Hyperbaric oxygen therapy for acute ischaemic stroke

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A substantive amendment to this systematic review was last made on 21 March 2005. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background: Most cases of stroke are caused by impairment of blood flow to the brain (ischaemia) which results in a reduction in oxygen available and subsequent cell death. It has been postulated that hyperbaric oxygen therapy (HBOT) may reduce the volume of brain that will die by greatly increasing the oxygen available, and it may further improve outcome by reducing brain swelling. Some centres are using HBOT routinely to treat stroke.

Objective: To assess the effectiveness and safety of adjunctive HBOT in the treatment of acute ischaemic stroke.

Search strategy: We searched the Cochrane Stroke Group Trials Register (last searched 9 January 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3, 2004), MEDLINE (1966 to July 2004), EMBASE (1980 to July 2004), CINAHL (1982 to July 2004), and DORCTHIM (Database of Randomised Controlled Trials in Hyperbaric Medicine) (from inception to 2004). We handsearched journals and conference proceedings, searched reference lists of articles, and contacted researchers in an effort to identify additional published and unpublished studies.

Selection criteria: We included all randomised controlled trials that compared the effect of adjunctive HBOT with no HBOT (no treatment or sham).

Data collection and analysis: Two authors used standardised forms to extract the data independently. Each trial was assessed for internal validity with differences resolved by discussion. Data were extracted and entered into RevMan 4.2.

Main results: Three randomised controlled trials (106 participants) satisfied the inclusion criteria. The methodological quality of the trials varied but was generally high. Data could be pooled for a limited number of clinically important outcomes. There were no significant differences in mortality rate at six months in those receiving HBOT compared to the control group (relative risk 0.61, 95% confidence interval (CI) 0.17 to 2.2, P value 0.45). Two of 15 scale measures of disability and functional indicated an improvement following HBOT, both at one year follow up: the mean Trouillas Disability Scale was lower with HBOT (mean difference (MD) 2.2 points reduction with HBOT, 95% CI 0.15 to 4.3, P value 0.04) and the mean Orgogozo Scale was higher (MD 27.9 points, 95% CI 4.0 to 51.8, P value 0.02). These improvements were not reflected in other trials or functional scales.

Reviewers' conclusions: This systematic review has not found evidence to show that HBOT improves clinical outcomes when applied during the acute presentation of ischaemic stroke. While evidence from the three randomised controlled trials is insufficient to provide clear guidelines for practice, clinical benefit does not seem likely. Further research is required to better define the role of HBOT in this condition.

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Background

Stroke may be defined as a sudden neurological deficit that is of presumed vascular origin (Bath 2000). It is both a leading cause of mortality worldwide, accounting for an estimated 4.4 million deaths in 1990 (Murray 1997), and a leading cause of disability. About one third of survivors require significant assistance in daily life at one year after an event (Bamford 1991; Bath 2000).

Stroke is divided into two broad subgroups: ischaemic (impairment of blood flow), and haemorrhagic (bleeding within the brain); with the former accounting for 73% to 86% of all cases (Sudlow 1997). On average, ischaemic stroke has a lower case fatality rate than haemorrhagic stroke (23% versus 62% at one year), and treatment differs for the two subgroups (Bamford 1991; Bath 2000). Therefore, early and accurate diagnosis is desirable. Because clinical assessment is unreliable in determining the stroke type, neuroimaging (preferably using computerised tomography (CT) scan) is required for optimal management (Wardlaw 2004).

During a cerebral ischaemic event neurological tissue suffers hypoxia. When hypoxia is prolonged neurons lose their ability to maintain ionic homeostasis. Free oxygen radicals accumulate and degrade the cell membranes (Ikeda 1990; Siesjo 1989); irreversible changes result in unavoidable cell death. These changes may occur rapidly and before therapy can be instituted but in some patients the symptoms worsen gradually or in a step-wise fashion over a matter of hours or days (Robertson 1989). This latter observation suggests that the close management of haemodynamic, respiratory and metabolic factors designed to maintain oxygenation might be beneficial. Indeed, intensive stroke management protocols and antiplatelet therapy have been shown to positively influence the outcome (CASTCG 1997; ISTCG 1997; SUTC 2004).

Hyperbaric oxygen therapy (HBOT) is an adjunctive therapy that has been proposed for the treatment of ischaemic stroke (Hart 1971; Ingvar 1965). HBOT is the therapeutic administration of 100% oxygen at environmental pressures greater than 1.0 atmosphere absolute (ATA). Administration involves placing the patient in an airtight vessel, increasing the pressure within that vessel, and administering 100% oxygen for respiration. In this way it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. Typically, treatments involve pressurisation to between 1.5 and 3.0 ATA for periods between 60 and 120 minutes, once or twice daily.

The potential benefits of HBOT include the reversal of hypoxia through increased oxygen delivery and reduction of cerebral oedema (Hills 1999; Sukoff 1982), and several specific effects of hyperoxia that include decreased lipid peroxidation, inhibition of leukocyte activation and restoration of the functional blood-brain barrier (Mink 1995a; Mink 1995b; Thom 1993). It has been proposed that HBOT protects marginally viable brain (often termed 'the ischaemic penumbra') from further damage on reperfusion through these mechanisms that act to regulate abnormal cellular metabolites (Badr 2001; Selman 2004). Conversely, oxygen in high doses may increase oxidative stress through the production of oxygen free-radical species and is potentially toxic (Yusa 1987). Indeed, the brain is particularly at risk (Clark 1982). For this reason, it is appropriate to postulate that in some stroke patients HBOT may do more harm than good.

Therefore, HBOT is associated with some risk of adverse effects, including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of shortsightedness, claustrophobia and oxygen poisoning. Although serious adverse events are rare HBOT cannot be regarded as an entirely benign intervention.

Despite 40 years of interest in the delivery of HBOT in stroke patients, little comparative evidence of effectiveness exists. Most reports have been of single or multiple cases, with the largest study being a series of 122 cases reported in 1980 (Neubauer 1980). A review of these studies calculated that more than half of cases improved clinically or electrophysiologically with

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HBOT and concluded that there was a case for setting up controlled studies (Nighoghossian 1997).

Objectives

The objective of this review was to examine the effectiveness and safety of adjunctive HBOT in the treatment of acute ischaemic stroke. Effectiveness was assessed using a number of clinically important outcomes, such as mortality, functional disability and activities of daily living assessment.

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials that compared the effect of adjunctive HBOT with no HBOT (no treatment or sham).

Types of participants

We focused on participants, of any age or sex, with acute ischaemic stroke. Acute ischaemic stroke was defined as a sudden neurological deficit of presumed vascular origin and where haemorrhage had been excluded by CT or magnetic resonance imaging (MRI).

Types of intervention

Trials comparing any standard treatment regimens designed to promote recovery after acute ischaemic stroke, including intensive combined therapies, with and without HBOT.

Studies were eligible for inclusion if HBOT was administered in a compression chamber at pressures between 1.5 ATA and 3.0 ATA for treatment times between 30 minutes and 120 minutes, at least once daily.

Types of outcome measures

Studies were eligible for inclusion if they reported any of the following outcome measures.

- Primary outcomes
- (1) Mortality rate.
- (2) Severe functional disability rate (or death) defined as 'drowsy/stuporose/unconscious or unable to feed/dress independently'. Care was taken to ensure death was included as a bad outcome when extracting data.

- Secondary outcomes
- (1) Functional status scale (e.g. National Institutes of Health Stroke Scale (NIHSS), Rankin Score, Glasgow Outcome Scale).
- (2) Deemed to have a good functional outcome assessed as a binary outcome using any of the above scales.
- (3) Activities of daily living (ADL), e.g. the Barthel Index.
- (4) CT or MRI estimate of infarct size or volume.
- (5) Adverse events following 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); other recorded adverse effects were reported and discussed.

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Due to variations in clinical practice the timing and recording of outcomes were divided into three stages for analysis: early (immediately after the treatment course), medium term (four to eight weeks after treatment) and longer term (at the end of scheduled follow up). There were a number of assessment scales used to quantify outcome in the trials. We have taken information concerning these scales from the Internet Stroke Centre Stroke Trials Directory at http://www.strokecenter.org/trials/scales/index.htm.

Search strategy for identification of studies

See: Cochrane Stroke Group search strategy

We searched the Cochrane Stroke Group Trials Register (which was last searched by the Review Group Co-ordinator on 9 January 2004). In addition we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, Issue 3, 2004), MEDLINE (1966 to July 2004), EMBASE (1980 to July 2004), CINAHL (1982 to July 2004), and DORCTHIM (Database of Randomised Controlled Trials in Hyperbaric Medicine) (from inception to 2004). We handsearched journals and conference proceedings, searched reference lists of articles, and contacted researchers in an effort to identify additional published and unpublished studies.

The DORCTHIM database was compiled from an unfocused search of PubMed using 'hyperbaric oxygenation' as a MeSH term, handsearching of primarily hyperbaric journals (see below) since first publication, and checking references in identified RCTs. The site is now interactive and receives citations for formal review from healthcare professionals in the field.

In MEDLINE the following search strategy was combined with the optimum trial search strategy described in the Cochrane Reviewers' Handbook (Alderson 2004). No language restrictions were applied. The search strategy was adapted for other databases.

- MEDLINE (Ovid)
- 1. Cerebrovascular disorders/
- 2. exp Brain ischemia/
- 3. Carotid artery diseases/ or Carotid artery thrombosis/
- 4. exp Cerebrovascular accident/
- 5. exp Hypoxia-ischemia, brain/
- 6. Cerebral arterial diseases/ or Intracranial arterial diseases/
- 7. exp "Intracranial embolism and thrombosis"/
- 8. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
- 9. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
- 10. or/1-9
- 11. Hyperbaric Oxygenation/
- 12. Oxygen Inhalation Therapy/
- 13. Oxygen/ae, tu [Adverse Effects, Therapeutic Use]
- 14. atmospheric pressure/
- 15. Atmosphere Exposure Chambers/
- 16. (hyperbar$ or HBO$).tw.
- 17. (high pressure oxygen or 100% oxygen).tw.
- 18. ((monoplace or multiplace) adj5 chamber$).tw.
- 19. or/11-18
- 20. 10 and 19
- 21. limit 20 to human

We also handsearched the following relevant publications.

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- Hyperbaric textbooks (Jain 1999; Kindwall 1999; Oriani 1996).
- Journals (Undersea and Hyperbaric Medicine 1992 to 2004, Hyperbaric Medicine Review 1986 to 1992, South Pacific Underwater Medicine Society (SPUMS) Journal 1973 to 2004, European Journal of Hyperbaric Medicine 1998 to 2004, and Aviation, Space and Environmental Medicine Journal 1980 to 2004)
- Conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published from 1980 to 2003.

We checked the reference lists of the trials and reviews. We also contacted current researchers in the field for information on unpublished data and ongoing trials.

Methods of the review

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

- Data extraction
- Data from the studies were extracted independently by three authors (MB, AS and CF) using standardised forms developed for this review. The authors of primary studies were contacted to provide information when missing or incomplete data were encountered. All differences were resolved by discussion among the review authors.

- Quality assessment
- Study quality was assessed using an adaptation of the method outlined in Schulz 1995. Results from the study quality are presented in a descriptive manner. The following characteristics were assessed.

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

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

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

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

- Analyses
- We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and planned to use a random-effects model when such heterogeneity was likely (DerSimonian 1986). Consideration was to be given to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. Statistical heterogeneity was assessed using the I2 statistic and consideration was given to the appropriateness of pooling and meta-analysis. Heterogeneity was to be explored and subgroup analyses performed, if appropriate.

For proportions (dichotomous outcomes), relative risk (RR) was used. Continuous data were converted to the mean difference (MD) using the inverse variance method and an overall MD calculated. Publication bias was to be tested using funnel plots; however, this was not appropriate given the small number of studies located.

Subgroup analysis was planned by calculation of RR or MD in each subgroup and examination of the 95% confidence intervals (CI). Non-overlap in intervals would have been taken to indicate a statistically significant difference between subgroups; however, no subgroup analysis was appropriate with the data available.

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

We intended to perform sensitivity analyses for missing data and study quality, where appropriate.

- Missing data
- We had planned to employ sensitivity analyses using different approaches to imputing missing data, however, no binary outcome involved incomplete data and this analysis was not required.

- Study quality
- If appropriate, we had also planned to conduct a sensitivity analysis by study quality based on the presence or absence of a reliable random allocation method, concealment of allocation, and blinding of participants or outcome assessors.

If appropriate data existed, we planned to consider subgroup analysis based on:

- time elapsed between stroke and institution of HBOT;
- dose of oxygen received (pressure less than 2.0 ATA versus greater than or equal to 2.0 ATA), time of treatment (less than 60 minutes versus more than or equal to 60 minutes) and length of treatment course (less than five sessions versus more than or equal to five sessions);
- nature of the comparative treatment modalities;
- volume of cerebral infarction as measured by baseline presentation of CT imaging.

Description of studies

A total of 962 references were identified. Independent scrutiny of the titles and abstracts identified 16 potentially relevant articles. We have been unable to obtain the abstract or full text of six articles. These are mostly short reports in the Russian literature and none of the titles give a strong suggestion that these represent randomised studies. We continue to request translated

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texts. Of the 10 articles assessed in full-text form, seven were excluded because they were a mixture of case reports, case series, non-random comparative trials and narrative reviews. The remaining three randomised trials formed the basis of this review.

Rusyniak 2003 enrolled 33 participants (22 men) presenting to the emergency department within 24 hours of stroke onset; with a deficit on an acute impairment scale, the National Institutes of Health Stroke Scale (NIHSS) of less than 23 (30 is maximum disability); and without evidence of haemorrhage on CT. Those randomised to the HBOT arm received a single session (breathing 100% oxygen for 60 minutes in a monoplace chamber at 2.5 ATA), while those in the control arm received a sham treatment (breathing air at 1.14 ATA). Primary outcome measures included the percentage of participants with improvements at 24 hours and 90 days. Secondary measurements included complications of treatment and mortality at 90 days. Outcomes included mortality; adverse effects of treatment and changes in the NIHSS (24 hours and 90 days); a functional assessment scale, the modified Rankin Scale (90 days); and two outcome scales, the Barthel Index of ADL (90 days) and the Glasgow Outcome Scale (90 days).

Nighoghossian 1995 enrolled 34 participants (21 men), aged between 20 and 75 years, presenting with a neurological deficit highly suggestive of middle cerebral artery occlusion. All participants presented within 24 hours of the cerebral event and with a score of less than 80 on the Orgogozo functional scale (0 = completely unresponsive, 100 = no deficit). Once enrolled, all participants received supportive care including low-dose heparin (10,000 units divided into two doses daily), nursing care, rehabilitation, speech therapy and occupational therapy. Those allocated to HBOT received 100% oxygen (in a monoplace chamber at 2.5 ATA daily for 40 minutes for 10 days), while controls received a sham therapy (at 2.5 ATA) breathing air on the same schedule. Outcomes included mortality and changes in three healthcare scales (acute assessment scale: Orgogozo (100 to 0), Trouillas (0 to 10) and functional assessment scale: Rankin Scale) that were used to assess neurological outcome at six months and one year.

Anderson 1991 enrolled 39 non-pregnant participants, sex distribution not given and aged between 20 and 90 years, presenting with a neurological deficit and a score of more than 20 on a scale devised for this trial (0 = no deficit, 100 = completely unresponsive). The deficit was presumed to be due to ischaemic cerebral infarction in the brain region perfused by one carotid artery and occurring during the preceding two weeks. Once enrolled, all participants received standard care in a neurological intensive care and Vitamin A 400 mg daily. Those randomised to the HBOT arm received 100% oxygen (for 60 minutes at 1.5 ATA) every eight hours to a total of 15 sessions while those in the control arm received a sham treatment breathing air (at 1.5 ATA) on the same schedule. Changes in the graded neurological examination used on admission were used to assess neurological outcome at day five, week six and one year. Infarct volume was estimated by CT at four months and deaths were recorded.

Methodological quality

In general, study quality was assessed as fair to high with regard to methodology but all trials were small and had low power to detect useful clinical differences between groups.

- Randomisation
- Randomisation procedures were described by Rusyniak 2003 (sealed envelopes) but not in the other two trials. Allocation concealment was adequately described by Rusyniak 2003while in the other two reports it was not clear that the investigators were unable to predict the prospective group to which a participant would be allocated.

- Participant baseline characteristics
- All trials enrolled participants with clinical evidence of neurological deficit attributable to ischaemic stroke and lasting more than 24 hours. Only Rusyniak 2003 specifically excluded haemorrhagic stroke with CT prior to enrolment. Rusyniak 2003 and Nighoghossian 1995 enrolled participants within 24 hours of the cerebral event; while Anderson 1991 accepted participants up to two weeks following the event. The extent and severity of deficit on enrolment was poorly described and difficult to compare

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across trials given that all three used different neurological and health status scales to establish baseline status. Nighoghossian 1995 and Anderson 1991 specified a clinical appearance of deficit in an area supplied by one internal carotid artery: Anderson 1991 specified the anterior cerebral artery territory, Nighoghossian 1995 the anterior or middle cerebral territory; while Rusyniak 2003 did not specify the area. All trials enrolled both male and female adults. In total, 41 participants (21%) were female.

- Blinding
- All trials utilised a sham therapy in order to mask participants to HBOT. Rusyniak 2003 and Anderson 1991 also blinded the investigators; Anderson 1991 also specified outcome assessor blinding. No author formally tested the success of their blinding strategy.

- Participants lost to follow up
- Nighoghossian 1995 reported a total of seven participants who were withdrawn from therapy (control group: four, all because of worsening neurological status with one dead at six-month follow up; HBOT group: three, one with worsening of neurological state, one myocardial infarction and one claustrophobia). Anderson 1991 lost a total of 12 participants to follow up at six months (control group: five, two deaths, two unavailable and one refusal; HBOT group: seven, two deaths, one unavailable, three refusals and one suffered a second stroke), while Rusyniak 2003 lost seven participants to final follow up (control group: six, two dead, four not explained; HBOT group: one dead). No comparisons of baseline characteristics between those lost to follow up and those remaining in the study were made. All trials reported the fate of all enrolled participants with respect to binary outcomes so the planned sensitivity analyses for missing data were not required.

- Intention-to-treat analysis
- Rusyniak 2003 and Nighoghossian 1995 made intention-to-treat analyses as they reported inclusion of those lost to follow up or not completing the allocated therapy. For mortality, Anderson 1991 also used intention to treat, however, it is not clear if this approach was used for other outcomes.

Results

Data from the three studies could be pooled for only a limited number of clinically important outcomes. For the majority of outcomes we have been limited to a description of outcomes reported individually for each study.

- Primary outcomes
- Death at three to six months (longer-term outcome) (comparison 01, outcome 01)
- Data were available for all three trials, involving 106 participants. There were no significant differences in mortality (three deaths (6%) in those receiving HBOT versus five (10%) with sham therapy). The relative risk (RR) of dying after receiving HBOT was 0.61, 95% CI 0.17 to 2.2, P = 0.45. There was no indication of significant heterogeneity between trials (I2 = 0%). No participants were lost to follow up for this outcome.

- Severe functional disability (comparison 02)
- No trial presented data for this outcome.

- Secondary outcomes
- Functional scales scores (comparison 03)
- Mean neurological assessment score early (day five) (comparison 03, outcome 01)
- Only Anderson 1991 reported this outcome. The mean score was lower (better outcome) in the control group (38.5 versus 43.8: MD 5.3 points, 95% CI -7.5 to 18.1, P value 0.42).

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- Mean neurological assessment score at medium term (week six) (comparison 03, outcome 02)
- Only Anderson 1991 reported this outcome. The mean score was lower (better outcome) in the control group (28.3 versus 38.5: MD 10.2 points, 95% CI -8.5 to 28.9, P value 0.28).

- Mean neurological assessment score at longer term (one year) (comparison 03, outcome 03)
- Only Anderson 1991 reported this outcome. The mean score was lower (better outcome) in the control group (25.8 versus 31.4: MD 5.6 points, 95% CI -15.1 to 26.2, P value 0.59).

- Mean Orgogozo Scale at longer term (six months) (comparison 03, outcome 04)
- Only Nighoghossian 1995 reported this outcome. The mean score was higher (better outcome) in the HBOT group (72.9 versus 54.7: MD 18.2 points, 95% CI -5.2 to 41.6, P value 0.13).

- Mean Orgogozo Scale at longer term (one year) (comparison 03, outcome 05)
- Only Nighoghossian 1995 reported this outcome. The mean score was higher (better outcome) in the HBOT group (78.2 versus 50.3: MD 27.9 points, 95 %CI 4.0 to 51.8, P value 0.02).

- Mean Trouillas Disability Scale at longer term (six months) (comparison 03, outcome 06)
- Only Nighoghossian 1995 reported this outcome. The mean score was lower (better outcome) in the HBOT group (4.6 versus 6.1: MD 1.5 points, 95% CI -1.2 to 4.2, P value 0.27).

- Mean Trouillas Disability Scale at longer term (one year) (comparison 03, outcome 07)
- Only Nighoghossian 1995 reported this outcome. The mean score was lower (better outcome) in the HBOT group (4.1 versus 6.3: MD 2.2 points, 95% CI 0.15 to 4.3, P value 0.04).

- Mean Modified Rankin Functional Assessment Scale at longer term (six months) (comparison 03, outcome 08)
- Only Nighoghossian 1995 reported this outcome. The mean score was lower (better outcome) in the HBOT group (2.6 versus 3.2: MD 0.6 points, 95% CI -0.18 to 1.4, P value 0.13).

- Mean Modified Rankin Functional Assessment Scale at longer term (one year) (comparison 03, outcome 09)
- Only Nighoghossian 1995 reported this outcome. The mean score was lower (better outcome) in the HBOT group (2.4 versus 3.0: MD 0.6 points, 95% CI -0.18 to 1.4, P value 0.13).

- Deemed to have achieved a good outcome (comparison 04, outcomes 01 to 04)
- Rusyniak 2003 reported the number of participants achieving a pre-defined 'good outcome' using four different outcome scales. Differences are reported below.
- NIHSS zero or improved four points at early outcome (24 hours) (comparison 04, outcome 01)
- Three participants in the HBOT group achieved this outcome versus five in the control group (RR 1.8, 95% CI 0.5 to 6.2, P value 0.37 for a good outcome with control therapy).

- Rankin Score less than two at medium term (90 days) (comparison 04, outcome 02)

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- Five participants in the HBOT group achieved this outcome versus nine in the control group (RR 1.9, 95% CI 0.8 to 4.5, P value 0.14 for a good outcome with control therapy).

- Glasgow Outcome Score of five at medium term (90 days) (comparison 04, outcome 03)
- Six participants in the HBOT group achieved this outcome versus ten in the control group (RR 1.8, 95% CI 0.8 to 3.7, P value 0.13 for a good outcome with control therapy).

- NIHSS score less than two at medium term (90 days) (comparison 04, outcome 04)
- Five participants in the HBOT group achieved this outcome versus eight in the control group (RR 1.7, 95% CI 0.7 to 4.1, P value 0.24 for a good outcome with control therapy).

- Activities of daily living (comparison 05)
- Barthel Index of 95 or 100 at medium term (90 days) (comparison 05, outcome 01)
- Only Rusyniak 2003 reported the number of participants with this outcome. Eight participants in the HBOT group achieved this score versus nine in the control group (RR 0.8, 95% CI 0.43 to 1.6, P value 0.6 for a good outcome with HBOT).

- Mean infarct volume (comparison 06)
- Mean infarct volume at longer term (four months) (comparison 06, outcome 01)
- Only Anderson 1991 reported this outcome. The mean infarct volume was smaller in the control group (29.0 cm3 versus 49.2 cm3) but not significantly so (MD 20.2 cm3, 95% CI -13.4 to 53.8, P value 0.24).

- Adverse effects of treatment (comparison 07)
- Ear barotrauma during therapy (comparison 07, outcome 01)
- Only Rusyniak 2003 reported on this outcome. One participant in the HBOT group suffered significant ear pain versus none in the control group (RR 2.8, 95% CI 0.1 to 64.9, P value 0.51).

Claustrophobia and related discomfiture was a significant problem in the monoplace vessels used in all trials for both arms. The severity of these problems varied across studies and was differentially reported. Anderson 1991 reported 15 participants (39%) who could not complete scheduled therapy, while Rusyniak 2003 did not withdraw any participants from therapy. This is likely to reflect the single-treatment design of the Rusyniak 2003 study on the one hand and the very intensive schedule planned by Anderson 1991 on the other.

Discussion

This review has included data from three trials. We believe these represent all randomised trials in this area, both published and unpublished, at the time of searching the databases. We found no convincing evidence that HBOT improves outcomes when applied during the acute presentation of ischaemic stroke. Pooled data from all trials did not suggest any significant benefit in mortality in the six months following presentation. There was some indication from one trial (Nighoghossian 1995) for improvement in one disability scale (Trouillas) and one clinical descriptive scale (Orgogozo). These improvements were not reflected in other trials or functional scales, and were present at one year but not six months after therapy was completed.

Only three trials with 106 participants were available for evaluation using our planned comparisons and meta-analysis was not appropriate or possible for most outcomes. Another major problem for this review was the multiple outcome scales used to assess functional ability and clinical severity across the trials. No scale was used and reported by more than one of these trials, making pooling of data for analysis impossible. Further, the analysis of these ordinal scales to produce mean scores for group comparisons may not be appropriate. This is

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particularly true of the Rankin and Trouillas scales, given their limited range of scores from zero to 10, but none of the reports produced plots of the experimental data for any of these scales in order to justify the use of such parametric tests. The usefulness of such scales to estimate outcome at all has been questioned (Van Gijn 1992). There are distinct disadvantages in many scales used, including the tendency to equate multiple small deficits with a few major deficits and a poor ability to estimate stroke deficit at the extremes of severity (Orgogozo 1998). One review concluded that of nine stroke scales tested the NIHSS was one of the three most reliable, while the Barthel Index was the most reliable disability scale (D'Olhaberriague 1996). Other problems in assessing data include failure to report on primary functional outcomes, the variability in time interval between stroke event and enrolment and the variable dose of HBOT. These problems demand a cautious interpretation of the results.

These trials were published over a 12-year period, up to 2003. We had planned to perform subgroup analyses with respect to time elapsed between stroke and institution of HBOT, dose of oxygen received and length of treatment course. None of these analyses were appropriate given the small number of pooled analyses and the relatively uniform lack of effect shown in individual studies. In the two pooled analyses that were possible, heterogeneity was not an issue (I2 = 0%). There was a wide range of oxygen dose across these studies. Rusyniak 2003 gave one session only; Anderson 1991 gave an intensive regimen of eight hourly exposures for three days; while Nighoghossian gave daily therapy for 10 days. Both Nighoghossian 1995 and Anderson 1991 applied a modest hyperbaric pressure of 1.5 ATA versus the 2.5 ATA applied by Rusyniak 2003 in his single therapy session. This review does not permit firm conclusions with regard to oxygen dosing schedule, but we note that the only generally positive trends were those reported by Nighoghossian 1995.

Pooled data analysis for clinical outcomes of interest could be performed with respect to only one primary analysis: mortality. Although fewer participants had died in the HBOT group at last reported follow up the numbers are very small and death of only one or two further participants of those lost to follow up might reverse this trend. Among the results of the individual studies there were non-significant trends in favour of HBOT for three neurological status scales (Orgogozo, Trouillas and modified Rankin) at six months, and for the modified Rankin Scale at one year in Nighoghossian 1995, while all other outcomes listed above showed a trend towards better outcomes in the sham control group.

HBOT is regarded as a relatively benign intervention. There are few possible major adverse effects (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire), and none of the included studies reported any such events. There are a number of more minor complications that may occur commonly but which were similarly not reported in the included studies. Visual disturbance, usually 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). While the great majority of patients experiencing visual distubances recover spontaneously over a period of days to weeks, a small proportion of patients continue to require correction to restore sight to pre-treatment levels. 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 and is largely surrounded by bone and the sensitive tympanic membrane. It 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. Less commonly, HBOT may be associated with acute neurological toxicity manifesting as seizure.

While we have made every effort to locate further unpublished data it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting. With regard to long-term outcomes following HBOT and any effect on the quality of life for these patients, we have located no relevant data.

Reviewers' conclusions

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Implications for practice

We found very little clinical data on which to base recommendations. In the three small trials published, there is insufficient evidence to suggest that HBOT significantly affects outcome following acute ischaemic stroke. The use of HBOT in stroke patients cannot be justified by this review.

Implications for research

Given the small number of participants in the trials included, we cannot be certain that a benefit from HBOT has been excluded. While there is a case for further trials such investigations would need to be carefully planned. More information may be useful on a subset of disease severity and the timing of therapy. 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 clinically important 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 those listed in this review;
- careful elucidation of any adverse effects;
- the cost-utility of the therapy.

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Potential conflict of interest

None known. Dr. Bennett is a hyperbaric physician who does not routinely treat stroke.

Tables

Characteristics of included studies

Study	Anderson 1991
Methods	RCT stratified for disease severity. Allocation concealment not clear, method of randomisation not stated. Patient, investigator, treating team and outcome assessors unaware of group. Powered to find a 30% relative improvement in HBOT group with 45 subjects in each group (stopped early, no clear stopping rule applied).
Participants	39 adults with onset of ischaemic cerebral infarction within two weeks and greater than 20 severity score out of 100 on a graded neurological

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	scale designed to test for deficits in the areas supplied by the internal carotid. No contraindications to HBOT or unstable medical conditions.
Interventions	Both groups received standard measures in neurological intensive care. Vitamin E 400 mg eight hourly during compression period.Control: Sham therapy on air at 1.5 ATA for 60 minutes within six hours of enrollment and then every eight hours to a total of 15 exposures (over 5 days).HBOT: 100% oxygen at 1.5 ATA on the same schedule as above.
Outcomes	Graded neurological examination on a 0 to 100 scale as at admission. Repeated at day 5, week 6, year 1.Infarct volume on CT scan at four months.
Notes	Schulz rating: randomisation B; allocation concealment B; selection bias B; blinding A.
Allocation concealment	B
Study	Nighoghossian 1995
Methods	RCT with allocation concealment and blinding unclear. Participants must have been blinded because sham therapy was employed.
Participants	34 adults (21 men) with ischaemic cerebral infarction confirmed with CT and presenting within 24 hours of onset of neurological deficit suggestive of middle cerebral artery occlusion and scoring less than 80 on the Orgogozo scale (100 is normal). No contraindications to HBOT, old infarct, congestive heart failure or uncontrolled hypertension. 17 allocated to each arm.
Interventions	Both groups received standard measures including low dose heparin and supportive care. Control: Sham therapy on air at 1.2 ATA daily for 40 minutes for 10 days.HBOT: 100% oxygen at 1.5 ATA on the same schedule as above.Subjects were withdrawn from protocol if they deteriorated to coma or did not tolerate therapy (7 total - 4 sham, 3 HBOT).
Outcomes	Graded neurological examination on three scales: Orgogozo (100 to 0), Trouillas (0 to 10) and Rankin Disability Scale. Orgogozo was calculated at baseline, while all were calculated at six months and one year.Adverse effects of HBOT.
Notes	Schulz rating: randomisation B; allocation concealment B; selection bias B; blinding C.
Allocation concealment	B
Study	Rusyniak 2003
Methods	RCT stratified by time from onset to enrolment (0 to 12 hours and 12 to 24 hours) with allocation concealment by sealed envelopes and blinding of subjects and investigators (including outcome assessors).
Participants	33 adults with presumed ischaemic cerebral infarction with no evidence of cerebral bleed on CT and presenting within 24 hours of onset of neurological deficit. All subjects scored less than 23 points on the

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	NIHSS. No contraindications to HBOT, previous infarct within three months or evidence of potentially serious cardiac arrhythmia.
Interventions	Control: Sham therapy on air at 1.14 ATA for 60 minutes.HBOT: 100% oxygen at 2.5 ATA on the same schedule as above.
Outcomes	NIHSS measured at 24 hours and 90 days. Barthel Index , Rankin Scale (modified) and Glasgow Outcome Scale calculated at 90 days.Mortality.Adverse effects of HBOT.
Notes	Schulz rating: randomisation A; allocation concealment A; selection bias B; blinding A.
Allocation concealment	A

ATA: atmosphere absolute
CT: computerised tomography
HBOT: hyperbaric oxygen therapy
NIHSS: National Institutes of Health Stroke Scale
RCT: randomised controlled trial

Characteristics of excluded studies

Study	Reason for exclusion
Belokurov 1988	Review only, not focused on stroke.
Efuni 1987	Not a RCT, non-random controls.
Elinsky 1984	Not a RCT, non-random controls.
Gusev 1990	Not a RCT, case series only.
Holbach 1979	RCT, all patients received HBOT.
Kaasik 1988	Not a RCT.
Sarno 1972a	Not a RCT, case series only.

HBOT: hyperbaric oxygen therapy
RCT: randomised controlled trial

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Rusyniak 2003 *{published data only}*

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* *indicates the major publication for the study*

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Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

01 Mortality				
Outcome title	No. of	No. of	Statistical method	Effect size

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	studies	participants		
01 Death at three to six months	3	106	Relative Risk (Fixed) 95% CI	0.61 [0.17, 2.20]

03 Functional scales

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean neurological score at day five	1	38	Weighted Mean Difference (Fixed) 95% CI	5.30 [-7.47, 18.07]
02 Mean neurological score at week six	1	32	Weighted Mean Difference (Fixed) 95% CI	10.20 [-8.48, 28.88]
03 Mean neurological score at one year	1	25	Weighted Mean Difference (Fixed) 95% CI	5.60 [-15.02, 26.22]
04 Mean Orgogozo score at six months	1	27	Weighted Mean Difference (Fixed) 95% CI	-18.20 [-41.62, 5.22]
05 Mean Orgogozo score at one year	1	27	Weighted Mean Difference (Fixed) 95% CI	-27.90 [-51.79, -4.01]
06 Mean Trouillas score at six months	1	20	Weighted Mean Difference (Fixed) 95% CI	-1.50 [-4.16, 1.16]
07 Mean Trouillas score at one year	1	27	Weighted Mean Difference (Fixed) 95% CI	-2.20 [-4.25, -0.15]
08 Mean Rankin score at six months	1	27	Weighted Mean Difference (Fixed) 95% CI	-0.60 [-1.38, 0.18]
09 Mean Rankin score at one year	1	27	Weighted Mean Difference (Fixed) 95% CI	-0.60 [-1.38, 0.18]

04 Deemed to have a good outcome

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 NIHSS zero or improved four points at 24 hours	1	33	Relative Risk (Fixed) 95% CI	1.77 [0.50, 6.23]
02 Modified Rankin Score less than two at 90 days	1	33	Relative Risk (Fixed) 95% CI	1.91 [0.81, 4.49]
03 Glasgow Outcome Score of five	1	33	Relative Risk (Fixed) 95% CI	1.77 [0.84, 3.74]
04 NIHSS less than two	1	33	Relative Risk	1.70 [0.70,

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			(Fixed) 95% CI	4.12]

05 Activities of daily living

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Barthel Index 95 or 100 at 90 days	1	33	Relative Risk (Fixed) 95% CI	1.20 [0.62, 2.32]

06 Mean volume of infarct on CT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean volume of infarct at four months	1	27	Weighted Mean Difference (Fixed) 95% CI	20.20 [-13.37, 53.77]

07 Adverse effects of therapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Ear pain	1	33	Relative Risk (Fixed) 95% CI	2.83 [0.12, 64.89]

Cover sheet

Hyperbaric oxygen therapy for acute ischaemic stroke

Reviewer(s)	Bennett MH, Wasiak J, Schnabel A, Kranke P, French C
Contribution of Reviewer(s)	MH Bennett: conception of review, background, critical appraisal, hyperbaric medicine content expert, statistical analysis, co-author for description of studies and discussion. J Wasiak: search strategy and execution, critical appraisal, systematic review expert, co-author for description of studies and discussion. C French: background to review, neurology context expert, critical appraisal. P Kranke: critical appraisal, hyperbaric content expert, text editor. A Schnabel: protocol development, critical appraisal and text editor.
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Date reviewers' conclusions section amended	Information not supplied by reviewer
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Synopsis

Little evidence that stroke patients benefit from hyperbaric oxygen therapy.

Hyperbaric oxygen therapy (HBOT) is a treatment designed to increase the supply of oxygen to the part of the brain affected by stroke and reduce the extent of irreversible damage. HBOT involves people breathing pure oxygen in a specially designed chamber (such as those used for deep sea divers with the bends). Our review found only three randomised trials with a limited number of participants. Too few patients have been studied to say whether or not HBOT decreases the chance of dying and only one trial suggested any improvement in the ability to do everyday tasks. Overall, there is currently little evidence to support the use of HBOT for stroke patients.

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