusion criteria. Full-text articles were retrieved and reviewed by three authors (MB, AS and CF) for the purpose of applying inclusion criteria independently. In all instances, differences of opinion were resolved by discussion among the review authors.

Data extraction

Data from the studies were extracted independently by two authors (MB and AS) using standardised forms developed for this review. Primary study investigators were contacted to provide information when missing data were encountered. All differences were resolved by discussion among the review authors.

Quality assessment

Study quality was assessed using an adaptation of the method outlined in Schulz 1995. Quality assessment is presented in a descriptive manner using the following characteristics:

Adequacy of the randomisation process:
A - Adequate sequence generation is reported using random number tables, computer random number generator, coin tossing or shuffling.
B - Did not specify one of the adequate reported methods in (A) but mentioned randomisation method.
C - Other methods of allocation that appear to be unbiased.

Adequacy of the allocation concealment process:
A - Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained convincing elements of concealment.
B - Unclearly concealed trials in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in (A).
C - Inadequately concealed trials in which method of allocation is not concealed, such as alteration methods or use of case record numbers.

Potential for selection bias after allocation:
A - Trials where an intention-to-treat analysis is possible and few losses to follow up are noted.
B - Trials that reported exclusions (as listed in A but exclusions were less than 10%).
C - No reporting on exclusions, or exclusions greater than 10%, or wide differences in exclusions between groups.

Level of masking (treatment provider, patient, outcome assessor):
A - Double- or triple-blind.
B - Single-blind.
C - Non-blind.

Analyses

Data from trials enrolling patients with migraine were analysed separately from those enrolling patients with cluster headache. We used a fixed-effect model where there was no evidence of significant heterogeneity between studies, and a random-effects model when such heterogeneity was likely (DerSimonian 1986). Consideration was given to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. Statistical heterogeneity was assessed using the I2 statistic, and consideration was given to the appropriateness of pooling and meta-analysis.

For proportions (dichotomous outcomes), relative risk (RR) was used. When data from cross-over trials contributed to an analysis, we intended to use the Peto method for taking joint conditional probabilities into account, as described in Curtin 2002. However this was not possible with the data available and we have analysed these trials as if they were parallel-group in design. This is a generally conservative approach that ignores the reduction in inter-patient variability in cross-over studies. Continuous data were converted to the mean difference (MD) using the inverse variance method, and an overall MD calculated. Testing for publication bias was not appropriate for the data available.

We performed subgroup analysis where appropriate by calculation of RR or MD in each subgroup and examination of the 95% confidence intervals (CIs). Non-overlap in intervals was taken to indicate a statistically significant difference between subgroups.

All analyses were made on an intention-to-treat basis where possible. Tests of interaction were calculated to determine if the results for subgroups were significantly different. Statistical heterogeneity was assumed to be significant if the I2 analysis suggested more than 30% of the variability in an analysis was due to differences between trials. Consideration was then given to the appropriateness of pooling and meta-analysis; when analysis was undertaken in the face of statistical or clinical heterogeneity, we used a random-effects model.

We performed sensitivity analyses for missing data where appropriate, but sensitivity analysis for study quality was not appropriate. In the case of missing data, we employed different approaches to imputing missing data. The best-case scenario assumed that none of the originally enrolled patients missing from the primary analysis in the treatment group had the negative outcome of interest while all those missing from the control group did. The worst-case scenario was the reverse.

We considered subgroup analyses based on the following factors, but such analyses were not appropriate:

Dose of oxygen received - NBOT versus HBOT;

Dose of oxygen received during HBOT - variables to be considered: pressure (< 2.0 atmospheres absolute [ATA] versus >/= 2.0 ATA), time (< 60 min versus >/= 60 min), and length of treatment course (< 5 sessions versus >/= 5 sessions);

Migraine with aura versus without aura;

Comparator treatment (where oxygen has been compared to different alternative treatments).

M E T H O D O L O G I C A L   Q U A L I T Y

R E S U L T S

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 24 publications dealing with the use of HBOT for the treatment of headache. Initial examination confirmed three were case series, eight were reviews without new data and four were non-random comparative trials. These 15 reports were excluded and the reasons for exclusion of each are given in the 'Characteristics of excluded studies' table. The remaining nine trials were accepted into the review (Kudrow 1981; Fogan 1985; Fife 1992; Hill 1992; Di Sabato 1993; Myers 1995; Wilson 1998; Nilsson Remahl 2002; Eftedal 2004).

The included trials were published between 1981 (Kudrow 1981) and 2004 (Eftedal 2004), and the reviewers are unaware of any ongoing RCTs in the area. Five trials enrolled a total of 103 patients experiencing acute migraine, all of which employed HBOT in one arm (Fife 1992; Hill 1992; Myers 1995; Wilson 1998; Eftedal 2004). The remaining four trials enrolled a total of 98 patients with cluster headache. Two of these evaluated one atmosphere oxygen breathing (NBOT) (Kudrow 1981; Fogan 1985), and the other two administered HBOT (Di Sabato 1993; Nilsson Remahl 2002). Several studies utilized a cross-over design (Kudrow 1981; Fogan 1985; Hill 1992; Wilson 1998; Nilsson Remahl 2002). In total, these nine trials include 201 patients with oxygen being administered in 158 cases and a control therapy in 155 cases. Details of methodology and interventions are included in the table 'Characteristics of included studies'.

The dose of oxygen per treatment session and for the total course of treatment varied somewhat between studies. Of the trials investigating the treatment of migraine, all administered HBOT at 2.0 ATA except Wilson 1998, who utilized 2.4 ATA. The period of exposure to HBOT varied from 30 minutes on 3 consecutive days in Eftedal 2004 to a maximum of 60 minutes in Wilson 1998. All migraine trials except Eftedal 2004 gave a single exposure only. The two cluster headache trials investigating NBOT administered oxygen for 15 minutes, while the two investigating HBOT both administered oxygen at 2.5 ATA, Di Sabato 1993 for 30 minutes on a single occasion and Nilsson Remahl 2002 for 70 minutes on two consecutive days.

All trials except Kudrow 1981 provided a sham therapy and blinded patients and assessors to the treatment received. For the HBOT trials sham procedures varied, with the use of air at atmospheric pressure (Di Sabato 1993), air at 2 ATA (Hill 1992; Eftedal 2004), 10% oxygen at 2 to 2.5 ATA in order to maintain inspired oxygen tension near that of air at atmospheric pressure (Fife 1992; Nilsson Remahl 2002) and 100% oxygen administration at or near atmospheric pressure (Myers 1995; Wilson 1998). Fogan 1985 had masked cylinders of air or oxygen to maintain blinding to patient and assessor.

Inclusion and exclusion criteria varied widely across the trials. Of the migraine trials, three accepted patients with confirmed diagnoses by a neurologist or physician (Fife 1992; Myers 1995; Wilson 1998), while Eftedal 2004 used the criteria of the International Headache Society (IHS 1988) and Hill 1992 the criteria of the Ad Hoc Committee of the National Institute of Neurological Diseases and Blindness (AHC 1962). Of the cluster headache trials, two used the criteria of the AHC (Fogan 1985; Di Sabato 1993), one the criteria of the IHS (Nilsson Remahl 2002) and Kudrow 1981 did not define the diagnosis. Most trials investigated the efficacy of oxygen for the termination of an acute headache attack, while Nilsson Remahl 2002 and Eftedal 2004 were primarily designed to investigate prophylaxis. Details of both inclusion and exclusion criteria where recorded are given in the 'Characteristics of included studies' table.

For most studies, control arms used no specific anti-headache treatment (other than sham oxygen), except for Kudrow 1981, in which sublingual ergotamine tartrate was used in the control group, and Myers 1995, where NBOT was used in the control group. Most trials did not follow patients after the end of the therapy period with the exception of Nilsson Remahl 2002 (1 week), and both Di Sabato 1993 and Eftedal 2004 (2 months).

Other outcomes (including non-clinical) reported included: number of doses of attack-terminating medicine and plasma endothelin levels (Eftedal 2004); jugular venous plasma levels of calcitonin gene-related peptide, vasoactive intestinal peptide and neuropeptide Y (Nilsson Remahl 2002); and pericranial tenderness with algometry (Wilson 1998).

Risk of bias in included studies

Study quality using the criteria of Schulz 1995 is described in the 'Characteristics of included studies' table. Study quality was generally assessed as moderate to low, and two of the included reports were presented as abstracts only (Hill 1992; Fife 1992).

Randomisation

Allocation concealment was inadequate in Di Sabato 1993 and unclear in the remaining studies. Fife 1992 described a randomisation by random draw of sealed envelopes, but the remaining studies gave no details. Di Sabato 1993 did not specifically use the term 'randomisation' and this trial may not have been truly random. Sensitivity analyses with and without this trial were considered during analysis. For none of the studies is there a clear indication that the investigators were unable to predict the prospective group to which a participant would be allocated.

Hill 1992 was a cross-over design where the cross-over occurred after a 5-minute period breathing air at 2.0 ATA. Because any individual with relief from the first treatment period could not receive further relief during the second, we accepted only the response to the initial treatment period into this review. The cross-over trials in general were poorly reported and only for Fogan 1985 could we extract data on the response of each individual to both arms of the study.

Patient baseline characteristics

Patient baseline diagnosis was poorly described in most of the trials.

Migraine: All trials used published diagnostic criteria (either the AHC 1962 or IHS 1988) or diagnosis by a specific neurologist or physician. Wilson 1998 accepted only patients at least 18 months from first diagnosis of migraine with aura and Eftedal 2004 required from 2 to 8 attacks per month for the preceding 3 months. All trials entered patients during acute attacks except Eftedal 2004 where the main outcome was prophylaxis rather than acute headache termination.

Cluster: All trials used published diagnostic criteria (either the AHC 1962 or IHS 1988) except Kudrow 1981, who did not define diagnosis. Nilsson Remahl 2002 enrolled both episodic and chronic cluster patients who had experienced at least six attacks in the previous week and in whom the cluster was expected to persist for at least 4 further weeks, Di Sabato 1993 enrolled

only episodic cluster patients in the 'florid phase' from day 10 to 15 of their cluster, while Kudrow 1981 and Fogan 1985 did not report further baseline details.

Blinding

All trials blinded the outcome assessor to therapy except Kudrow 1981 (no blinding). Di Sabato 1993 and Myers 1995 blinded the assessor only, while all other trials blinded patients, investigators and assessors. All trials provided a sham therapy except Kudrow 1981, who provided a sublingual preparation as the comparator therapy.

Patients lost to follow up

One patient was lost to final follow up in the control group of Eftedal 2004. One patient did not receive either therapy in the cross-over trial of Hill 1992 (no reason given), while in Eftedal 2004, six patients were enrolled but did not complete therapy and were not analysed (one hyperbaric and five control) - one suffered a technical problem with the chamber and could not be treated, two withdrew because of claustrophobia, one withdrew with a respiratory tract infection, one had a pathological chest X-ray and the final patient withdrew for unknown reasons. Some patients failed to cross for the second arm of therapy in Fogan 1985, Fife 1992 and Kudrow 1981 and this accounts for the uneven numbers in the different therapy arms of those trials. None of the remaining studies suffered any losses to follow up, or reported any violation of allocated treatment.

Intention-to-treat analysis

Most trials delivered the intended therapy and analysed by intention to treat. No data were generated or analysed where patients withdrew from the study before therapy was delivered or where an individual failed to cross and receive the alternative therapy. Eftedal 2004 supplied the raw data to allow intention-to-treat analysis for the missing patient in the control group.

Effects of interventions

Migraine

HBOT for an acute attack

1. Proportion of patients with relief of acute migraine (Analysis 01.01)

No trials specifically reported on complete resolution of headache. Three trials reported the proportion of patients with resolution or significant relief of migraine with 40 to 45 minutes of HBOT (Hill 1992; Fife 1992; Myers 1995). These studies involved a total of 43 patients receiving 76 occasions of therapy (40 HBOT versus 36 sham). Two were of cross-over design, and in these, following initial group assignment, cross-over was undertaken at 5 minutes (Hill 1992) and 30 minutes (Fife 1992). Individual patient responses to each arm were not reported, nor were any cross-over effects. There was a statistically significant increase in the proportion of patients with substantial relief of headache with HBOT (RR 5.97, 95% CI 1.46 to 24.38, P = 0.01). Because there was an indication of substantial heterogeneity (I2 = 43%), this RR was calculated with a random-effects model. There was no evidence of a substantially different effect when HBOT was compared to air or 100% normobaric oxygen (administered as an HBOT sham). The absolute risk difference of 0.64 between sham and HBOT suggests the number needed to treat (NNT) to achieve one extra case of relieved headache is 2 (95% CI 1 to 2). Myers 1995 compared HBOT with NBOT (administered as an HBOT sham). With subgroup analysis by comparator therapy, Myers 1995 reported a similar magnitude of effect to the other two trials, but did not account for the heterogeneity between trials (Myers 1995: RR for relief with HBOT 9.00, 95% CI 1.39 to 58.44, P = 0.02; Hill 1992 and Fife 1992 combined: RR 6.23, 95% CI 0.47 to 82.92, P = 0.17, I2 = 68%). There were no data reported for longer term outcomes.

2. Proportion of patients requiring rescue medication

Only Eftedal 2004 reported on this outcome, enrolling 40 patients (20 HBOT, 20 sham). There was no statistically significant reduction in the proportion of patients requiring rescue medication for the first week after therapy (Analysis 01.02: 18 of 19 for the HBOT group versus 12 of 15 for the sham therapy; RR 0.84, 95% CI 0.64 to 1.11, P = 0.23). The best case scenario for the allocation of withdrawals (Analysis 01.03) did not alter this finding (RR 0.94, 95% CI 0.75 to 1.19, P = 0.63); however, on a worst case scenario (Analysis 01.04) the risk of requiring rescue medication was significantly lower with sham (RR 0.63, 95% CI 0.44 to 0.92, P = 0.02).

3. Proportion of patients with nausea and vomiting after therapy

Only Eftedal 2004 reported on this outcome, enrolling 40 patients (20 HBOT, 20 sham). There was no statistically significant reduction in the proportion of patients suffering nausea with or without vomiting in the week after therapy (Analysis 01.05: 9 of 19 for the HBOT group versus 9 of 15 for the sham therapy; RR 1.27, 95% CI 0.68 to 2.38, P = 0.46). Best and worst case scenarios for the allocation of withdrawals did not alter this finding (best case (Analysis 01.06): RR 1.56, 95% CI 0.89 to 2.73, P = 0.12; worst case (Analysis 01.07): RR 0.90, 95% CI 0.47 to 1.73, P = 0.75).

4. Pain intensity score (Analysis 01.08)

Only Wilson 1998 reported on this outcome (immediately following therapy), enrolling eight patients in a cross-over study of NBOT versus HBOT. The cross-over was made when the individual patient presented for treatment of a second headache. Pain intensity on a visual analogue scale of 0 (no pain) to 10 (worst pain) was lower following HBOT, but this difference was not statistically significant (mean pain score 3.5 (SD 10.7) versus 6.3 (SD 14); MD 2.80, 95% CI -4.69 to 10.29, P = 0.46). The reduction in intensity from pre-treatment to post-treatment was reported as significantly greater in the HBOT arm than the NBOT arm (HBOT 4.4 units reduction versus NBOT 0.2 reduction, P = 0.03), however the standard deviations for these reductions were not available for analysis.

HBOT for prevention of attacks

5. Number of headache days per week (Analysis 02.01)

Only Eftedal 2004 reported on this outcome, enrolling 40 patients (20 HBOT, 20 sham). There was no statistically significant difference in the mean number of days with headaches for the first week after therapy (HBOT 3.0 versus sham 2.87; MD -0.13, 95% CI -1.41 to 1.15, P = 0.84), nor during the fourth week (HBOT 2.52 versus sham 2.27; MD -0.25, 95% CI -1.52 to 1.02, P = 0.70) or the eighth week (HBOT 2.89 versus sham 2.14; MD -0.75, 95% CI -2.06 to 0.56, P = 0.26).

No trials reported any data on the frequency of headaches or days off work.

NBOT for an acute attack

Myers 1995 used NBOT (administered as an HBOT sham) as the comparator intervention for a trial of HBOT, see Analysis 01.01, above.

NBOT for prevention of attacks

No trials studied the use of NBOT for prevention of attacks.

Adverse effects

Myers 1995 noted that 'no untoward effects were reported'. Eftedal 2004 reported that following enrolment, two patients refused to complete therapy due to claustrophobia, one developed an upper respiratory chest infection and was withdrawn by the investigators and a further patient was withdrawn following a pathological chest X-ray. No other trials made any reference to adverse effects.

Cluster headache

HBOT for an acute attack

6. Proportion of patients with resolution of headache (Analysis 03.01)

Only one small trial reported on the use of HBOT to relieve cluster headache (Di Sabato 1993). This trial enrolled 13 patients and reported the proportion achieving complete resolution within 20 minutes (six of seven (86%) with HBOT versus none of six with sham). There was however no statistically significant difference (RR in favour of HBOT 11.38, 95% CI 0.77 to 167.85, P = 0.08).

7. Proportion with sustained relief for 48 hours (Analysis 03.02)

Only one small trial reported on this outcome following HBOT (Di Sabato 1993). This trial enrolled 13 patients and reported the proportion achieving sustained resolution for at least 48 hours (six of seven (86%) with HBOT versus none of six with sham). There was however no statistically significant difference (RR in favour of HBOT 11.38, 95% CI 0.77 to 167.85, P = 0.08).

HBOT for prevention of attacks

8. Headache index (Analysis 04.01)

One trial reported on this outcome and enrolled 16 patients in a cross-over design comparing HBOT with a sham therapy (Nilsson Remahl 2002). Twelve patients were defined as having episodic cluster headaches, while four were classified as having chronic cluster headache. Each headache was scored on a scale of 0 to 4 and the headache index (HI) was defined over a week as the sum of the number of headaches multiplied by severity on each occasion. (For example, a week with two headaches scoring 3 and one headache scoring 4 would have a headache index of (2 x 3) + (1 x 4) = 10.) Treatment was regarded as effective if the HI was reduced by 50% or more in the week following therapy compared to the week before therapy. Individual patient responses to each therapy were not reported. Overall, treatment was effective in five of 14 patients (36%) receiving HBOT versus six of 16 (38%) receiving sham. There was no advantage for sham or HBOT overall (RR for a 50% reduction in HI with HBOT 0.98, 95% CI 0.40 to 2.41, P = 0.97), nor when each diagnosis was analysed separately (episodic RR 0.80, 95% CI 0.31 to 2.06, P = 0.64, acute RR 3.00, 95% CI 0.16 to 57.4, P = 0.47).

NBOT for an acute attack

9. Proportion of patients with resolution of headache (Analysis 05.01)

Two cross-over trials reported the proportion of patients responding to the administration of NBOT versus control (Fogan 1985; Kudrow 1981). These trials enrolled a total of 69 patients, with Kudrow 1981 enrolling 50 of these. Individual patient responses were reported in Fogan 1985, but not Kudrow 1981. Fogan 1985 did not administer any specific therapy to the control group and found a significantly greater proportion of patients achieved relief from 15 minutes of NBOT compared to a sham therapy with air: 9 of 16 patients (56%) versus 1 of 14 (7%) reported complete relief or significant reduction in headache intensity (RR 7.88, 95% CI 1.13 to 54.66, P = 0.04). This analysis suggests an NNT of 2, 95% CI 1 to 5. Kudrow 1981 compared NBOT to the administration of ergotamine tartrate and did not find a statistically significant difference between groups for the proportion of patients reporting relief of at least 7 out of 10 attacks treated (41 of 50 patients with NBOT (82%) versus 35 of 50 patients with air (70%); RR 1.17, 95% CI 0.94 to 1.46, P = 0.16).

10. Degree of relief following therapy (Analysis 05.02)

One trial reported the pain intensity score following treatment with NBOT versus sham (air) and enrolled 19 patients in a cross-over design where 16 received NBOT and 14 sham (Fogan 1985). Relief was measured on a scale of 0 (no relief) to 3 (complete relief). There was no statistically significantly greater relief following NBOT (MD 1.16 in favour of NBOT, 95% CI -1.25 to 3.57, P = 0.35).

NBOT for prevention of attacks

No trials studied the use of NBOT for prevention of attacks.

Adverse effects

Di Sabato 1993 reported that no adverse reactions were noted in any patient. No other trial made any reference to adverse effects.

D I S C U S S I O N

Discussion

This review has included data from nine trials and we believe these represent all randomised controlled trials in this area, both published and unpublished. Five trials evaluated HBOT for the termination of an acute migraine attack (103 migraine patients), two trials evaluated HBOT for cluster headache and the remaining two evaluated NBOT for cluster headache (98 cluster patients). While we have made every effort to locate further unpublished data, it remains possible this review is subject to a positive publication bias, with generally favourable trials more likely to achieve publication.

Generally the methodological quality of the nine trials was assessed as moderate to low. Randomisation was poorly described in all the trials and none appear to have been based on sound sample size calculations for expected differences. One trial did not attempt to blind patients to therapy (Kudrow 1981). Other problems were the failure to clearly report on primary outcomes in many of the trials, poor reporting of means and standard deviations and the variable methods used to report similar outcomes. The results of this review must therefore be interpreted with great caution.

We found some evidence using pooled data from three trials that the administration of HBOT can substantially relieve an acute migraine attack (Fife 1992; Hill 1992; Myers 1995). This analysis suggests more than 70% of patients will obtain relief within about 40 minutes, with an NNT of 2 (95% CI 1 to 2) compared to a sham therapy. There was no evidence from a single trial that HBOT could prevent migraine episodes, reduce the incidence of nausea and vomiting or reduce the requirement for rescue medication (Eftedal 2004). Only one very small cross-over trial reported pain intensity following HBOT (Wilson 1998). While this trial reported a significant reduction in pain intensity in the HBOT group, but not in the NBOT group, there was no statistically significant reduction in intensity when directly comparing HBOT and NBOT.

Only a single trial investigated the use of HBOT for the termination of cluster headache, and although there was a trend to better outcomes with HBOT, this very small trial (13 patients) was underpowered to reliably demonstrate even a large difference between groups (Di Sabato 1993). Eighty-six per cent of the HBOT group obtained relief versus none of the sham group and all of these patients were reported as remaining free of headache for at least 48 hours. There was some indication that NBOT may also terminate acute cluster headache. Fogan 1985 reported that more than 50% of patients achieved relief from headache within 15 minutes compared to a sham therapy with an NNT of 2 (95% CI 1 to 5), while Kudrow 1981 demonstrated no benefit from NBOT when compared to the administration of ergotamine tartrate. Combining the NBOT arms of each of these studies suggests that a high proportion of cluster headaches will respond to NBOT (76%). There was no evidence from a single trial that HBOT can prevent cluster headaches (Nilsson Remahl 2002).

We had planned to perform subgroup analyses with respect to the dose of oxygen received (HBOT versus NBOT), session time and length of treatment course. This was only appropriate with respect to oxygen dose in the relief of migraine. In that analysis, HBOT appeared equally effective when compared to either air or NBOT.

Only one trial specifically mentioned adverse effects (Eftedal 2004), and this trial reported claustrophobia in two patients. Otherwise no complications of HBOT or NBOT were noted. HBOT is

regarded as a relatively benign intervention. There are few major adverse effects (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire). There are a number of more minor complications that may occur commonly. Visual disturbance, usually a reversible reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported - perhaps as many as 50% of those having a course of 30 treatments (Khan 2003). This is not likely to be a problem after the single exposures used in most of these trials. The second most common adverse effect associated with HBOT is barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result of compression. Aural barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the patient in order to inflate the middle ear through the eustachian tube on each side. Barotrauma is thus not a consequence of HBOT directly, but rather of the physical conditions required to administer it. Most episodes of barotrauma are mild, easily treated or recover spontaneously and do not require the therapy to be abandoned.

While HBOT administration may be an effective means for terminating migraine, there are problems of both cost and availability in applying this therapy in routine clinical practice. For safe administration, HBOT requires relatively sophisticated equipment, and for this reason is generally available only in specialist units whether free-standing or hospital based. Many migraineurs would not have easy access to such facilities. While the cost of hyperbaric therapy varies greatly around the world, one facility in Australia has recently estimated the cost of a single session of treatment for an uncomplicated patient at $A304.00 (Gomez-Castillo 2005). This is not likely to be cost-effective compared to established therapeutic options. HBOT may be a useful option for patients who are refractory to other medications; however, this subgroup of patients has not been selected for study and the efficacy of HBOT in these patients is not known.

NBOT has been widely recommended for the treatment of cluster headache since the description of Horton in 1956 (Horton 1956). It is generally accepted that about 70% of patients will receive significant relief, based on the small studies of Kudrow and Fogan included here, and clinical experience (Dodick 2000). While it is perhaps surprising that this recommendation is based on such little randomised evidence, the popularity of oxygen may rest on an effect approaching an 'all or nothing' phenomenon, as well as the low cost and high safety of short periods of oxygen breathing.

AUTHORS' CONCLUSIONS

Implications for practice

While there is some evidence that HBOT may effectively terminate migraine headache in a general population of migraineurs, the practical problems involved in delivery of therapy suggest that HBOT should be reserved for those migraineurs resistant to standard pharmacological therapies. There is, however, insufficient evidence of the efficacy of HBOT in this subgroup of patients to recommend HBOT as a routine therapy. HBOT cannot be recommended as a prophylactic therapy for migraine. There is no evidence to support the practice of administering NBOT to patients with acute migrainous headache.

There is insufficient evidence from randomised trials to establish the effects of HBOT on cluster headache as a treatment for an acute episode or as a prophylaxis against future clusters. Two small randomised trials suggest that the administration of NBOT to treat acute cluster headache is likely to be effective in more than 70% of cases, and given the safety and ease of administration of NBOT, the use of NBOT is likely to continue. There is no evidence to support the use of NBOT as a prophylactic measure.

Implications for research

Given the findings of this review, there is a case for further investigation of HBOT as a possible therapy for acute migraine and cluster headache resistant to standard therapies. There is also a case for confirming the apparent effectiveness of NBOT for cluster headache in a study with sufficient power to produce valid conclusions. Any further investigations would need to be carefully justified. The effect of differing oxygen dosage and of other therapies administered simultaneously is not known. Any future trials would need to consider in particular:

appropriate sample sizes with power to detect expected differences;

careful definition and selection of target patients;

appropriate range of oxygen doses per treatment session (pressure and time);

appropriate and carefully defined comparator therapy;

use of an effective sham therapy;

effective and explicit blinding of outcome assessors;

appropriate outcome measures including all those listed in this review;

careful elucidation of any adverse effects;

the cost-utility of the therapy;

appropriate and full reporting.

N O T E S

R E F E R E N C E S

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