Normobaric and hyperbaric oxygen therapy for migraine and cluster headache (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
The objective of the review will be 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 will be assessed using a number of clinically important outcomes, including pain, as detailed below.

BACKGROUND

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 US 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 US for reduced productivity due to migraine range from US$5.6 billion to US$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; such 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 will consider 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 are likely to be relevant in this review. Regardless of the particular pathology being treated, HBOT is associated with some risk of adverse events, including damage to the ears, sinuses, and lungs from the effects of pressure; temporary worsening of shortsightedness; claustrophobia; and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention.

OBJECTIVES

The objective of the review will be 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 will be assessed using a number of clinically important outcomes, including pain, as detailed below.

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 will be included.

Types of participants

Trials that include patients of any age and either sex with migraine (with or without aura) or cluster headache will be eligible. Headache classification will follow the guidelines of the International Headache Society (IHS 2004).

Types of intervention

We will consider interventions that include NBOT at any concentration above ambient air (whether administered in a health facility or at home) or HBOT administered in a compression chamber. We will include any suitable trials where NBOT is compared to HBOT, or where either is compared to a standard therapy or no treatment. The comparator groups may be somewhat diverse. We

will accept any standard treatment regimen designed to prevent or terminate headache or prevent recurrence, including combined therapies. We will compare treatment regimens including adjunctive NBOT or HBOT against similar regimens excluding NBOT or HBOT. Where regimens differ significantly between studies, we will state this clearly and discuss the implications.

Types of outcome measures

We anticipate that studies concerning relief of acute migraine or cluster headaches will report outcomes at several different time points post-intervention, but that short-term response would be of greatest clinical importance. We propose that the primary outcome assessments will be at 1 and 2 hours for migraine, and 15 and 30 minutes for cluster headache.

For outcomes relating to headache intensity, we will generally prefer those that measure headache relief or change in headache intensity, since these are more comparable among patients with different baseline scores. A recurrent migraine will be considered as any migraine that occurred after discharge from the emergency department, clinic, or physician's office. Data on cost-effectiveness, if available, will be discussed in the text of the review.

Primary effectiveness outcomes

Treatment of acute attack
1) Proportion of patients with pain-free response (complete resolution of headache pain). Assessment will be at 1 and 2 hours for migraine, 15 and 30 minutes for cluster headache.
2) Proportion of patients with headache pain reduction from moderate/severe to mild or none (timing as for 1, above).
3) Proportion of patients with sustained relief for 24 hours.

Prevention
1) Frequency of attacks.
2) Number of headache days.
3) Time to rescue medication.
4) Days lost to work.

Secondary effectiveness outcomes

Treatment of acute attack
1) Degree of headache relief or headache intensity.
2) Functional status or disability.
3) Pain-free response at 4 hours for migraine and 2 hours for cluster headache.
4) Proportion of patients requiring rescue medication.
5) Proportion of patients with sustained relief at 48 hours.
6) Proportion of patients with photophobia or phonophobia (migraine only).
7) Proportion of patients with nausea and/or vomiting (migraine only).

Prevention
1) Self-reported assessment of treatment success.
2) Frequency of attacks rated by patient as 'severe'.
3) Pain intensity scores.
4) Quality of life.
5) Functional status or disability.
6) Headache index (nature and calculation will be discussed).

Adverse events/safety
1) Adverse events 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).
2) Any other recorded adverse events will be reported and discussed.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pain, Palliative and Supportive Care Group methods used in reviews.

It is our intention to capture both published and unpublished trials. Relevant trials will be identified in the Cochrane Central Register of Controlled Trials (CENTRAL, latest issue), MEDLINE (1966 to present), EMBASE (1980 to present), CINAHL (1982 to present), and an additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine (Bennett 2004)).

The following search strategy will be 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 will make a systematic search for relevant controlled trials by other means available. We will contact experts in the field of headache and leading hyperbaric therapy centres; contact authors of relevant studies to request details of unpublished or ongoing investigations; hand search 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 present; and check the reference lists of the trials and reviews identified by the above strategies.

METHODS OF THE REVIEW

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

Data extraction
Data from the studies will be extracted independently by three authors (MB, AS, and CF) using standardised forms developed for this review. Primary study investigators will be contacted to provide information if missing data are encountered or if necessary data, such as adverse events, are not clearly stated. All differences will be resolved by discussion among the review authors.

Quality assessment
Study quality will be assessed using an adaptation of the method outlined in Schulz 1995. Results from the study quality will be presented in a descriptive manner. The following characteristics will be assessed:

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 will be analysed separately from those enrolling patients with cluster headache. We propose to use a fixed-effect model where there is no evidence of significant heterogeneity between studies, and a random-effects model when such heterogeneity is likely (DerSimonian 1986). Consideration will be given to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. Statistical heterogeneity will be assessed using the I^2 statistic, and consideration will be given to the appropriateness of pooling and meta-analysis. Heterogeneity will be explored and subgroup analyses will be performed if appropriate.

For proportions (dichotomous outcomes), relative risk (RR) will be used. Continuous data will be converted to the weighted mean difference (WMD) using the inverse variance method, and an overall WMD calculated. If trials use different scales or measures of the same outcome, we will calculate standardised mean difference (SMD). Publication bias will be tested using funnel plots or other corrective analytical methods, depending on the number of clinical trials included in the systematic review.

Subgroup analysis will be performed where appropriate by calculation of RR or WMD in each subgroup and examination of the 95% confidence intervals. Non-overlap in intervals will be taken to indicate a statistically significant difference between subgroups.

All analyses will be made on an intention-to-treat basis where possible, and where not possible this will be clearly stated.

We intend to perform sensitivity analyses for missing data and study quality. In the case of missing data, we will employ sensitivity analysis using different approaches to imputing missing data. The best-case scenario will assume that none of the originally enrolled patients missing from the primary analysis in the treatment group had the negative outcome of interest whilst all those missing from the control group did. The worst-case scenario will be the reverse. If appropriate, we will also conduct sensitivity analysis by study quality based on the presence or absence of a reliable random allocation method, concealment of allocation, and blinding of participants or outcome assessors.

Where appropriate data exist, we will consider subgroup analyses based on:

- 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).

POTENTIAL CONFLICT OF INTEREST

None known.

SOURCES OF SUPPORT

External sources of support

- International Headache Society (for administrative costs associated with editorial review and peer review) TRANSNATIONAL

Internal sources of support

- No sources of support supplied

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