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Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache (Review)

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[Intervention Review]

Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache

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ABSTRACT

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. This is an updated version of the original Cochrane review published in Issue 3, 2008 under the title 'Normobaric and hyperbaric oxygen for migraine and cluster headache'.

Objectives

To examine the efficacy and safety of normobaric oxygen therapy (NBOT) and hyperbaric oxygen therapy (HBOT) in the treatment and prevention of migraine and cluster headache.

Search methods

We updated searches of the following databases up to 15 June 2015: CENTRAL (the Cochrane Library), MEDLINE, EMBASE, and CINAHL. For the original review we searched the following databases up to May 2008: CENTRAL, MEDLINE, EMBASE, CINAHL, DORCTIHM, and reference lists from relevant articles. We handsearched relevant journals and contacted researchers to identify trials.

Selection criteria

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

Data collection and analysis

Three review authors independently extracted data and assessed the quality of the evidence using the GRADE approach.

Main results

In this update, we included 11 trials with 209 participants. Five trials (103 participants) compared HBOT versus sham therapy for acute migraine, three trials compared NBOT to sham therapy or ergotamine tartrate for cluster headache (145 participants), two trials evaluated HBOT for cluster headache (29 participants), and one trial (56 participants) compared NBOT to sham for a mixed group of headache. The risk of bias varied considerably across these trials but in general trial quality was poor to moderate. One trial may not have been

truly randomised and two included studies were reported as abstracts only. Seven trials did not indicate allocation concealment or randomisation method. Notably, 10 of the 11 trials used a sham comparator therapy and masked the outcome assessor to allocation.

We pooled data from three trials, which suggested that HBOT was effective in relieving migraine headaches compared to sham therapy (risk ratio (RR) 6.21, 95% CI 2.41 to 16.00; 58 participants, three trials). The quality of evidence was low, having been downgraded for small crossover studies with incomplete reporting. There was no evidence that HBOT could prevent migraine episodes, reduce the incidence of nausea and vomiting, or reduce the requirement for rescue medication. There was no evidence that HBOT was effective for the termination of cluster headache (RR 11.38, 95% CI 0.77 to 167.85; P = 0.08) (one trial), but this trial had low power.

NBOT was effective in terminating cluster headache compared to sham in a single small study (RR 7.88, 95% CI 1.13 to 54.66), but not superior to ergotamine administration in another small trial (RR 1.17, 95% CI 0.94 to 1.46; P = 0.16). A third trial reported a statistically significant difference in the proportion of attacks successfully treated with oxygen (117 of 150 attacks were successfully treated with NBOT (78%) versus 30 of 148 attacks treated with NBOT (20%)). The proportion of responders was consistent across these three trials, and suggested more than 75% of headaches were likely to respond to NBOT.

No serious adverse events during HBOT or NBOT were reported.

Authors' conclusions

Since the last version of this review, two new included studies have provided additional information to change the conclusions. There was some evidence that HBOT was effective for the termination of acute migraine in an unselected population, and some 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.

PLAIN LANGUAGE SUMMARY

Normal pressure oxygen therapy and hyperbaric oxygen therapy for migraine and cluster headaches

Background

Migraine and cluster headaches are severe and disabling. Hyperbaric oxygen therapy (HBOT, that is the breathing of pure oxygen at pressures greater than one atmosphere in a pressurised chamber) and normal pressure oxygen therapy (NBOT) can be delivered via a mask at home or in a clinic. These treatments may help to end acute attacks and prevent future attacks.

Results

We originally searched the literature widely in May 2008, and most recently in June 2015. We looked for high quality trials that would help define whether or not there was good evidence for or against the use of oxygen for migraine or cluster headache. We included 11 trials in this review.

Quality of the evidence

We found some low quality evidence to suggest that HBOT relieves pain with acute migraine headaches and possibly cluster headaches, and that NBOT may relieve pain with cluster headache. We found no evidence that either treatment can prevent future attacks. Many migraines can be treated simply with appropriate drug therapy, so further research is needed to help choose the most appropriate patients (if any) to receive HBOT.

Summary of findings for the main comparison. Hyperbaric oxygen therapy for acute migraine

Hyperbaric oxygen therapy for the relief of acute migraine

Patient or population: Acute migraine
Setting: Hospital care
Intervention: HBOT (2.0 to 2.4 ATA for 40 to 45 minutes)
Comparison: Sham therapy (air at pressure or 100% oxygen at 1 ATA)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with sham therapy	Risk with HBOT				
Chance of obtaining substantial headache relief (Relief). Assessed with: Patient self-assessment	Study population		RR 6.21 (2.41 to 16.00)	58 (3 RCTs)	Low[1]	We included 3 small RCTs but all showed large effect size with HBOT compared to either air or 100% oxygen sham.
	111 per 1000	663 per 1000 (162 to 1000)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **ATA:** atmospheres absolute; **HBOT:** hyperbaric oxygen therapy.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]The evidence has been downgraded from moderate to low due to two of these trials being incompletely reported crossover trials reported only in abstract. [Two of the three included studies were planned as crossover trials. In those two, many patients obtained relief during the first treatment period and were not crossed to the second period. For Hill 1992, where all patients are not clearly accounted for we have included the results only from the first treatment period.]

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 3, 2008 under the title 'Normobaric and hyperbaric oxygen for migraine and cluster headache' (Bennett 2008).

Description of the condition

Migraine and cluster headache are disabling health problems among adults and migraine has been identified as a leading contributor to years lived with disability in an analysis for the Global Burden of Disease Study 2010 (Vos 2013). Both types of headache are frequently severe and associated with features other than pain (IHS 2014). While the diagnosis and classification of headaches can be difficult and 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 can be bilateral and are often described as throbbing). Migraine may be preceded by an aura—most often a visual disturbance—in some people.

Severe headache is common; in a review of studies on the prevalence of severe headache, Smitherman 2013 suggests about 16% of the adult population in the USA will complain of at least one severe headache over a three-month period, most of which are labelled as 'migraine' or 'probable migraine'. Surveys from the USA and elsewhere suggest that 6% to 7% of men and 15% to 18% of women experience migraine headaches, while about 0.1 to 0.2% of the population suffer with cluster headache (Mathew 2001; Nesbitt 2012; Russell 2004). First-degree relatives of those with cluster headaches are five to 18 times more likely to have such headaches than individuals in the general population. The mechanisms involved in both types of headache remain incompletely understood and are active areas of research (Nesbitt 2012). Migraine is generally seen as a vascular headache that seems to result from a mixture of environmental and genetic factors (Piane 2007), while cluster headache is classified among the trigeminal autonomic cephalalgias and probably involves the hypothalamus (Nesbitt 2012). Migraine results in significant disability, work loss, and costs to the individual (Burton 2002; Hu 1999; Munakata 2009; Stokes 2011); estimated aggregate indirect costs to employers in the USA for reduced productivity due to migraine range from USD 5.6 billion to USD 17.2 billion annually (Munakata 2009; Osterhaus 1992). The social and economic impact of cluster headache is less clear, but data from Germany suggest time lost to work and healthcare costs are substantial (Gaul 2011).

The traditional view has been that migraine is primarily a vascular event. This view focuses on explaining the pain involved, but more recently migraine is seen as a sensory processing disturbance, primarily of the sub-cortical aminergic sensory modulatory systems. Such a brain-centered explanation helps to explain the symptomatology of migraine beyond the headache and has implications for treatment (Goadsby 2012).

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 or intensity of attacks, or both, 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) (Law 2013a; Law 2013b; Géraud 2004). Epidemiological studies suggest that 80% of all analgesic prescriptions for migraine are triptans, mainly sumatriptan (Smitherman 2013). These drugs are effective in most cases, although headache may 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 (HBOT).

Pharmacological and non-pharmacological therapies used for the prevention of migraine include various beta-blockers, amitriptyline, topiramate; sodium valproate, gabapentin, relaxation, biofeedback, feverfew, and cognitive-behavioural therapy (Géraud 2004; Linde 2013a; Linde 2013b; Wider 2015). 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 HBOT.

The standard acute treatment for cluster headache is sumatriptan and inhalation of 100% oxygen, while steroids are commonly used both as treatment and prophylaxis (Law 2013c). Secondary agents include methysergide, lithium, and topiramate. A number of agents have been used for prophylaxis, including verapamil, ergotamine, lithium, and steroids (May 2006). 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 2006).

Description of the intervention

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 (HBOT). NBOT is delivered by a mask connected to an oxygen cylinder and may be administered in a hospital, general practice, or home setting. HBOT requires the patient to be subjected to a higher than atmospheric pressure in a specialised vessel designed for the purpose. For the treatment of headache, each session of therapy

typically involves exposure to pressure for 30 minutes to one hour at between 2.0 and 2.4 atmospheres absolute (ATA, equivalent to 101.3 kPa of 760 mmHg), although some workers cease treatment on the resolution of headache. Treatment therefore takes place at 2.0 to 2.4 times the normal air pressure at sea level (1 ATA). While at pressure, the patient breathes 100% oxygen via a hood tent or a tight-fitting mask designed for the purpose. 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.

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 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.

How the intervention might work

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). 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). 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; Sümen 2001).

Why it is important to do this review

While the use of NBOT is relatively common for cluster headache, the evidence for this practice is less well known. For this reason we felt an assessment of the strength of the evidence was appropriate. NBOT is rarely used for the treatment of migraine. 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.

OBJECTIVES

To examine the efficacy and safety of normobaric oxygen therapy (NBOT) and hyperbaric oxygen therapy (HBOT) in the treatment and prevention of migraine and cluster headache.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) that evaluate the effectiveness of NBOT or HBOT for the prevention or treatment of migraine or cluster headache were included. We accepted any comparator including drug or sham interventions.

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 2014).

Types of interventions

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 measured headache relief or change in headache intensity, since these are more comparable among participants with different baseline scores. The outcomes we considered eligible for inclusion in this review were:

Primary outcomes

Treatment of acute attack

1. Proportion of participant with pain-free response (complete resolution of headache pain). Assessment times preferred were one and two hours for migraine, and 15 and 30 minutes for cluster headache.
2. Proportion of participants with headache pain reduction from moderate/severe to mild or none (timing as for 1, above).
3. Proportion of participants with sustained relief for 24 hours.

Prevention

1. Frequency of attacks.

2. Number of days with headache in the week after therapy.
3. Days lost to work.

Secondary outcomes

Treatment of acute attack

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

Prevention

1. Self-reported assessment of treatment success.
2. Frequency of attacks rated by participant as 'severe'.
3. Quality of life.
4. Functional status or disability.
5. Headache index (nature and calculation discussed).
6. Proportion of participants requiring rescue medication.
7. Proportion of participants with nausea and/or vomiting, or both (migraine only).

Adverse events/safety

1. Adverse events during HBOT, such as the proportion of participants 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 were reported and discussed.

Search methods for identification of studies

We intended to capture both published and unpublished trials. We did not impose language restrictions.

Electronic searches

We searched the following databases up to 15 June 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library), Issue 6 2015;
- MEDLINE & MEDLINE in Process (OVID) (1966 to 15 June 2015);
- EMBASE (OVID) (1980 to 15 June 2015);
- CINAHL (EBSCO) (1982 to June 2015);
- An additional database developed in our hyperbaric facility (the Database of Randomised Trials in Hyperbaric Medicine (Bennett 2004) was searched for the original review in 2005 and for subsequent updates).

Searching other resources

In addition we made a systematic search for relevant RCTs by other means available. For the initial review in 2005 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.

Both Bennett 2005 and all subsequent updates, we handsearched relevant hyperbaric textbooks (latest editions for this update: Jain 2009; Kindwall 2008; Mathieu 2006), relevant journals up to 15 June 2015 (*Undersea and Hyperbaric Medicine*; *Hyperbaric Medicine Review*; *Diving and 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 15 June 2015. We also searched the USA NIH database of registered trials at https://clinicaltrials.gov/. Finally, we checked the reference lists of the trials and reviews identified by the above strategies.

Data collection and analysis

We analysed data from trials enrolling patients with migraine separately from those enrolling patients with cluster headache.

Selection of studies

Two review authors (MB and JW) scanned the records retrieved by the initial search and the updated searches and excluded obviously irrelevant studies by title. Subsequently, MB and AS read the abstracts of the citations remaining in order to identify trials that may have met the inclusion criteria. We retrieved the full-text articles and these were assessed by three review authors (MB, AS, and CF) independently and a decision made on inclusion/exclusion. We resolved any differences of opinion by discussion among the review authors.

Data extraction and management

Two review authors (MB and AS) independently extracted data from the included trials using standardised forms we developed for this review. We collected data on trial methodology, numbers of participants enrolled, number reaching analysis and all outcomes reported. We contacted primary study investigators to provide further information when we encountered missing data. We resolved any differences in opinion by discussion among the review authors. All included trials were available in English.

Assessment of risk of bias in included studies

Two review authors (MB and SW) independently undertook assessment of the risk of bias of the included trials with the following taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009):

- Sequence generation;
- Allocation concealment;
- Blinding;
- Incomplete outcome data;
- Selective outcome reporting; and
- Other sources of bias.

We used the Cochrane 'Risk of bias' assessment tool in RevMan 5.3 (RevMan 2014,) in which each of these domains is described as reported in the trial and then a judgement assigned about the adequacy of each entry: either 'low', 'high', or 'unclear' (or unknown) risk of bias.

Measures of treatment effect

For proportions (dichotomous outcomes), we used relative risk (RR).

We converted continuous data to the mean difference (MD) using the inverse variance method, and calculated an overall MD.

Unit of analysis issues

We intended to include cluster randomised trials but did not find any.

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-participant variability in cross-over studies.

Dealing with missing data

All analyses were made on an intention-to-treat (ITT) basis where possible. 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.

Assessment of heterogeneity

We assessed statistical heterogeneity using the I^2 statistic, and gave consideration to the appropriateness of pooling and meta-analysis by interpretation of both statistical and clinical heterogeneity.

Assessment of reporting biases

If 10 or more trials contributed data to a meta-analysis, we intended to investigate the possibility of publication bias through the use of funnel plots, however this was inappropriate.

Subgroup analysis and investigation of heterogeneity

Tests of interaction were calculated to determine if the results for subgroups were significantly different. 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).

We performed subgroup analyses 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.

We considered subgroup analyses based on the following factors, but such analyses were inappropriate:

- 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 (< five sessions versus ≥ five sessions);
- Migraine with aura versus without aura;
- Comparator treatment (where oxygen has been compared to different alternative treatments).

We assumed statistical heterogeneity to be significant if the I^2 statistic 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.

Sensitivity analysis

We performed sensitivity analyses for missing data where appropriate, but sensitivity analysis for study quality was inappropriate.

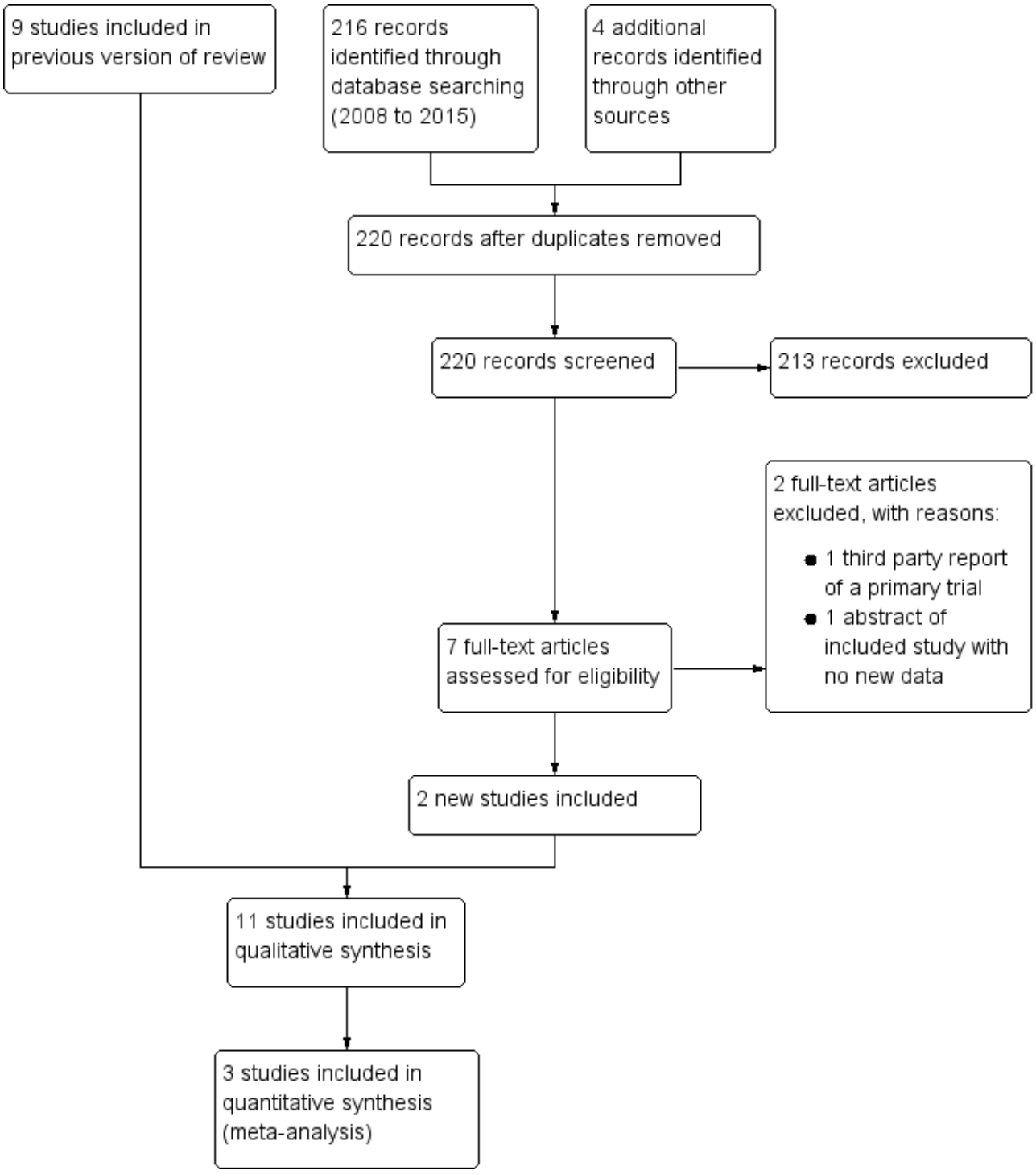
RESULTS

Description of studies

Results of the search

In the previous version of this review, nine trials met the inclusion criteria (Bennett 2008). For this review update we identified seven potential articles for inclusion after searching the literature up to 15 June 2015 (Figure 1). Two of these articles were reviews of the treatment of cluster or migraine headache with no new data and a third was a third party report on an included trial. We excluded these three articles (see 'Characteristics of excluded studies'). Of the remaining three reports, two dealt with a single trial (Ozkurt 2012 (an abstract) and Ozkurt 2012 (full report)). Therefore two new trials met the inclusion criteria (Cohen 2009; Ozkurt 2012) and we pooled data where possible with the nine trials included in Bennett 2008 (Di Sabato 1993; Eftedal 2004; Fife 1992; Fogan 1985; Hill 1992; Kudrow 1981; Myers 1995; Nilsson Remahl 2002; Wilson 1998). Cohen 2009 was a crossover trial and four cluster headache attacks were treated in each individual. The trial authors reported the proportion of attacks that responded to normobaric oxygen rather than the proportion of participants. We requested further information but at this time this report is included in qualitative analysis of this review only.

Figure 1. Study flow diagram.



Included studies

We included 11 trials in the quantitative analysis. Included trials were published between 1981 (Kudrow 1981) and 2012 (Ozkurt 2012), and we are unaware of any ongoing RCTs in the area. One trial, Ozkurt 2012, enrolled all types of headache and evaluated one atmosphere oxygen breathing (NBOT). We included the results of those with migraine (56 participants) and cluster headache (two participants) in the relevant analyses in this review. Six trials enrolled a total of 159 patients experiencing acute migraine; all of which, except Ozkurt 2012, employed HBOT in one arm (Eftedal 2004; Fife 1992; Hill 1992; Myers 1995; Wilson 1998). Six trials enrolled a total of 209 patients with cluster headache. Four of these evaluated NBOT (Cohen 2009; Fogan 1985; Kudrow 1981; Ozkurt 2012), and the other two administered HBOT (Di Sabato 1993; Nilsson Remahl 2002). Several studies utilized a cross-over design (Cohen 2009; Fogan 1985; Hill 1992; Kudrow 1981; Nilsson Remahl 2002; Wilson 1998). In total, these 11 trials included

363 participants. We have listed details of the methodology and interventions in the 'Characteristics of included studies' table.

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 with HBOT, 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 three consecutive days (Eftedal 2004) to a maximum of 60 minutes (Wilson 1998). All migraine trials except Eftedal 2004 gave a single exposure only. The single trial using NBOT for migraine employed 15 litres of 100% oxygen versus air for 15 minutes (Ozkurt 2012). The three cluster headache trials investigating NBOT administered oxygen for 15 minutes. The two trials 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 participants 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 2.0 ATA (Hill 1992; Eftedal 2004), 10% oxygen at 2.0 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 participant 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 and Ozkurt 2012 used the criteria of the International Headache Society (IHS 1988) and Hill 1992 used the criteria of the Ad Hoc Committee of the National Institute of Neurological Diseases and Blindness (AHC 1962). Of the cluster headache trials, two RCTs used the AHC 1962 criteria (Di Sabato 1993; Fogan 1985), three RCTs used the criteria of the IHS 1988 (Cohen 2009; Nilsson Remahl 2002; Ozkurt 2012), 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. We have given details of both inclusion and exclusion criteria, where recorded, 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 which used sublingual ergotamine tartrate in the control group, and Myers 1995 which used NBOT in the control group. Most trials did not follow participants after the end of the therapy period with the exception of Nilsson Remahl 2002 (one week), and both Di Sabato 1993 and Eftedal 2004 (two 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), length of stay in the emergency department (Ozkurt 2012); and pericranial tenderness with algometry (Wilson 1998).

Excluded studies

We excluded 18 reports following examination of the full report. We have listed the details of these reports in the Characteristics of excluded studies table. Ten were reviews with no new data, four were non-random comparative studies, three were case series, and one was a third party report of an included study.

Risk of bias in included studies

See the 'Characteristics of included studies' table for further details. These trials varied in methodological quality and only eight were full reports of completed trials and available in a peer-reviewed publication. Two of the included reports were presented as abstracts only (Fife 1992; Hill 1992). We have presented the 'Risk of bias' assessments for each included RCT in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: each 'Risk of bias' item presented as percentages across all included studies.

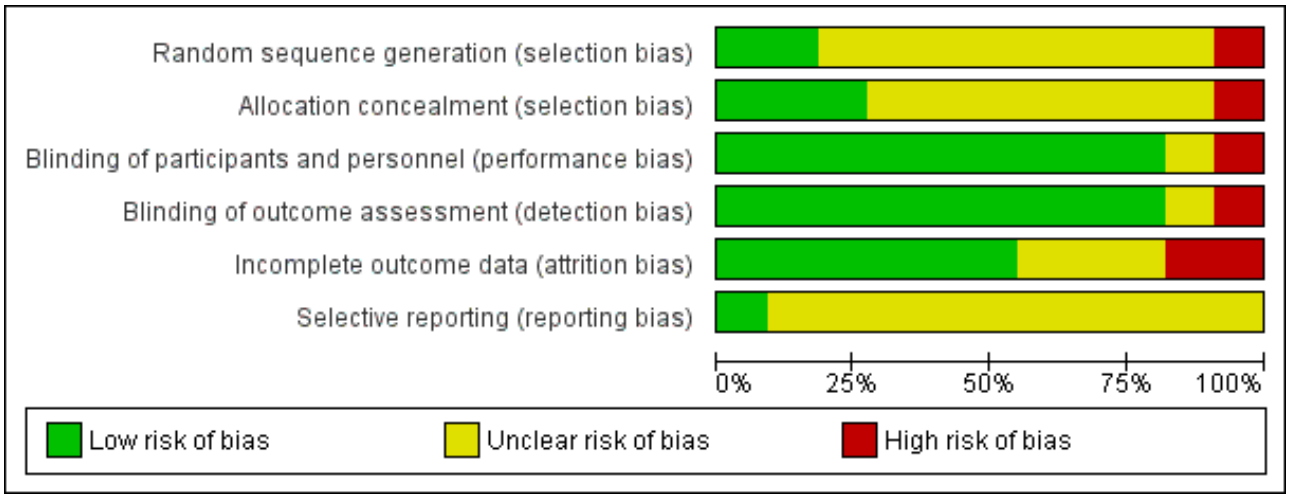
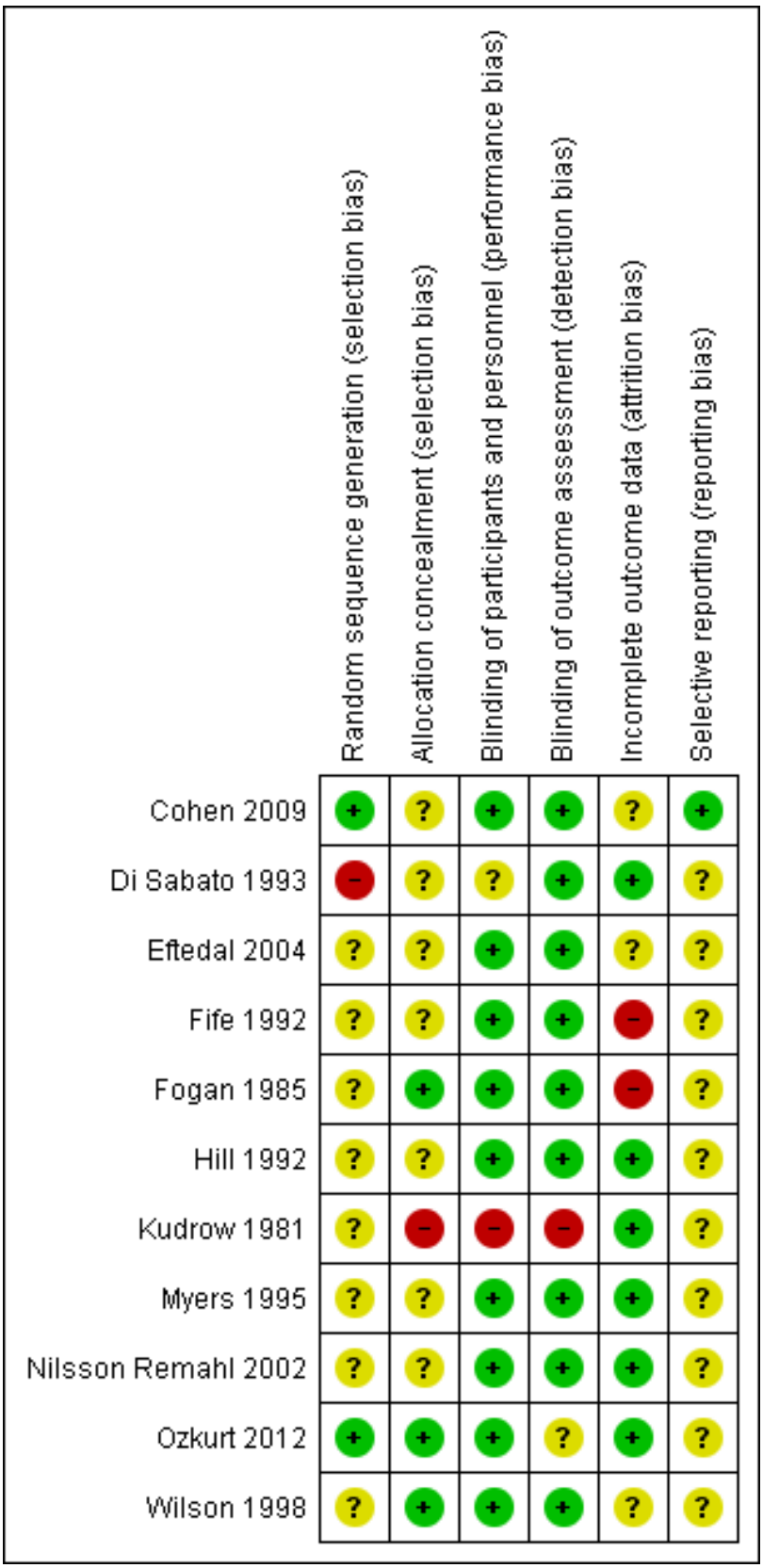


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Patient baseline characteristics

Most included trials poorly described patient baseline diagnosis.

Migraine

All trials used published diagnostic criteria (either 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 two to eight attacks per month for the preceding three 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 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 four further weeks, Di Sabato 1993 enrolled only episodic cluster patients in the 'florid phase' from day 10 to 15 of their cluster and Cohen 2009 enrolled both episodic and chronic cluster patients, while Kudrow 1981 and Fogan 1985 did not report further baseline details.

Allocation

Allocation concealment was inadequate in one RCT (Di Sabato 1993), clearly indicated in three RCTs (Fogan 1985; Ozkurt 2012; Wilson 1998), and unclear in the remaining studies. Cohen 2009 and Ozkurt 2012 described the randomisation procedure, 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 randomised. Sensitivity analyses with and without this trial were considered during analysis. There is not a clear indication for any of the included trials that the trial authors 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 five-minute period breathing air at 2.0 ATA. As 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. In general, the cross-over trials were poorly reported and we could only extract data for Fogan 1985 on the response of each individual to both study arms.

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 participants, investigators, and assessors. All trials provided a sham therapy except Kudrow 1981, who provided a sublingual preparation as the comparator therapy.

Incomplete outcome data

One participant was lost to final follow-up in the control group of Eftedal 2004. Six participants 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 participant withdrew for unknown reasons. Some participants failed to cross for the second arm of therapy in five included trials (Cohen 2009; Fife 1992; Fogan 1985; Hill 1992; Kudrow 1981) and this accounts for the uneven numbers of participants in the different therapy arms of those trials. Cohen enrolled 109 participants but 33 dropped out (17 came out of the headache, nine were lost to follow-up, six withdrew from the study, and one died). None of the remaining studies suffered any losses to follow-up, or reported any violation of allocated treatment.

Most trials delivered the intended therapy and analysed by ITT. No data were generated or analysed where participants 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 ITT analysis for the missing participant in the control group.

Selective reporting

There was little evidence of any selective reporting of pre-determined outcomes, mainly because there was no evidence of trial registration for all included trials except Cohen 2009. We included this trial in the qualitative review only. The trial authors indicated an intention to report the proportion of participants pain free after 15 minutes of treatment comparing oxygen and air, but actually reported the proportion of attacks treated that had responded.

Other potential sources of bias

There was no indication of other potential sources of bias in the included trials.

Effects of interventions

See: **Summary of findings for the main comparison** Hyperbaric oxygen therapy for acute migraine

Migraine

HBOT for an acute attack

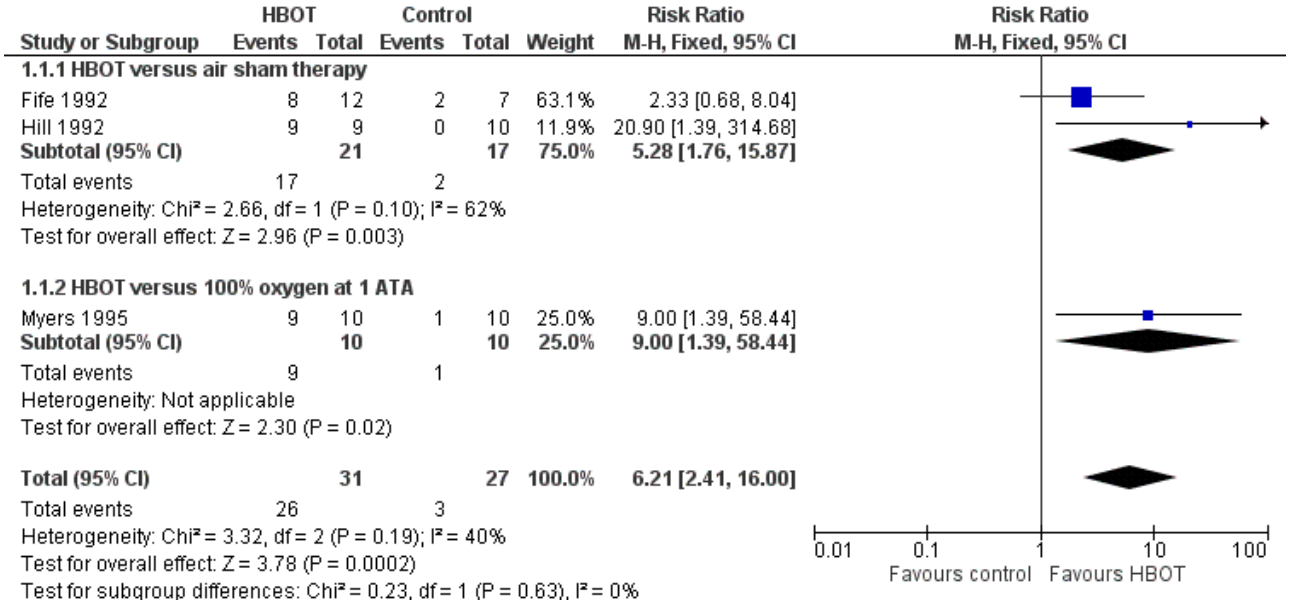
Primary outcomes

1. Proportion of participant with pain-free response (complete resolution of headache pain)

No trials specifically reported on complete resolution of headache. Three trials reported the proportion of participants with resolution or significant relief of migraine with 40 to 45 minutes of HBOT (Fife 1992; Hill 1992; Myers 1995). These studies involved a total of 58 participants receiving 56 occasions of therapy (29 HBOT versus 27 sham). Two were of cross-over design, and in these, following initial group assignment, cross-over was undertaken at five minutes (Hill 1992) and 30 minutes (Fife 1992). Individual participant responses to each arm were not reported in Hill 1992, nor were any cross-over effects reported in either trial. Our detailed approach to data extraction is indicated in Appendix 2. There was a statistically significant increase in the proportion of participants with substantial relief of headache with HBOT (RR 6.21, 95% CI 2.41 to 16.00; I^2 statistic = 40%; Analysis 1.1; Figure 4). We investigated the evidence of moderate heterogeneity by subgroup analysis by comparator therapy. 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 0.72 between sham and HBOT suggests the number needed to treat for an additional beneficial outcome

(NNTB) to achieve one extra case of relieved headache is two (95% CI 1 to 2). Myers 1995 compared HBOT with NBOT (administered as an HBOT sham). With subgroup analysis by comparator therapy on the grounds of clinical heterogeneity, Myers 1995 reported a similar magnitude of effect to the other two trials, and did not account for the heterogeneity between trials. There were no data reported for longer term outcomes.

Figure 4. Forest plot of comparison: 1 HBOT versus control for acute migraine attack, outcome: 1.1 Substantial acute relief of headache.



The evidence for this outcome was of low quality (see Summary of findings for the main comparison).

2. Proportion of participants with headache pain reduction from moderate/severe to mild or none

No trials reported this outcome.

3. Proportion of participants with sustained relief for 24 hours

No trials reported this outcome.

Secondary outcomes

1. Degree of headache relief or headache intensity

Only Wilson 1998 reported on this outcome (immediately following therapy), enrolling eight participants in a cross-over study of NBOT versus HBOT. The cross-over was made when the individual participant presented for treatment of a second headache. Pain intensity on a visual analogue scale of 0 (no pain) to 10 (worst pain) was significantly lower following HBOT (7.9 Standard Deviation (SD) 0.64 pre-treatment versus 3.5 SD 1.34 after treatment, P = 0.03), but not when receiving NBOT (6.5 SD 0.87 pre-treatment versus 6.3 SD 1.75, P = 0.99 after treatment).

2. Functional status or disability

No trials reported this outcome.

3. Pain-free response at four hours for migraine and two hours for cluster headache

No trials reported this outcome.

4. Proportion of participants requiring rescue medication

No trials reported this outcome.

5. Proportion of participants with sustained relief for 48 hours

No trials reported this outcome.

6. Proportion of participants with photophobia or phonophobia

No trials reported this outcome.

7. Proportion of participants with nausea and/or vomiting, after therapy

No trials reported this outcome.

HBOT for prevention of attacks

Primary outcome

1. Frequency of attacks

No trials reported this outcome.

2. Number of days with headache in the week after therapy

Only Eftedal 2004 reported on this outcome, enrolling 40 participants (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 SD 1.63 versus sham 2.87 SD 2.07), nor during the fourth week (HBOT 2.52 SD 1.78 versus sham 2.27 SD 1.94). P values were not given in the report.

3. Days lost to work

No trials reported this outcome.

Secondary outcomes

1. Self-reported assessment of success

No trials reported this outcome.

2. Frequency of attacks rated by participant as 'severe'

No trials reported this outcome.

3. Quality of life

No trials reported this outcome.

4. Functional status or disability

No trials reported this outcome.

5. Headache index

No trials reported this outcome.

6. Proportion of participants requiring rescue medication

Only Eftedal 2004 reported on this outcome, enrolling 40 participants (20 HBOT, 20 sham). There was no statistically significant reduction in the proportion of participants requiring rescue medication after being given HBO as a prophylaxis. Most participants who were followed-up required therapy at week 1, 4, and 8 after the intervention (e.g. at week 1: 18 of 19 for the HBOT group versus 12 of 15 for the sham therapy required some rescue medication; no P -values were given; RR 0.84, 95% CI 0.64 to 1.11; P = 0.23). The best case scenario for the allocation of withdrawals did not alter this finding (RR 0.94, 95% CI 0.75 to 1.19; P = 0.63); however, on a worst case scenario the risk of requiring rescue medication was significantly lower with sham (RR 0.63, 95% CI 0.44 to 0.92; P = 0.02).

7. Proportion of participants with nausea and vomiting after therapy

Only Eftedal 2004 reported on this outcome, enrolling 40 participants (20 HBOT, 20 sham). There was no statistically significant reduction in the proportion of participants suffering nausea with or without vomiting after being given HBO as a prophylaxis. Roughly half of the participants reported nausea with or without vomiting at week 1, 4, and 8 after the intervention (e.g. at week 1: 9 of 19 for the HBOT group versus 9 of 15 for the sham therapy. No P values were given).

NBOT for an acute attack

Primary outcomes

1. Proportion of participants with pain-free response (complete resolution of headache pain)

No trials reported this outcome

2. Proportion of participants with headache pain reduction from moderate/severe to mild or none

No trials reported this outcome

3. Proportion of participants with sustained relief for 24 hours

No trials reported this outcome

Secondary outcomes

1. Degree of headache relief or headache intensity

Only Ozkurt 2012 reported on this outcome, enrolling 56 participants (27 HBOT, 29 sham). There was a significant reduction in the intensity of pain recorded on a VAS (0 - 100) at one hour after administration of 15 minutes of 100% oxygen at 15 litres per minute versus air on the same schedule. Mean pain intensity score in the sham group was 30 (SD 14) versus 17 (SD 14) in the NBOT group, 13 points lower in the NBOT group, 95% CI -5.5 to -20.5).

(Myers 1995 used NBOT (administered as an HBOT sham) as the comparator intervention for a trial of HBOT; see Analysis 1.1, above.)

2. Functional status or disability

No trials reported this outcome.

3. Pain-free response at four hours for migraine and two hours for cluster headache

No trials reported this outcome.

4. Proportion of participants requiring rescue medication

No trials reported this outcome.

5. Proportion of participants with sustained relief for 48 hours

No trials reported this outcome.

6. Proportion of participants with photophobia or phonophobia

No trials reported this outcome.

7. Proportion of participants with nausea and/or vomiting, after therapy

No trials reported this outcome.

NBOT for prevention of attacks

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

Adverse events

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

Cluster headache

HBOT for an acute attack

Primary outcomes

1. Proportion of participant with pain-free response (complete resolution of headache pain)

Only one small trial reported on the use of HBOT to relieve cluster headache (Di Sabato 1993). This trial enrolled 13 participants and reported the proportion achieving complete resolution within 20 minutes (six of seven (86%) with HBOT versus none of six with sham). No measure of statistical significance was given in the report.

2. Proportion of participants with headache pain reduction from moderate/severe to mild or none

No trials reported this outcome

3. Proportion of participants with sustained relief for 24 hours

No trials reported this outcome

Secondary outcomes

1. Degree of headache relief or headache intensity

No trial reported this outcome.

2. Functional status or disability.

No trials reported this outcome.

3. Pain-free response at four hours for migraine and two hours for cluster headache

No trials reported this outcome.

4. Proportion of participants requiring rescue medication

No trials reported this outcome.

5. Proportion of participants with sustained relief for 48 hours

Only one small trial reported on this outcome following HBOT (Di Sabato 1993). This trial enrolled 13 participants and reported the proportion achieving sustained resolution for at least 48 hours (six of seven (86%) with HBOT versus none of six with sham). No measure of statistical significance was given in the report.

HBOT for prevention of attacks

Primary outcomes

1. Frequency of attacks

No trials reported this outcome.

2. Number of days with headache in the week after therapy

No trials reported this outcome.

3. Days lost to work.

No trials reported this outcome.

Secondary outcomes

1. Self-reported assessment of treatment success

No trials reported this outcome.

2. Frequency of attacks rated by participant as 'severe'

No trials reported this outcome.

3. Quality of life

No trials reported this outcome.

4. Functional status or disability

No trials reported this outcome.

5. Headache index

One trial reported on this outcome and enrolled 16 participants in a cross-over design comparing HBOT with a sham therapy (Nilsson Remahl 2002). Twelve participants 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 participant responses to each therapy were not reported. Overall, treatment was effective in five of 14 participants (36%) receiving HBOT versus six of 16 (38%) receiving sham. There was no advantage for sham or HBOT.

6. Proportion of participants requiring rescue medication

No trials reported this outcome.

NBOT for an acute attack

Primary outcomes

1. Proportion of participant with pain-free response (complete resolution of headache pain)

Three cross-over trials reported the proportion of participants responding to the administration of NBOT versus control (Cohen 2009; Fogan 1985; Kudrow 1981). Kudrow 1981 used a control of subcutaneous ergotamine tartrate and defined successful response to treatment as "complete or almost complete reduction of pain in seven of ten attacks, within 15 minutes", while Fogan 1985 and Cohen 2009 compared NBOT to air. Fogan 1985 reported the mean relief score (0 = no relief to 3 = complete relief) obtained from between one and 10 episodes of treatment with each of NBOT and air. Cohen 2009 reported the number of attacks that were successfully treated and enrolled 109 participants of whom 76 were analysed for a total of 298 cluster episodes. These trials together enrolled a total of 178 participants, with Kudrow 1981 enrolling 50 and Fogan 1985 enrolling 19. Fogan 1985 reported individual participant responses and an overall mean response, while Kudrow 1981 reported the proportion of participants and Cohen 2009 the proportion of attacks responding to treatment. Given the clear clinical and reporting heterogeneity we did not pool the results.

The two trials using air as the comparator reported a better outcome following NBOT versus control. Cohen 2009 reported a statistically significant difference in the proportion of attacks successfully treated with oxygen. Of 150 attacks, 117 were successfully treated with NBOT (78%, 95% CI 71% to 85%) versus 30 of 148 attacks treated with NBOT (20%, 95% CI 17% to 24%). Fogan 1985 reported a significantly increased chance of benefit from NBOT. Three participants did not have any headaches treated with NBOT, while five different individuals did not have any headaches treated with air. Nine of 16 participants (56%) versus one of 14 (7%) reported complete relief or significant reduction in headache intensity (defined as a mean relief score of ≥ 2, that is, where the mean score was at least rated as 'significant relief') and this result suggests an NNT of 2 (95% CI 1 to 5) to obtain this outcome with NBOT. Kudrow 1981 reported a successful response in 41 of 50 participants with NBOT (82%) versus 35 of 50 participants with ergotamine (70%), but this difference was not statistically significant.

2. Proportion of participants with headache pain reduction from moderate/severe to mild or none

No trials reported this outcome.

3. Proportion of participants with sustained relief for 24 hours

No trials reported this outcome.

Secondary outcomes

1. Degree of headache relief or headache intensity

One trial reported the pain intensity score following treatment with NBOT versus sham (air) and enrolled 19 participants 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). After NBOT administration, participants rated their degree of relief at 1.93 Standard Error (SE) 0.22 and after air at 0.77, SE 0.23, and this was reported as statistically significant (P < 0.01).

2. Functional status or disability

No trials reported this outcome.

3. Pain-free response at four hours for migraine and two hours for cluster headache

No trials reported this outcome.

4. Proportion of participants requiring rescue medication

No trials reported this outcome.

5. Proportion of participants with sustained relief for 48 hours

No trials reported this outcome.

NBOT for prevention of attacks

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

Adverse events

Di Sabato 1993 reported that no adverse reactions were noted in any participant while Cohen 2009 reported there were no serious adverse events related to the treatments. Two participants reported an empty cylinder before completing the trial gas administration. No other trial made any reference to adverse events.

DISCUSSION

Summary of main results

Since the last version of this review, Bennett 2008, two new included studies have provided additional information to change the conclusions of this review. In this review update we included data from 11 trials in total and believe these represent all RCTs in this area, both published and unpublished. 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 participants obtained relief within about 40 minutes, with a NNT = 2 (95% CI 1 to 2) compared to a sham therapy. We have presented our pooled estimate in Summary of findings for the main comparison. One trial showed no evidence to suggest 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 HBOT use for the termination of cluster headache, and this very small trial (13 participants) was underpowered to reliably demonstrate even a large difference between groups (Di Sabato 1993). Eleven of 13 participants in the HBOT group obtained relief versus none of the same 13 when they received sham therapy; all of these participants were reported as remaining free of headache for at least 48 hours. There was some evidence that NBOT may also terminate acute cluster headache. Cohen 2009 reported 78% of cluster headaches were terminated with HBOT versus 20% with air, and this supported the findings of Fogan 1985 (more than 50% of participants achieved relief from headache within 15 minutes). Kudrow 1981 demonstrated no benefit from NBOT when compared to the administration of ergotamine tartrate. However, combining the NBOT arms of each of these studies suggests that a high proportion of cluster headaches will respond to NBOT (50 of 66 participants). We could not pool these trials because of clinical heterogeneity, specifically because comparators and outcomes measured differed between trials. There was no evidence from a single trial that HBOT can prevent cluster headaches (Nilsson Remahl 2002).

Overall completeness and applicability of evidence

While we can have some confidence that HBOT will terminate a migraine headache in many people, and similarly that NBOT can terminate a cluster headache, there is little evidence in answer to our other clinical questions. In particular, there is no indication based on the sparse evidence available that either HBOT or NBOT can prevent headaches of either type, and very little evidence that HBOT has any added value over NBOT for cluster headache.

Data from the included trials suggest both potential treatments are relatively safe. Only two trials specifically mentioned adverse events (Cohen 2009; Eftedal 2004). There were two reported cases of claustrophobia in the former, while two participants ran out of trial gas in the other. Otherwise no complications directly related to HBOT or NBOT were noted.

HBOT is regarded as a relatively benign intervention. There are few major adverse events (pulmonary barotrauma, drug reactions, injuries, or death related to chamber fire). There are a number of more minor complications that may commonly occur. 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 unlikely to be a problem after the single exposures used in most of these included 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 AUD 304.00 (Gomez-Castillo 2005). This is unlikely 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 unknown.

NBOT has been widely recommended for the treatment of cluster headache since Horton 1956. It is generally accepted that about 70% of patients will receive significant relief, based on the small studies of Fogan 1985, Kudrow 1981, and the larger study from Cohen 2009.

We 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.

Quality of the evidence

We rated the quality of the evidence as low for HBOT for the relief of acute migraine (GRADEPro GDT 2015). Generally we assessed the methodological quality of the 11 included trials as moderate to low. Randomisation was poorly described in all but three included trials and none appear to have been based on sound sample size calculations for expected differences. One trial did not attempt to blind participants 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.

Potential biases in the review process

Six trials evaluated HBOT for the termination of an acute migraine attack (161 migraine participants), two trials evaluated HBOT for cluster headache, and three evaluated NBOT for cluster headache (202 cluster headache 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.

Agreements and disagreements with other studies or reviews

There are few recent reviews of oxygen therapy for migraine headache. In a review concentrating on potential mechanisms of action, Taylor 2011 discussed the use of HBOT for both migraine and cluster headaches, but did not make therapeutic recommendations. In agreement with our review, Holland 2012 considered the prevention of migraine and concluded there was insufficient evidence to justify the use of HBOT for this purpose. For cluster headache, a recent review recommends both sumatriptan and oxygen to abort ongoing headaches and suggest the evidence available to support their use is good (Class I) (Leone 2010).

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 support the use of HBOT for this purpose. The use of HBOT as a prophylactic therapy for migraine is not supported by the evidence. While one small trial supports the practice of administering NBOT to patients with acute migrainous headache, further evidence is required to support the use of NBOT for this purpose.

There is insufficient evidence from good quality RCTs to establish the effects of HBOT on cluster headache as a treatment for an acute episode or as a prophylaxis against future clusters. Three RCTs 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, NBOT use is likely to continue. There is no evidence to support NBOT use as a prophylactic measure.

Implications for research

Given the findings of this review update, 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 events;
- The cost-utility of the therapy;
- Appropriate and full reporting.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cohen 2009

Methods	Blinded, crossover randomised trial of normobaric oxygen versus air (placebo) for cluster headache. Each participant was treated for a total of four headaches during the study period.
Participants	109 patients with a diagnosis of chronic or episodic cluster headache as defined by the International Headache Society. Excluded if previously treated with oxygen or receiving preventative medication.
Interventions	Control: Air breathing at 12 litres per minute for 15 minutes at the start of a cluster headache attack. HBOT: 100% oxygen breathing at 12 litres per minute for 15 minutes at the start of a cluster headache attack. Each gas was delivered alternately for four attacks. Random allocation to which gas was used first. Final follow-up at 2 months. Total reports of 76 participants having 289 attacks.

Cohen 2009 *(Continued)*

Outcomes	Pain relief from 15 minutes to 1 hour. Requirement for rescue medication. Functional state and effect on associated symptoms. Adverse events.
Notes	Paper reports outcomes per attack treated rather than per participant. We contacted trial authors for-further information that might allow inclusion in quantitative analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization...was performed using opaque sealed envelopes, inside of which was a card labelled “A” or “B,” which determined the order the patient received active treatment or placebo."
Allocation concealment (selection bias)	Unclear risk	No clear statement that participants were allocated prior to inclusion in the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A face mask and 2 standard CD-sized, 2-liter cylinders with integral valve, regulator, flowmeter, and operating instructions were delivered to each participant’s home, one labelled “treatment 1”; the other, “treatment 2". Copies of the randomization code were locked in the office of the principal investigator and the manufacturer, where they remained unbroken until the end of the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors and participants unaware of allocation (see above).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	109 participants were randomised, but only 76 received treatment and were analysed. Dropouts were reported to have done so because they did not receive treatment (33): came out of bout (17); lost to follow-up (9); withdrew from study (6); died (1). All 76 remaining participants accounted for with little loss of data. See figure in the trial report.
Selective reporting (reporting bias)	Low risk	The report gives data for all outcomes indicated in the trial registration at isrctn.org. However, rather than reporting the primary outcome as "Proportion of patients pain free after 15 minutes of treatment comparing oxygen and air" as indicated, the trial authors reported the proportion of attacks treated that responded.

Di Sabato 1993

Methods	Acute therapy and prophylaxis trial. RCT with randomisation not described. Assessor blinded. No power calculation recorded.
Participants	13 patients (1 female) with a diagnosis of episodic cluster headache according to the Ad Hoc Committee on Classification of Headache 1988. Excluded if any concomitant diseases or taking prophylactic therapy.
Interventions	Control: Air breathing at 2.5 ATA for 30 minutes. HBOT: 100% oxygen breathing at 2.5 ATA for 30 minutes.

Di Sabato 1993 *(Continued)*

	Final follow-up at 2 months: 1005 follow-up.
Outcomes	Duration of the attack.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Only a vague description of the method of allocation; "Five minutes after the onset of the attack, the patients were placed into a...hyperbaric chamber...the patients chosen for the placebo treatment were placed in the same environment".
Allocation concealment (selection bias)	Unclear risk	No specific statement regarding concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No specific account of blinding methods for personnel, but participants were clearly intended to be blinded because or the use of the sham therapy described (air at 2.4 ATA).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An observer who did not know the nature of the administration registered the duration of the attack" and participant assessors blinded as above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants reached final follow-up.
Selective reporting (reporting bias)	Unclear risk	No pre-registration of trial by which to judge selective reporting.

Eftedal 2004

Methods	Prophylaxis trial. RCT with blinding of participants and investigators. Randomisation method not stated. No power calculation recorded.
Participants	Forty patients (2 females) with a diagnosis of migraine with or without aura according to the IHS classification, on 2 to 8 occasions per month for the previous 3 months. Patients excluded if any contraindication to HBOT. Six participants did not complete the study and did not contribute to the outcome (1 HBO, 5 control).
Interventions	Control: Air breathing at 2 ATA for 30 minutes on three consecutive days. HBOT: 100% oxygen breathing on the same schedule. Final follow-up at 8 weeks after therapy.
Outcomes	Hours of headache per week. Number of days with headache per week. Doses of attack terminating medication per week. Blood endothelin levels.
Notes	

Eftedal 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given of the randomisation procedure: "the patients were randomly assigned to the treatment or control group."
Allocation concealment (selection bias)	Unclear risk	No specific statement concerning allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Only the chamber operator had knowledge of which treatment was given, the participants and all medical personnel were blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six of 40 participants enrolled did not reach final follow-up.
Selective reporting (reporting bias)	Unclear risk	No trial pre-registration with which to compare.

Fife 1992

Methods	Acute therapy trial. Partial cross-over RCT with blinding of participants and investigators. Participants with no relief had the choice of undergoing the second arm of the study 30 minutes after completion of the first arm assigned. Randomisation by sealed envelopes. No power calculation recorded.
Participants	Fourteen patients (23 to 67 years, 9 females) with a diagnosis of migraine documented by neurologist evaluation. Patients excluded if narcotic users, daily headaches or any contraindication to HBOT. Six patients did not complete the study and did not contribute to the outcome.
Interventions	Control: 10% oxygen breathing via Scott mask at 2 ATA for 45 minutes. HBOT: 100% oxygen at 2 ATA on the same schedule. If initial exposure failed, participants could opt to undertake the alternative therapy after a 30-minute break. No other follow-up recorded.
Outcomes	Proportion of participants with significant pain relief using a Blanchard pain inventory from 0 to 5. Significant relief defined as reduction on this scale of 2 or more points.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.

Fife 1992 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No clear statement of concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and assessors blinded by sham therapy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and assessor unaware.
Incomplete outcome data (attrition bias) All outcomes	High risk	Ten participants did not progress to the second arm of this study because of headache relief in first treatment.
Selective reporting (reporting bias)	Unclear risk	No indication of missed outcomes.

Fogan 1985

Methods	Acute therapy trial. Cross-over RCT with allocation concealment and blinding of participants and investigator. Cross-over was made after six episodes were treated with the first assigned gas. Randomisation method not stated. No power calculation recorded.
Participants	Nineteen patients (20 to 50 years, all male) with a diagnosis of cluster headache according to AHC 1962. No indication of any exclusions, but participants were instructed not to take prophylactic or pain relief medication. Eleven of 19 were successfully crossed to receive both gases, but the remaining 8 received only one of the gases (3 air, 5 oxygen).
Interventions	Control: Air breathing from masked cylinder using a non-rebreathing face mask for 15 minutes on at least six occasions. Oxygen: 100% oxygen breathing on the same schedule. No follow-up after treatment period.
Outcomes	Subjective score of pain relief after 15 minutes of oxygen breathing: 0 = no relief, 1= slight relief, 2 = substantial relief, 3 = no relief.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Little detail of method: "That department randomly assigned each patient a special study-coded "E"-size portable gas cylinder."
Allocation concealment (selection bias)	Low risk	Principle investigator enrolled then sent to another location for allocation: "I examined each man and then they were immediately directed to the inhalation department of our medical facility."
Blinding of participants and personnel (performance bias)	Low risk	"The type of cylinder assigned was recorded and known only to the inhalation department. The patients and I were unaware of the cylinder contents until the conclusion of the study."

Fogan 1985 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	All enrolled participants are reported, but 3 of 19 participants did not receive NBOT for any headaches, while a different 5 of 19 did not receive air for any headaches. Furthermore, participants received treatment for between 1 and 10 headaches.
Selective reporting (reporting bias)	Unclear risk	No pre-registration with which to compare.

Hill 1992

Methods	Acute therapy trial. Cross-over RCT with blinding of participants and investigators. Cross-over was made 5 minutes after completing the first assigned treatment. Randomisation method not stated. No power calculation recorded.
Participants	Nineteen patients with a diagnosis of migraine according to AHC 1962. Migraine needed to be stable with regular headaches. Patients excluded if narcotic used to treat the headache on the occasion under study or with any contraindication to HBOT.
Interventions	Control: Air breathing at 2.0 ATA for 45 minutes. HBOT: 100% oxygen breathing on the same schedule. These two periods were separated by a 5-minute air break period before the alternative arm was instituted.
Outcomes	Pain relief. No follow-up after therapy period.
Notes	Abstract only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not clearly described.
Allocation concealment (selection bias)	Unclear risk	No specific account of methods.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient, the neurologist nor the inside observer knew which gas the patient received".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above - participant blinded.

Hill 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All reported participants reached assessment.
Selective reporting (reporting bias)	Unclear risk	No preregistration with which to compare.

Kudrow 1981

Methods	Acute therapy trial. Cross-over RCT with randomisation not described. Cross-over was made after 10 attacks were treated in the first assigned group. No blinding employed. No power calculation recorded.
Participants	Fifty patients (8 females) with a diagnosis of episodic (36) or chronic (14) cluster headache. No exclusion criteria recorded. No losses to follow-up.
Interventions	Control: Sublingual ergotamine tartrate, three tablets allowed at intervals of 15 minutes. Oxygen: 100% oxygen by mask at 7 litres per minute for 15 minutes. Ten attacks treated. Final follow-up at end of therapy period.
Outcomes	Proportion with successfully aborted attacks.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not defined: "Twenty-five randomly selected patients".
Allocation concealment (selection bias)	High risk	No allocation concealment indicated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding described.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were reported upon.
Selective reporting (reporting bias)	Unclear risk	No pre-registration report with which to compare.

Myers 1995

Methods	Acute therapy trial. RCT with randomisation not described. Assessor blinded. No power calculation recorded.
Participants	Twenty patients (14 female) with a diagnosis of migraine confirmed by a physician. Patients were evaluated for inclusion while experiencing an acute episode. Exclusion criteria not recorded.
Interventions	Control: Sham treatment breathing 100% oxygen at 1 ATA for 40 minutes. HBOT: 100% oxygen breathing using a hood at 2.0 ATA. Final follow-up following therapy.
Outcomes	Proportion with significant headache relief measured by improvement on a six category scale from 'none' to 'most severe ever'.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not clearly described: "The patients were initially assigned at random".
Allocation concealment (selection bias)	Unclear risk	No specific mention of concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded: "Patients were blinded to the level of pressure".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No specific mention of this, but blinding for participant as assessor of pain relief.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No pre-registration of trial with which to compare.

Nilsson Remahl 2002

Methods	Acute therapy and prophylaxis trial. RCT with randomisation not described. Participant, operator and assessor blinded with cross-over. Cross-over was made 1 week after treatment with the first assigned breathing gas. No power calculation recorded.
Participants	Sixteen patients (20 to 62 years, 3 females) with a diagnosis of episodic (12) or chronic (4) cluster headache according to IHS criteria and who had suffered at least six headaches during the previous week. Excluded if taking prophylactic therapy. Two patients had sham only and did not cross to receive HBOT.
Interventions	Control: Sham therapy breathing 10% oxygen for 70 minutes at 2.5 ATA for two sessions 24 hours apart. Rescue simple analgesia if required.

Nilsson Remahl 2002 *(Continued)*

	HBOT: 100% oxygen at 2.5 ATA for 70 minutes on the same schedule as control.
Outcomes	Headache index improved by more than 50%. (HI = sum of (number of attacks multiplied by degree of severity)). Severity measured on a scale of 0 (no headache) to 4 (very severe headache). Jugular venous plasma calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and neuropeptide Y (NPY) Final follow-up 1 week after therapy.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described: "If the patients fulfilled the inclusion criteria, they were randomly given one of the two breathing gases by mask".
Allocation concealment (selection bias)	Unclear risk	No clear statement of allocation concealment, but likely to be so given cross-over nature of trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study used a double-blind, placebo-controlled, cross-over protocol."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor included in the statement above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants were in final follow-up.
Selective reporting (reporting bias)	Unclear risk	No pre-registration of trial with which to compare.

Ozkurt 2012

Methods	Acute therapy trial enrolled all primary headache patients. Migraine headaches reported separately. RCT with blinding of participants and investigators. Randomisation by computer generated numbers.
Participants	56 adult migraineurs presenting to an emergency department for the treatment of acute migraine.
Interventions	100% NBOT using 15 litres per minute flow through non-rebreather mask for 15 minutes. Sham the same using air.
Outcomes	Reduction of pain intensity using a VAS (0 to 100) up to one hour after administration. Rescue analgesia. Emergency Department length of stay.
Notes	A total of 204 participants enrolled with mixed headache aetiology. One cluster headache in each group was not reported separately. Communication with editor did not provide further data concerning the migraine participants. Outcome only available for VAS.

Ozkurt 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to the treatment or placebo group according to a computer-generated randomization table."
Allocation concealment (selection bias)	Low risk	Likely entered into trial before randomisation "After the treating physician decided the patient's eligibility for the study, a study nurse applied oxygen or room air according to the randomization scheme".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and the treating physicians were blinded to the treatment." "We used this special room and wall outlet system for all patients who were enrolled. Patients in the placebo group were connected to the wall outlet system that appeared to be oxygen but was actually room air."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participant as assessor of pain was blinded, but no specific mention of other outcome assessor blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled migraine participants were reported.
Selective reporting (reporting bias)	Unclear risk	Trial was not registered on a trial database so it is unclear all outcomes were reported.

Wilson 1998

Methods	Acute therapy trial. Cross-over RCT with blinding of participants and investigators. Randomisation method not stated. Cross-over was done when presenting for treatment of the second migraine after initial entry into trial. No power calculation recorded.
Participants	Eight female patients (mean age 38.8) with a diagnosis of migraine with aura confirmed by a neurologist at 18 months prior to entry into the study. Migraine needed to be stable with regular headaches. Patients excluded if severe migraine lasting longer than 4 days, fewer than two attacks per month, if fully responsive to standard therapy, with existing neurological deficit or with any contraindication to HBOT. Six participants did not complete the study and did not contribute to the outcome.
Interventions	Control: Sham hyperbaric therapy using brief compressions to 0.1 ATA to simulate descent, then 1.1 ATA 100% oxygen until pain cessation plus 20 minutes or 60 minutes. HBOT: 100% oxygen inhalation in a monoplace chamber at 2.4 ATA to pain cessation plus 20 minutes or a maximum of 60 minutes. Final follow-up at end of second treatment session.
Outcomes	Headache severity on a VAS 0 = no headache, 10 = intolerable headache. Pericranial tenderness on palpation. Algometry using a dolorimeter at points of pericranial tenderness.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Wilson 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No specific description of randomisation method: "Subjects were randomly assigned to either treatment group."
Allocation concealment (selection bias)	Low risk	"After obtaining informed consent, each subject underwent a history and physical examination and an explanation of HBO, therapy by the study physician and were shown a picture of a monoplace hyperbaric chamber. Subjects were randomly assigned to either treatment group."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All physicians, personnel, and subjects associated with the study were blinded to the groupings and previous results, except for the individual in charge of administering the treatments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if all subjects reached follow-up.
Selective reporting (reporting bias)	Unclear risk	No pre-registration of trial with which to compare.

ATA: atmospheres absolute; CGRP: calcitonin gene-related peptide; HBOT: hyperbaric oxygen therapy; HI: headache index; IHS: International Headache Society; NPY: neuropeptide Y; RCT: randomised controlled trial; VAS: visual analogue scale; VIP: vasoactive intestinal peptide.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Capobianco 2006	Review - no new data.
Chu 2010	Third party report of included trial.
Di Sabato 1996	Non-randomised comparative trial.
Di Sabato 1997	Non-randomised comparative trial.
Drummond 1985	Non-randomised comparative trial.
Ekbom 2004	Review - no new data.
Evers 1996	Non-randomised comparative trial.
Fife 1989	Case series.
Fife 1991	Review - no new data.
Francis 2010	Review - no new data.
Green 2003	Review - no new data.
Leone 2010	Review - no new data.

Study	Reason for exclusion
Mendizabal 1998	Review - no new data.
Nilsson Remahl 2003	Review - no new data.
Nwosu 2005	Review - no new data.
Pascual 1995	Case series.
Rozen 2004	Case series.
Rozen 2005	Review - no new data.

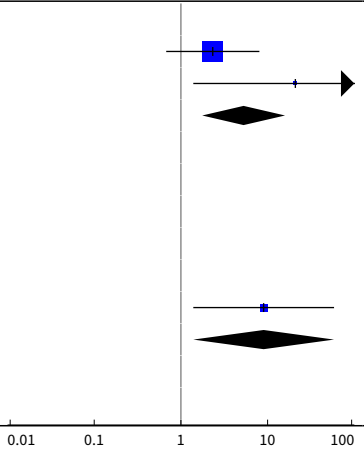
DATA AND ANALYSES

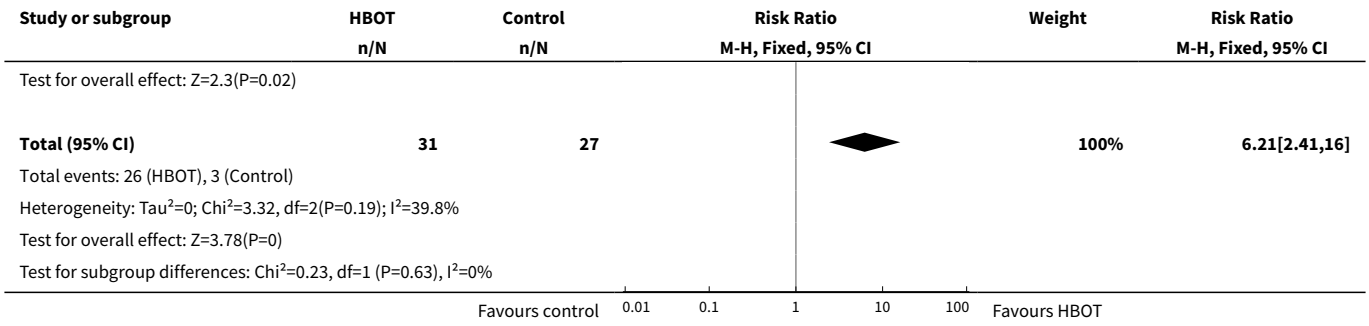
Comparison 1. HBOT versus control for acute migraine attack

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Substantial acute relief of headache	3	58	Risk Ratio (M-H, Fixed, 95% CI)	6.21 [2.41, 16.00]
1.1 HBOT versus air sham therapy	2	38	Risk Ratio (M-H, Fixed, 95% CI)	5.28 [1.76, 15.87]
1.2 HBOT versus 100% oxygen at 1 ATA	1	20	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [1.39, 58.44]

Analysis 1.1. Comparison 1 HBOT versus control for acute migraine attack, Outcome 1 Substantial acute relief of headache.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 HBOT versus air sham therapy					
Fife 1992	8/12	2/7		63.12%	2.33[0.68,8.04]
Hill 1992	9/9	0/10		11.9%	20.9[1.39,314.68]
Subtotal (95% CI)	**21**	**17**		**75.02%**	**5.28[1.76,15.87]**
Total events: 17 (HBOT), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.66, df=1(P=0.1); I^2=62.41%					
Test for overall effect: Z=2.96(P=0)					
1.1.2 HBOT versus 100% oxygen at 1 ATA					
Myers 1995	9/10	1/10		24.98%	9[1.39,58.44]
Subtotal (95% CI)	**10**	**10**		**24.98%**	**9[1.39,58.44]**
Total events: 9 (HBOT), 1 (Control)					
Heterogeneity: Not applicable					





APPENDICES

Appendix 1. Search strategies used for this Cochrane review update

CENTRAL (the Cochrane Library)

#1 MeSH descriptor: [Headache] this term only

#2 MeSH descriptor: [Headache Disorders] explode all trees

#3 (headache* or migrain* or cephalgi* or cephalalgi* or cluster):ti,ab,kw (Word variations have been searched)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Hyperbaric Oxygenation] this term only

#6 MeSH descriptor: [Oxygen Inhalation Therapy] this term only

#7 MeSH descriptor: [Oxygen] this term only and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU, Toxicity - TO]

#8 MeSH descriptor: [Hyperoxia] this term only

#9 MeSH descriptor: [Atmosphere Exposure Chambers] this term only

#10 (hyperbar* or HBO*):ti,ab,kw (Word variations have been searched)

#11 (high pressure oxygen or 100% oxygen):ti,ab,kw (Word variations have been searched)

#12 ((monoplace or multiplace) near/5 chamber*):ti,ab,kw (Word variations have been searched)

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 #4 and #13 Publication Date from 2008 to 2015

MEDLINE (OVID)

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

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. randomized controlled trial.pt.

15. controlled clinical trial.pt.

16. randomized.ab.

17. placebo.ab.

18. drug therapy.fs.

19. randomly.ab.

20. trial.ab.

21. or/14-20

22. exp animals/ not humans.sh.

23. 21 not 22

24. 4 and 13 and 23

25. (200805* or 200806* or 200807* or 200808* or 200809* or 200810* or 200811* or 200812* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).

26. 24 and 25

EMBASE (OVID)

1. Headache/

2. exp Headache/ and Facial Pain/

3. (headache$ or migrain$ or cephalgi$ or cephalalgi$ or cluster).tw.

4. or/1-3

5. Hyperbaric Oxygenation/

6. Oxygen Therapy/

7. Oxygen/ae, tu, to

8. Hyperoxia/

9. Air Quality Control/

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. random$.tw.

15. factorial$.tw.

16. crossover$.tw.

17. cross over$.tw.

18. cross-over$.tw.

19. placebo$.tw.

20. (doubl$ adj blind$).tw.

21. (singl$ adj blind$).tw.

22. assign$.tw.

23. allocat$.tw.

24. volunteer$.tw.

25. Crossover Procedure/

26. double-blind procedure.tw.

27. Randomized Controlled Trial/

28. Single Blind Procedure/

29. or/14-28

30. (animal/ or nonhuman/) not human/

31. 29 not 30

32. 4 and 13 and 31

33. (200805* or 200806* or 200807* or 200808* or 200809* or 200810* or 200811* or 200812* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015*).dd.

34. 32 and 33

CINAHL (EBSCO)

S24 S14 AND S23

S23 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22

S22 (allocat* random*)

S21 (MH "Quantitative Studies")

S20 (MH "Placebos")

S18 (random* allocat*)

S17 (MH "Random Assignment")

S16 (Randomi?ed control* trial*)

S15 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or

(doubl* mask*) or (singl* mask*)

S14 S12 AND S13

S13 EM 20080501-20140430

S12 S3 AND S11

S11 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10

S10 ((monoplace or multiplace) N5 (chamber*))

S9 (high pressure oxygen or 100% oxygen)

S8 (hyperbar* or HBO*)

S7 (MH "Hyperoxia")

S6 (MH "Oxygen/AE/TU")

S5 (MH "Oxygen Therapy")

S4 (MH "Hyperbaric Oxygenation")

S3 (S1 OR S2)

S2 (headache* OR migrain* OR cephalgi* OR cephalalgi* OR cluster)

S1 (MH "Headache+")

Appendix 2. Data extraction table for the relief of acute migraine attack

Study ID	Participants and condition	Study design	Treatment	Treatment duration	Outcomes	Data extracted
Fife 1992	14 patients (23 to 67 years, 9 females) with a diagnosis of migraine documented by neurologist evaluation.	Acute therapy trial. RCT with partial cross-over (patients with relief on first arm could not be crossed) with blinding of patients and investigators. Patients with no relief had the choice of undergoing the second arm of the study 30 minutes after completion of the first arm assigned.	Control: 10% oxygen breathing via Scott mask at 2 ATA. HBOT: 100% oxygen at 2 ATA on the same schedule.	45 minutes	Proportion of patients with significant pain relief using a Blanchard pain inventory from 0 to 5. Significant relief defined as reduction on this scale of 2 or more points.	Fife 1992 gave the response of all patients from both treatment periods. We have included responders for both initial treatment and on crossover. Total of 8 of 11 individuals obtained pain relief from HBOT and 2 of 7 obtained similar relief from air.
Hill 1992	19 patients with a diagnosis of migraine according to the AHC 1962.	Acute therapy trial. Cross-over RCT with blinding of patients and investigators. Cross-over was made 5 minutes after completing the first assigned treatment.	Control: Air breathing at 2.0 ATA. HBOT: 100% oxygen breathing on the same schedule.	45 minutes	Complete or partial pain relief.	Hill 1992 reported no patients given air and all patients given oxygen obtained some pain relief. (10 had air first and 9 had HBOT first). We included the results given as prior to crossover because of limited reporting. This was a more conservation approach than imputing the response for all crossovers.
Myers 1995	20 patients (14 female) with a diagnosis of migraine confirmed by a physician.	Acute therapy trial. RCT with randomisation not described.	Control: 100% oxygen at 1 ATA for 40 minutes. HBOT: 100% oxygen	40 minutes	Proportion with significant headache relief on a 6 category scale from	Myers 1995 reported 9 of 10 patients given HBOT obtained 'total' or 'near-total' relief of headache versus 1 of the 10 patients given air.

(Continued)

	breathing using a hood at 2.0 ATA.	'none' to 'most severe ever'.

Abbreviations: ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; RCT: randomised controlled trial.

FEEDBACK

Christy Ngo, 26 March 2009

Summary

I highly value the work that's been contributed to create the review on 'Normobaric and hyperbaric oxygen therapy for migraine and cluster headache'. I am part of a Technology Assessment Unit that reviews the literature on new and developing technologies for Kaiser Permanente and I find the systematic reviews to be extremely informative and useful. Please keep up the fantastic work and don't forget to update the reviews.

Submitter agrees with default conflict of interest statement, which reads as follows: 'I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback'.

Reply

The authors and the staff of the Pain, Palliative and Supportive Care Review Group thank Christy Ngo for her kind comments.

Contributors

Feedback: Christy Ngo

Response: Jessica Thomas

WHAT'S NEW

Date	Event	Description
4 January 2016	Review declared as stable	This review will be assessed for further updating in 2020.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 3, 2008

Date	Event	Description
15 June 2015	New search has been performed	We updated the literature searches to 15 June 2015.
15 June 2015	New citation required and conclusions have changed	We updated the review and included two new RCTs to the review (two to the qualitative analysis and one to the quantitative analysis). We added 'Risk of bias' tables for each included trial and a 'Summary of findings' table to the review. A review author has been added. We have modified the Background and Discussion sections using the available subheading structure in RevMan 2014.
10 August 2009	Amended	Contact details updated.
24 April 2009	Feedback has been incorporated	We incorporated feedback (26 March 2009) and response.

Date	Event	Description
24 March 2009	Amended	Contact details updated.
10 November 2008	Amended	We updated contact details for the Contact Person.
30 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MB conceived and coordinated this review, wrote to authors of papers for additional information, provided additional data about articles, and entered data into RevMan 2014.
MB and AS performed manual literature searches.
MB and JW screened the search results.
MB and AS organized retrieval of papers.
MB, AS, and CF screened retrieved papers against inclusion criteria.
MB and SW extracted data from articles, appraised the quality of included trials, performed data management, and performed double-entry of data in this review update; MB and AS did so for Bennett 2008.
MB and AS obtained and screened data on unpublished studies. MB and AS performed statistical analyses using RevMan 2014.
MB performed statistical inferences and other statistical analysis not using RevMan 2014.
MB, AS, PK, and SW interpreted data.
AS and MB wrote the review.
NR secured funding for the review.
MB and PK performed previous work that was the foundation of this review update.
MB is guarantor for this review.
CF, JW, and PK were responsible for reading and checking this review before submission.

DECLARATIONS OF INTEREST

Michael Bennett has no relevant conflict of interest to declare.
Christopher French has no relevant conflict of interest to declare.
Alexander Schnabel has no relevant conflict of interest to declare.
Jason Wasiak has no relevant conflict of interest to declare.
Peter Kranke has no relevant conflict of interest to declare.
Stephanie Weibel has no relevant conflict of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No internal source of support, Other.

External sources

- No external source of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this 2015 update, we added an author (SW) and two new trials (Cohen 2009; Ozkurt 2012). We have also amended the title from 'Normobaric and hyperbaric oxygen therapy for migraine and cluster headache' to 'Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache' for clarity.

We have formulated a Summary of findings for the main comparison and estimated the quality of the evidence using the GRADE Pro Guideline Development Tool software and methodology (GRADEPro GDT 2015) .

NOTES

The authors and editors have agreed that this review will be assessed for further updating in 2020. It is unlikely that new evidence will be published that has the potential to change the conclusions.

INDEX TERMS

Medical Subject Headings (MeSH)

Cluster Headache [*therapy]; *Hyperbaric Oxygenation; Migraine Disorders [*therapy]; *Oxygen Inhalation Therapy; Randomized Controlled Trials as Topic

MeSH check words

Humans