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## Hyperbaric oxygen therapy for acute ischaemic stroke (Review)

Bennett MH, Weibel S, Wasiak J, Schnabel A, French C, Kranke P

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[Intervention Review]

# Hyperbaric oxygen therapy for acute ischaemic stroke

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## ABSTRACT

### Background

Most cases of stroke are caused by impairment of blood flow to the brain (ischaemia), which results in a reduction in available oxygen 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 available oxygen, and it may further improve outcomes by reducing brain swelling. Some centres are using HBOT routinely to treat people with stroke. This is an update of a Cochrane Review first published in 2005.

### Objectives

To assess the effectiveness and safety of adjunctive HBOT in the treatment of people with acute ischaemic stroke.

### Search methods

We searched the Cochrane Stroke Group Trials Register (last searched April 2014), the Cochrane Central Register of Controlled Trials (CENTRAL) (April 2014), MEDLINE (1966 to April 2014), EMBASE (1980 to April 2014), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to April 2014), the Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTIHM) (searched April 2014) and the reference lists of articles. We handsearched relevant publications and contacted researchers to identify additional published and unpublished studies.

### Selection criteria

Randomised controlled trials (RCTs) that compared the effects of adjunctive HBOT versus those of no HBOT (no treatment or sham).

### Data collection and analysis

Three review authors independently extracted data, assessed each trial for internal validity and resolved differences by discussion.

### Main results

We included 11 RCTs involving 705 participants. The methodological quality of the trials varied. We could pool data only for case fatalities. No significant differences were noted in the case fatality rate at six months in those receiving HBOT compared with the control group (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.34 to 2.75, P value 0.96). Four of 14 scale measures of disability and functional performance indicated improvement following HBOT, for example, the mean Trouillas Disability Scale score was lower with HBOT (mean difference (MD) 2.2 point reduction with HBOT, 95% CI 0.15 to 4.3, P value 0.04), and the mean Orgogozo Scale score was higher (MD 27.9 points, 95% CI 4.0 to 51.8, P value 0.02).

## Authors' conclusions

We found no good evidence to show that HBOT improves clinical outcomes when applied during acute presentation of ischaemic stroke. Although evidence from the 11 RCTs is insufficient to provide clear guidelines for practice, the possibility of clinical benefit has not been excluded. Further research is required to better define the role of HBOT in this condition.

## PLAIN LANGUAGE SUMMARY

### Hyperbaric oxygen therapy for treating people with acute ischaemic stroke

#### Question

We wanted to compare the safety and effectiveness of hyperbaric oxygen therapy (HBOT) versus no HBOT (either no treatment or an ineffective intervention designed to mimic the true treatment) for treating people who had suffered an acute ischaemic stroke.

#### Background

Hyperbaric oxygen therapy (HBOT) is a treatment designed to increase the supply of oxygen to the part of the brain affected by stroke and to 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) for a period of about an hour and a half each day for 10 to 20 days.

#### Study characteristics

We identified 11 studies, involving 705 participants, up to April 2014. All studies included adult participants (41% female) who had suffered an acute stroke within the past two weeks, although most studies enrolled participants within three days of the stroke. All trials evaluated the addition of HBOT to standard practice for study participants. Most trials reported the number of deaths and some measure of functional ability, although the actual measures used varied considerably, making comparisons between trials difficult. Follow-up periods varied from 90 days to one year.

#### Key results

Too few patients have been studied to say whether HBOT decreases the chance of dying, and only three trials have suggested improvement in the ability to do everyday tasks. Overall, little evidence is currently available to support the use of HBOT for people with stroke.

#### Quality of the evidence

In general, the quality of the evidence was moderate, given the small numbers of participants and the many different instruments used to estimate the quality of life and the functional ability of participants. The methodology used in many of these trials was poorly described, making a good estimate of the reliability of the evidence difficult. We could pool data only for the chance of dying after the stroke, and although no evidence suggested that HBOT reduced the chance of death following a stroke, the confidence we have in this result is relatively low. We have not excluded the possibility that HBOT may be harmful or beneficial.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Should hyperbaric oxygen therapy be used as an adjuvant therapy to routine therapy and rehabilitation for acute ischaemic stroke?

#### Should hyperbaric oxygen therapy be used as an adjuvant therapy to routine therapy and rehabilitation for acute ischaemic stroke?

**Patient or population:** people with acute ischaemic stroke  
**Settings:** hospital inpatients  
**Intervention:** hyperbaric oxygen therapy used as adjuvant therapy to  
**Comparison:** routine therapy and rehabilitation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine therapy and rehabilitation	Hyperbaric oxygen therapy used as adjuvant therapy				
<b>Death</b>  Follow-up: 3 to 6 months	<b>Low-risk population</b>		<b>RR 0.97</b> (0.34 to 2.75)	144 (4 studies)	⊕⊕⊕⊖ <b>moderate<sup>a</sup></b>	
	<b>20 per 1000</b>	<b>19 per 1000</b> (7 to 55)				
	<b>Medium-risk population</b>					
	<b>80 per 1000</b>	<b>78 per 1000</b> (27 to 220)				
	<b>High-risk population</b>					
	<b>120 per 1000</b>	<b>116 per 1000</b> (41 to 330)				

\*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>a</sup> Small trials, with most not blinded to allocation.

## BACKGROUND

### Description of the condition

Stroke may be defined as a sudden neurological deficit 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 the 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 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 people the symptoms worsen gradually or in a step-wise fashion over a matter of hours or days (Robertson 1989). This latter observation suggests that 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).

### Description of the intervention

Hyperbaric oxygen therapy (HBOT) is an adjunctive therapy that has been proposed for the treatment of people with 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 pressure within that vessel and administering 100% oxygen for respiration. In this way, it is possible to deliver 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.

### How the intervention might work

Potential benefits of HBOT include reversal of hypoxia through increased oxygen delivery and reduction of cerebral oedema (Hills 1999; Sukoff 1982), as well as several specific effects of hyperoxia, which include decreased lipid peroxidation, inhibition of leucocyte 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, which 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 people with stroke, 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.

### Why it is important to do this review

Despite 40 years of interest in the delivery of HBOT for people with stroke, little comparative evidence of effectiveness can be found. Most reports have described single or multiple cases, and the largest study includes a series of 122 cases reported in 1980 (Neubauer 1980). A review of these studies revealed that more than half of cases improved clinically or electrophysiologically with HBOT and concluded that a case could be made for setting up controlled studies (Nighoghossian 1997).

This is an update of a Cochrane review first published in 2005.

## OBJECTIVES

To assess the effectiveness and safety of adjunctive HBOT in the treatment of people with acute ischaemic stroke.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included all randomised controlled trials (RCTs) that compared the effects of adjunctive HBOT versus those of 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 for which haemorrhage had been excluded by CT or magnetic resonance imaging (MRI) within 14 days of enrolment in the trial.

#### Types of interventions

Trials comparing 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 in the meta-analysis if they reported any of the following outcome measures. Because of variations in clinical practice, we divided timing and recording of outcomes 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). Several assessment scales were used to quantify trial outcomes. We have taken information concerning these scales from the Internet Stroke Centre Stroke Trials Directory at <http://www.strokecenter.org/trials/scales/index.htm>.

### Primary outcomes

1. Case fatality rate.
2. Severe functional disability rate (or death), defined as 'drowsy/stuporous/unconscious or unable to feed/dress independently.' Care was taken to ensure that death was included as a bad outcome when data were extracted.

### Secondary outcomes

1. Functional status scale scores (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 (ADLs) (e.g. the Barthel Index).
4. CT or MRI estimate of infarct size or volume.
5. Adverse events following HBOT, such as proportion of participants with visual disturbance (short and long term), barotrauma (aural, sinus, pulmonary short and long term) and oxygen toxicity (short term); other recorded adverse effects were reported and discussed.

### Search methods for identification of studies

See the 'Specialized register' section in the [Cochrane Stroke Group](#) module.

### Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor on 3 April 2014. In addition, we searched MEDLINE (1966 to April 2014; [Appendix 1](#)), EMBASE (1980 to April 2014; [Appendix 2](#)) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to April 2014; [Appendix 3](#)), as well as the Cochrane Central Register of Controlled Trials (CENTRAL) (8 April 2014; [Appendix 4](#)). We adapted the MEDLINE search strategy for the other databases. We applied no language restrictions. We also searched the Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTIHM) (from inception to April 2014) ([Bennett 2004](#)). The DORCTIHM database was compiled through an unfocused search of PubMed using 'hyperbaric oxygenation' as a medical subject heading (MeSH) term, handsearching of primarily hyperbaric journals (see below) since first publication and checking of references in identified RCTs. This site is now interactive and receives citations for formal review from healthcare professionals in the field.

### Searching other resources

1. We searched the reference lists of articles and contacted researchers in an effort to identify additional published and unpublished studies.
2. We handsearched the following relevant publications.
  - a. Hyperbaric textbooks ([Jain 1999](#); [Jain 2009](#); [Kindwall 1999](#); [Mathieu 2006](#); [Oriani 1996](#)).
  - b. Journals (*Undersea and Hyperbaric Medicine* 1992 to 2014, *Hyperbaric Medicine Review* 1986 to 1992, *South Pacific Underwater Medicine Society (SPUMS) Journal* 1973 to 2007, *European Journal of Hyperbaric Medicine* 1998 to 2007, *Diving*

*and Hyperbaric Medicine* 2007 to 2014 and *Aviation, Space and Environmental Medicine Journal* 1980 to 2014).

- c. Conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published from 1980 to 2014.

### Data collection and analysis

#### Trial identification

Three review authors (MB, JW and PK) scanned records identified through the electronic searches and excluded obviously irrelevant studies. Two review authors (MB and AS) assessed the remaining records and retrieved the full-text articles of all potentially relevant studies. From these, three review authors (MB, AS and PK) selected studies for inclusion based on the criteria described previously. In all instances, review authors resolved differences of opinion by discussion.

#### Data extraction

Three review authors (MB, AS and CF) independently extracted data from the studies using standardised forms developed for this review. We contacted the authors of primary studies to request further information when data were missing or incomplete. Review authors resolved all differences by discussion.

#### Quality assessment

We assessed study quality using the 'Risk of bias' tables for each individual study, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)); the results are presented both descriptively and graphically.

#### Analyses

We used a fixed-effect model when no evidence of significant heterogeneity between studies was found and planned to use a random-effects model when such heterogeneity was likely ([DerSimonian 1986](#)). We considered the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We assessed statistical heterogeneity using the  $I^2$  statistic. We planned to explore heterogeneity and to perform subgroup analyses if appropriate.

For proportions (dichotomous outcomes), we used risk ratio (RR). We converted continuous data to mean differences (MDs) using the inverse variance method and calculated an overall MD. We planned to test publication bias using funnel plots; however, this was not appropriate given the small number of studies found.

We planned to perform subgroup analysis by calculating the RR or MD in each subgroup and examining 95% confidence intervals (CIs). Non-overlap in intervals would have been taken to indicate a statistically significant difference between subgroups; however, subgroup analysis was not appropriate given the available data.

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

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



### Missing data

We had planned to employ sensitivity analyses by using different approaches to imputing missing data. However, no binary outcomes involved incomplete data, and this analysis was not required.

### Study quality

If appropriate, we had 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 were found, we planned to consider subgroup analysis based on the following.

1. Time elapsed between stroke and institution of HBOT.
2. 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 60 minutes or longer) and length of treatment course (fewer than five sessions versus five or more sessions).
3. Nature of comparative treatment modalities.

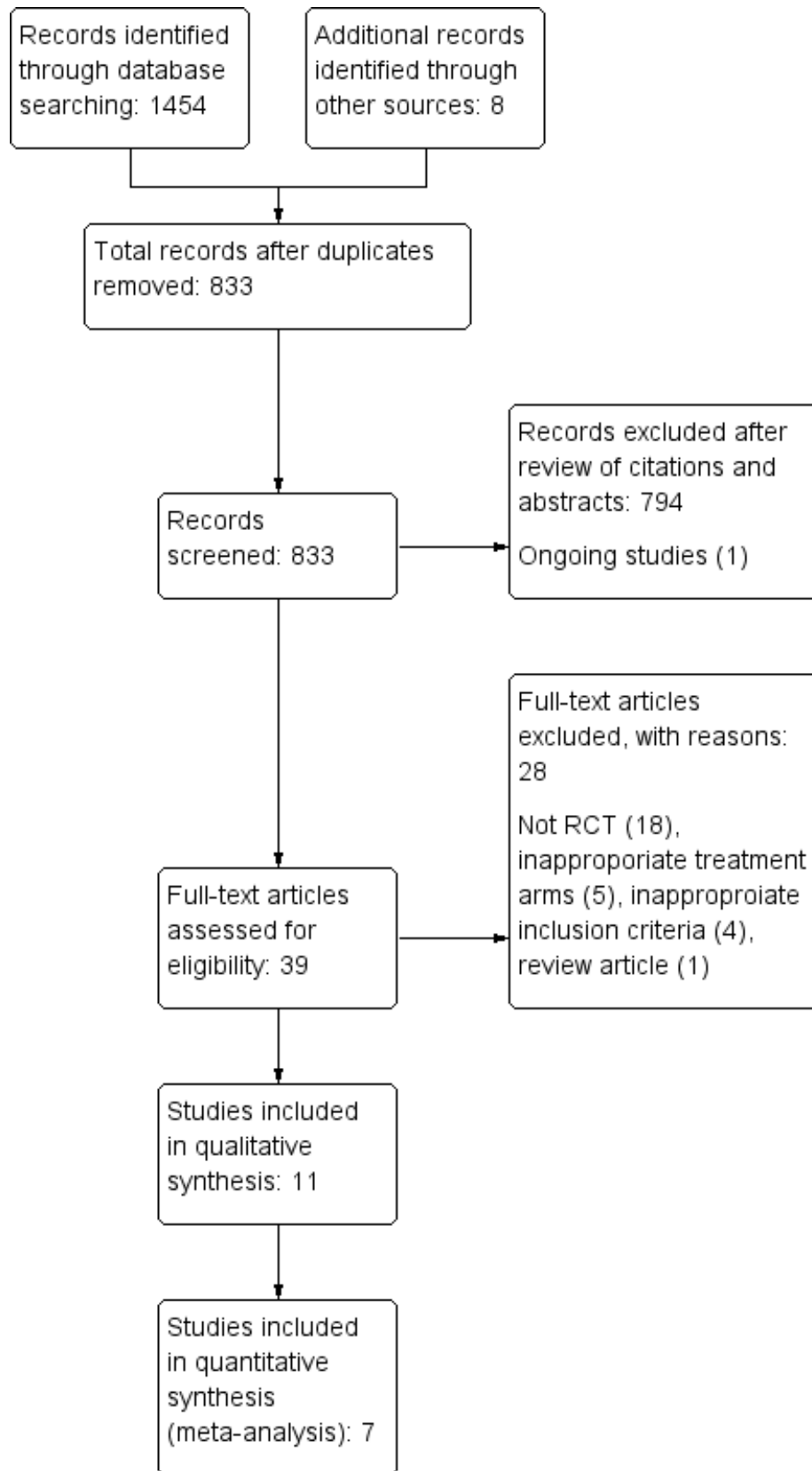
4. Volume of cerebral infarction as measured by baseline presentation of CT imaging.

## RESULTS

### Description of studies

We identified a total of 962 references in 2004, a further 104 by September 2008 and a further 396 by April 2014, yielding a total of 1462 citations. Following elimination of duplicates, independent scrutiny of the titles and abstracts revealed 40 potentially relevant articles. One was an ongoing trial first announced in 2008 ([Michalski 2008](#)), but our attempts to contact the study authors were unsuccessful, and this trial may have been abandoned. Following review of the full text of the remaining 39 articles, we excluded 18 further trials because they were not RCTs, five because they gave inappropriate treatment, four because they included inappropriate participants (with long-standing or haemorrhagic stroke) and one review article (see [Characteristics of excluded studies](#) and [Figure 1](#)). The remaining 11 randomised trials formed the basis of this review and are described below. Seven trials are now included in the quantitative review.

**Figure 1. Study flow diagram.**



Between the previous search in September 2008 and the most recent search in April 2014, we found 396 new citations, of which only one was a new trial, which contributed 38 further participants to the quantitative analysis (Imai 2006). In this review, we also included four relevant trials that did not report on our outcomes of interest and so did not contribute to the quantitative review. Together these trials enrolled a total of 334 participants.

In total, the 11 included trials enrolled 705 participants (361 into trials contributing to the quantitative review and 344 into trials contributing to the qualitative review only).

**Anderson 1991** enrolled 39 non-pregnant participants (sex distribution was not given) between 20 and 90 years of age, presenting with a neurological deficit and score greater 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 to have occurred during the preceding two weeks. Once enrolled, all participants received standard care in a neurological intensive care unit and 400 mg of vitamin A daily. Those randomly assigned to the HBOT arm received 100% oxygen (for 60 minutes at 1.5 ATA) every eight hours to a total of 15 sessions, and those in the control arm received a sham treatment of breathing air (at 1.5 ATA) on the same schedule. Changes in the graded neurological examination performed on admission were used to assess neurological outcomes at day five, week six and year one. Infarct volume was estimated by CT at four months, and deaths were recorded.

**Nighoghossian 1995** enrolled 34 participants (21 men), between 20 and 75 years of age, presenting with a neurological deficit highly suggestive of middle cerebral artery (MCA) occlusion. All participants presented within 24 hours of the cerebral event and with a score 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 1.5 ATA daily for 40 minutes for 10 days), while controls received sham therapy (at 1.2 ATA) of breathing air on the same schedule. Outcomes included case fatality rate and changes on 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 outcomes at six months and at one year.

**Sansone 1997** has been presented only in abstract format. This trial enrolled 17 participants with an average age of 62 years who had presented for therapy within 24 hours of CT scanning, showing a cerebral ischaemic event in the middle or anterior cerebral arterial territory. Study participants included 11 males. The degree of neurological deficit was not clear, although scores were provided in a table. Once enrolled, participants were randomly assigned by a method not stated to receive HBOT (1.5 to 1.8 ATA for 60 minutes daily for 8 to 10 days) or sham treatment of breathing air. A neurological recovery score (0 to 10) was used to assess outcomes at six and 12 months.

**Rusyniak 2003** enrolled 33 participants (including 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 randomly assigned 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 sham treatment (breathing oxygen at 1.14 ATA). Primary outcome measures included percentages of participants with improvement at 24 hours and at 90 days. Secondary measurements included complications of treatment and mortality at 90 days. Outcomes included case fatality rate; adverse effects of treatment and changes in the following: NIHSS score (at 24 hours and at 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).

**Yang 2003** enrolled 80 participants (43 men) with radiological or MRI evidence of ischaemic stroke within 72 hours of the event. These strokes occurred in a range of vascular territories. Participants were randomly assigned to receive HBOT at 2.0 ATA for 80 minutes daily, probably for 20 days, or a standard therapy that may have included a vasodilator, an anticoagulant or a 'nerve cell protectant.' The only outcome measure was a four-point scale from 'cure' to 'no effect' that was measured at 21 days.

**Yang 2004** enrolled 120 participants with radiological or MRI evidence of ischaemic stroke within 72 hours of the event; however 40 of these were randomly assigned to an arm that was not relevant to this review. The strokes were all 'first events,' associated with neurological deficits and during which the patient was conscious and co-operative. Eighty participants were randomly assigned to HBOT at 2.0 ATA for 60 minutes daily for 20 days or to a standard treatment regimen that was not described in detail. Outcomes measured include degree of neurological dysfunction (scale not described), Fugl-Meyer motor assessment score and Barthel Index of activities of daily living. The timing of these assessments was not stated.

**Imai 2006** enrolled 38 adult participants with acute embolic stroke in the MCA territory within 48 hours of the event. Initial diagnosis was determined by neurological signs and was confirmed by MRI. Patients were excluded if they had received fibrinolytic therapy. All participants received standard care plus a free-radical scavenger—edaravone 30 mg intravenously twice daily. In addition, the 19 participants in the HBOT group received 100% oxygen at 2.0 ATA for 60 minutes daily for 10 days. Reported outcomes included death, unfavourable outcomes by the Modified Rankin Scale (mRS), adverse events and median NIHSS scores—all at 90 days.

#### **Trials included but not contributing to the quantitative review**

**Li 1998** enrolled 86 participants with cerebral infarction (time not stated but described as 'acute') and provided 'routine' therapy with 'Salvia Milirrhiza Co.' to both groups. The 43 participants assigned to the HBOT group received 10 daily treatments at 2 ATA breathing 100% oxygen for 120 minutes. The study authors reported cerebral blood flow, electroencephalography (EEG), haemorrhology and serum superoxide dismutase (SOD) before and after the intervention period but included no outcomes of interest for this review. EEG, cerebral blood flow and serum SOD were reported as improved in the HBOT group versus the control group (P value < 0.01). Haemorrhology was not significantly different.

**Peng 2003** enrolled 60 participants with cerebral infarction within the previous seven days, and 30 were allocated to each arm of the study. All participants received 'standard pharmacological care,' while the HBOT group received 10 daily treatments at 2.3 ATA breathing 100% oxygen for 80 minutes. The study authors reported within-group differences for several markers of free-radical activity, including serum nitric oxide (NO), SOD and monoaldehyde (MDA) but did not directly compare groups. Levels of NO and SOD were significantly increased following HBOT, but not in the control group. Participants in the HBOT group had significantly improved scores on an undefined neurological deficit scale (HBOT  $9 \pm 8$  versus  $15 \pm 9$ ,  $t = -2.176$ ,  $P$  value  $< 0.05$ ). Researchers also reported improved 'clinical efficacy' in the HBOT group (HBOT 87% versus control 63%,  $\chi^2 = 4.356$ ,  $P$  value  $< 0.05$ ).

**Hong 2008** is an abstract only and has not been published in full. This trial enrolled 86 young inpatients with ischaemic stroke, but there are no further details. The cohort was randomised into two groups (method unknown), but the number of participants in each group is not given. One group received 'routine therapy' while the other received 'routine therapy and hyperbaric therapy'. Neither treatment arm was described. The authors reported the 'Nerve Function Deficit Score' (undefined) was improved in 70% in the HBOT group and 42.6% in the control group, that the effectiveness of treatment in the HBOT group was 81.4% compared with 35.9% in the control group, and that the total progress rate was 93% versus

60.5% in favour of the HBOT group. None of these outcomes were defined.

**Zhao 2008** enrolled 112 adults admitted with an acute stroke involving the internal carotid artery territory and confirmed with CT or MRI within 24 hours. They were randomised by a method not described. Sixty-two participants received routine therapy including anticoagulation, antiplatelet aggregation agents, cerebral vasodilators, reduction of intracranial pressure by dehydration, as well as supplementary rehabilitation exercise. Fifty participants received the same routine treatment plus HBOT for 60 minutes daily for 10 days at 2.0 ATA (plus a 30-minute decompression). Serum levels of soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule, soluble E-selectin, and matrix metalloproteinase-9 were significantly increased on admission and decreased over the study period in both groups. The decrease was significantly greater in the HBO group, compared with the routine treatment group ( $P$  value  $< 0.05$  or  $P$  value  $< 0.01$ ).

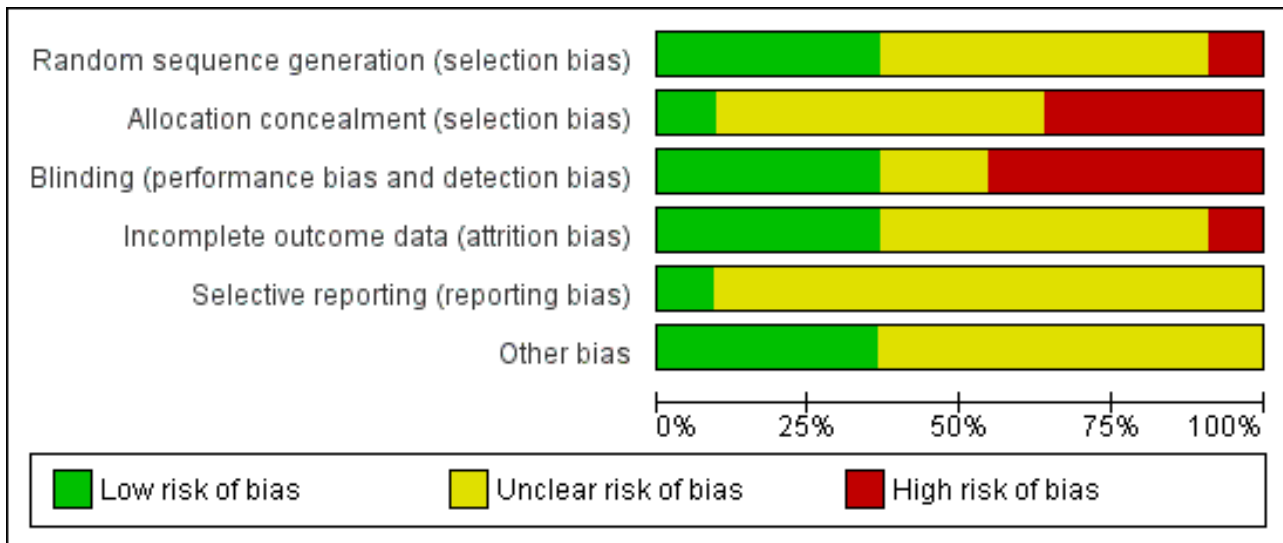
### Risk of bias in included studies

See the [Characteristics of included studies](#) table for further details. These trials varied in methodological quality, and only six provided full reports of completed trials in a peer-reviewed publication. Risk of bias dimensions are presented for each included study in [Figure 2](#) and [Figure 3](#).

**Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Anderson 1991	?	-	+	+	?	?
Hong 2008	?	?	-	?	?	?
Imai 2006	?	?	?	+	?	?
Li 1998	?	?	-	+	?	?
Nighoghossian 1995	?	-	+	+	?	+
Peng 2003	+	?	-	?	?	+
Rusyniak 2003	+	+	+	?	?	+
Sansone 1997	?	?	+	?	?	?
Yang 2003	+	-	-	-	?	?
Yang 2004	+	-	?	?	+	+
Zhao 2008	-	?	-	?	?	?

**Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**



**Randomisation**

Randomisation procedures were described in two trials - [Rusyniak 2003](#) (sealed envelopes) and [Peng 2003](#) (coin toss) - but not in the other nine trials. Allocation concealment was adequately described in [Rusyniak 2003](#), but in the other 10 reports, it was not clear whether 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 longer than 24 hours. Five trials specifically excluded haemorrhagic stroke with CT or MRI evidence before the time of enrolment ([Imai 2006](#); [Rusyniak 2003](#); [Yang 2003](#); [Yang 2004](#); [Zhao 2008](#)). Three trials enrolled participants within 24 hours of the cerebral event ([Rusyniak 2003](#); [Nighoghossian 1995](#); [Sansone 1997](#)), one trial within 48 hours ([Imai 2006](#)), two trials within 72 hours ([Yang 2003](#); [Yang 2004](#)) and one trial within seven days ([Peng 2003](#)), and one trial accepted participants up to two weeks following the event ([Anderson 1991](#)). The extent and severity of deficit on enrolment were poorly described and difficult to compare across trials, given the different neurological and health status scales used to establish baseline status. Three trials specified the clinical appearance of deficits in an area supplied by one internal carotid artery ([Anderson 1991](#); [Nighoghossian 1995](#); [Sansone 1997](#)): Two trials specified the anterior cerebral artery territory ([Anderson 1991](#); [Imai 2006](#)) and two the anterior or middle cerebral territory ([Nighoghossian 1995](#); [Sansone 1997](#)); three studies did not specify the area ([Rusyniak 2003](#); [Yang 2003](#); [Yang 2004](#)). All trials enrolled both male and female adults. In total, 118 participants (41%) were female.

**Blinding**

Four trials utilised sham therapy to mask participants to HBOT ([Anderson 1991](#); [Nighoghossian 1995](#); [Rusyniak 2003](#), [Sansone 1997](#)). Two trials blinded the investigators ([Anderson 1991](#); [Rusyniak 2003](#)); one trial also specified outcome assessor blinding ([Anderson 1991](#)). No study author formally tested the success of the blinding strategy applied.

**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 with myocardial infarction and one with 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 following a second stroke); [Rusyniak 2003](#) lost seven participants to final follow-up (control group: six - two dead, four not explained; HBOT group: one dead). [Yang 2003](#) reported a participant group of 80 but reported demographic and outcome data for only 70 participants—it is not clear whether this was an error or if 10 participants were lost to follow-up. No comparisons of baseline characteristics were made between those lost to follow-up and those remaining in the study.

**Intention-to-treat analysis**

Two trials performed intention-to-treat analyses as they reported inclusion of those lost to follow-up or not completing the allocated therapy ([Nighoghossian 1995](#); [Rusyniak 2003](#)). For mortality, one trial also used intention-to-treat; however, it is not clear if this approach was used for other outcomes ([Anderson 1991](#)).

**Effects of interventions**

See: [Summary of findings for the main comparison Should hyperbaric oxygen therapy be used as an adjuvant therapy to routine therapy and rehabilitation for acute ischaemic stroke?](#)

We could pool data from only seven studies enrolling a total of 361 participants and for a limited number of clinically important outcomes. For most outcomes, we have been limited to a description of outcomes reported individually for each study.



## Primary outcomes

### Comparison 1. Death at three to six months

Data were available for four trials involving 144 participants (45% of the total participants in this review) (Anderson 1991; Imai 2006; Nighoghossian 1995; Rusyniak 2003; ). No significant differences in case fatality rates were noted (six deaths (8%) in those receiving HBOT versus six (8.5%) among those given sham therapy). The risk ratio (RR) of dying after receiving HBOT was 0.97 (95% CI 0.34 to 2.75, P value 0.96). Moderate heterogeneity between trials was indicated ( $I^2 = 34.7\%$ ), which was explained by removal of the single trial testing the combination of HBOT and a free-radical scavenger (edaravone) versus edaravone only. No participants were lost to follow-up for this outcome (Analysis 1.1).

### Comparison 2. No effect of therapy

Only Yang 2003 presented data on this outcome, involving 70 participants (25% of the total). In the HBOT group, three of 38 participants (8%) were judged to have received 'no effect' from therapy and were unable to care for themselves, compared with seven of 32 cases (22%) in the control group. The risk ratio for a poor outcome with HBOT was 0.36 but was not statistically significant (95% CI 0.1 to 1.28, P value = 0.12) (Analysis 2.1).

## Secondary outcomes

### Comparison 3. Functional scales

#### Mean neurological assessment score at day five

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) (Analysis 3.1).

#### Mean neurological assessment score at week six

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) (Analysis 3.2).

#### Mean neurological assessment score at one year

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 -15.0 to 26.2, P value 0.59) (Analysis 3.3).

#### Mean Orgogozo Scale score at six months

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) (Analysis 3.4).

#### Mean Orgogozo Scale score at one year

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) (Analysis 3.5).

#### Mean Trouillas Disability Scale score at six months

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) (Analysis 3.6).

#### Mean Trouillas Disability Scale score at one year

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) (Analysis 3.7).

#### Mean Modified Rankin Functional Assessment Scale score at six months

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) (Analysis 3.8).

#### Mean Modified Rankin Functional Assessment Scale score at one year

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) (Analysis 3.9).

#### Mean Neurological Recovery Score at 12 months

Only Sansone 1997 reported this outcome. The mean score was better in the HBOT group (HBOT score 4.2 versus control 6.4, MD 2.2 points better with HBOT, 95% CI 1.6 to 2.8, P value < 0.0001) (Analysis 3.10).

#### Mean Neurological Functional Deficit Score at three weeks

Only Yang 2004 reported this outcome and did not define this scale. The mean score after therapy was better with HBOT than with sham (HBOT 17 versus control 20, MD 3 points better with HBOT, 95% CI 0.4 to 5.6, P value 0.03) (Analysis 3.11).

### Comparison 4. Deemed to have a good outcome

Two trials reported the numbers of participants achieving a predefined 'good outcome' (Imai 2006; Rusyniak 2003). Rusyniak 2003 used four different outcome scales, and Imai 2006 used the Modified Rankin Scale. Differences are reported below.

#### NIHSS zero or improved by four points at 24 hours

Three participants in the HBOT group achieved this outcome versus five in the control group (RR 0.56, 95% CI 0.2 to 2.0, P value 0.37, for a good outcome with HBOT) (Analysis 4.1).

#### Rankin Scale score less than two at 90 days

In Rusyniak 2003, five participants in the HBOT group achieved this outcome versus nine in the control group (RR 0.52, 95% CI 0.2 to 1.2, P value 0.14 for a good outcome with HBOT), while in Imai 2006, six participants achieved a good outcome with HBOT versus only one who received control (RR 6.0, 95% CI 0.8 to 45.2, P value 0.08). Pooled analysis was subject to high heterogeneity ( $I^2 = 82\%$ ) and has not been reported (Analysis 4.2).

#### Glasgow Outcome score of five at 90 days

Six participants in the HBOT group achieved this outcome versus 10 in the control group (RR 0.6, 95% CI 0.3 to 1.2, P value 0.13 for a good outcome with HBOT) (Analysis 4.3).

#### NIHSS score less than two at 90 days

Five participants in the HBOT group achieved this outcome versus eight in the control group (RR 0.59, 95% CI 0.2 to 1.4, P value 0.24 for a good outcome with HBOT) (Analysis 4.4).

### Deemed cured and self-caring at 21 days

Yang 2003 reported on the proportion of participants achieving 'cure' and able to provide self-care. Nine participants in the HBOT were 'cured' versus four in the control group (RR 1.9, 95% CI 0.6 to 5.6, P value 0.25 for a good outcome with HBOT) (Analysis 4.5).

### Comparison 5. Activities of daily living

#### Barthel Index of 95 or 100 at 90 days

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 1.2, 95% CI 0.6 to 2.3, P value 0.6 for a good outcome with HBOT) (Analysis 5.1).

#### Mean Barthel Index at three weeks

Only Yang 2004 reported this outcome. The mean Barthel Index was higher (better) in the HBOT group (74 versus 54). The MD of 20 points was statistically significant (95% CI 13.7 to 26.3, P value < 0.0001) (Analysis 5.2).

### Comparison 6. Mean volume of infarct on CT

#### Mean infarct volume at four months

Only Anderson 1991 reported this outcome. The mean infarct volume was smaller in the control group (29.0 cm<sup>3</sup> versus 49.2 cm<sup>3</sup>) but not significantly so (MD 20.2 cm<sup>3</sup>, 95% CI -13.4 to 53.8, P value 0.24) (Analysis 6.1).

### Comparison 7. Adverse effects of therapy

#### Ear pain

Two trials reported on this outcome, enrolling a total of 71 participants (22% of the total) (Imai 2006; Rusyniak 2003). Four participants in the HBOT group suffered significant ear pain versus none in the control group (RR 4.9, 95% CI 0.6 to 39.7, P value 0.14) (Analysis 7.1).

Claustrophobia with related discomfort 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, and Rusyniak 2003 did not report withdrawal of any participants from therapy. This is likely to reflect the single-treatment design of Rusyniak 2003 on the one hand and the very intensive schedule planned for Anderson 1991 on the other.

## DISCUSSION

### Summary of main results

Pooled data analysis for clinical outcomes of interest could be performed with respect to only one primary analysis: death at three to six months. We found no convincing evidence that HBOT improves outcomes when applied during the acute presentation of ischaemic stroke. Pooled data from four trials did not suggest significant benefit for the case fatality rate in the six months following presentation (RR 0.97) (Anderson 1991; Imai 2006; Nighoghossian 1995; Rusyniak 2003). Although no deaths were reported in the other trials, it is not clearly stated whether all participants enrolled reached final follow-up. It is of interest that the only trial to administer the combination of a free-radical scavenger and HBOT reported three deaths in the HBOT arm and

one in the control group (Imai 2006). Use of antioxidants during HBOT remains a controversial practice.

Some indications showed improvement on some functional and clinical scales, but this finding was not consistent. Given the heterogeneity of participants enrolled and the poor descriptors used for some of these scales, we believe that pooling of results using a standardised mean difference was not justified. In all, of the 15 comparisons made, three studies reported a total of four comparisons with a statistically significant difference in favour of HBOT, although the clinical importance of these differences is not clear (Nighoghossian 1995 (two scores); Sansone 1997 (one score); Yang 2004 (one score)). When estimated at longer follow-up times by Nighoghossian 1995, these improvements were present at one year but not at six months after therapy was completed.

### Overall completeness and applicability of evidence

This review has included data from 11 trials. We believe these represent all randomised trials in this area, both published and unpublished, at the time of our database search. Only seven trials with 361 participants were available for evaluation using our planned comparisons, and meta-analysis was not appropriate or possible for most outcomes. Four randomised trials enrolling a further 344 participants reported no outcomes of interest for our meta-analysis.

Although 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 provide reporting. With regard to long-term outcomes following HBOT and any effect on the quality of life of these study participants, we have located no relevant data.

These trials were published over a 17-year period, up to 2008. We had planned to perform subgroup analyses with respect to time elapsed between stroke and institution of HBOT, dose of oxygen received and duration 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 one pooled analysis that was possible, statistical heterogeneity was moderate ( $I^2 = 34.7%$ ), and the two included trials were clinically heterogeneous in that one trial included only participants with embolic stroke, while using combination therapy of HBOT and a free-radical scavenger (edaravone) (Imai 2006).

A wide range of oxygen doses was reported across these studies: Rusyniak 2003 gave one session only, Anderson 1991 provided an intensive regimen of eight-hourly exposures for three days, Imai 2006 held daily sessions for seven days, five trials reported daily therapy for 10 days (Li 1998; Nighoghossian 1995; Sansone 1997; Yang 2003; Zhao 2008) and Yang 2004 provided therapy for 20 days. Anderson 1991, Nighoghossian 1995 and Sansone 1997 applied modest hyperbaric pressure of 1.5 ATA versus the 2.5 ATA applied by Rusyniak 2003 in the single therapy session. Five trials used 2.0 ATA (Imai 2006; Li 1998; Yang 2003; Yang 2004; Zhao 2008). This review does not permit conclusions with regard to oxygen dosing schedule.

HBOT is regarded as a relatively benign intervention. Few possible major adverse effects have been described (pulmonary barotrauma, drug reactions, injury or death related to chamber fire), and none of the included studies reported any such events.



Various more minor complications may occur commonly but 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 in perhaps as many as 50% of those given a course of 30 treatments (Khan 2003). Although a great majority of people experiencing visual disturbances recover spontaneously over days to weeks, a small proportion of people continue to require correction to restore sight to pretreatment levels. The second most common adverse effect associated with HBOT is barotrauma. Barotrauma can affect any air-filled cavity in the body (including 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. Active effort by the individual is usually required to inflate the middle ear through the Eustachian tube on each side. Barotrauma is a consequence not 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.

### Quality of the evidence

A major problem for this review was the multiple outcome scales used to assess functional ability and clinical severity across trials. No scale was used and reported by more than one of these trials, making pooling of data for analysis impossible. Further, analysis of these ordinal scales to produce mean scores for group comparisons may not be appropriate. This is particularly true of Rankin, Trouillas and other unnamed recovery scales (Sansone 1997; Yang 2003; Yang 2004), given their limited range of scores from zero to 10, but none of the reports provided plots of experimental data for any of these scales to justify the use of such parametric tests. The usefulness of such scales for estimating outcomes at all has been questioned (Van Gijn 1992). Many of them offer distinct advantages, 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 and the Barthel Index was the most reliable disability scale (D'Olhaberriague 1996).

The problem of multiple alternative outcome measures when potential stroke therapies are investigated is not confined to the area of HBOT. Considerable efforts are being made to develop a standard suite of outcomes to improve this situation, most notably the 'Core Outcome Measures in Effectiveness Trials (COMET) initiative.' More information is available at <http://www.cometinitiative.org/>.

Other problems associated with assessing data include failure to report on primary functional outcomes, variability in time intervals between stroke event and enrolment, and variable doses of HBOT. These problems demand cautious interpretation of the results.

### Potential biases in the review process

We have made an exhaustive search of the literature, including handsearching of multiple proceedings and relevant journals in all languages. All apparently relevant study reports have been translated, and we believe we have not missed any significant

studies in the area. This review has been conducted in accordance with the Cochrane methodology and is explicit. We have reported potential biases noted in contributing studies.

### Agreements and disagreements with other studies or reviews

A number of reviews have examined the use of HBOT in neurological conditions, including acute stroke. Despite this, the question of the efficacy and effectiveness of HBOT for this purpose remains controversial. The conclusions reached by individual authors are largely dependent on the relative weight given to animal experimentation and non-randomised clinical trials on the one hand versus randomised clinical trials on the other. Al-Waili 2005 reviewed both clinical and preclinical evidence and concluded that "previous studies have demonstrated promising results—strong enough to warrant further clinical study of HBO therapy in patients with stroke," implying agreement with our analysis that the clinical case is not yet sufficiently strong to support routine use of HBOT.

Similarly, in a systematic review of the clinical data, Carson 2005 suggested that the best evidence shows no benefit of hyperbaric oxygen therapy in people with stroke. However, review authors agree that because of considerable clinical heterogeneity, particularly with respect to timing and dose of HBOT, firm conclusions are difficult to make.

## AUTHORS' CONCLUSIONS

### Implications for practice

We found very few clinical data on which to base recommendations. In the 11 small trials published in full or as abstracts, evidence is insufficient to confirm that HBOT significantly affects outcomes following acute ischaemic stroke. Use of HBOT as routine therapy for people with stroke cannot be justified by this review.

### Implications for research

Given the small number of participants in the included trials, we cannot be certain that benefit from HBOT can be excluded. Although a case can be made for further trials, such investigations would have to be carefully planned. More information may be useful on a subset of disease severity, particularly on the timing of therapy. The effects of differing oxygen dosage and of other therapies administered simultaneously are not known. Future trials will need to consider, in particular:

1. appropriate sample sizes with power to detect clinically important differences;
2. careful definition and selection of target patients;
3. appropriate range of oxygen doses per treatment session (pressure and time);
4. appropriate and carefully defined comparator therapy;
5. use of an effective sham therapy;
6. effective and explicit blinding of outcome assessors;
7. appropriate outcome measures, including those listed in this review;
8. careful elucidation of adverse effects; and
9. the cost-effectiveness of the treatment.

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**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies** [ordered by study ID]

**Anderson 1991**

Methods	RCT stratified for disease severity Powered to find a 30% relative improvement in HBOT group with 45 participants in each group (stopped early, no clear stopping rule applied)
Participants	39 adults with onset of ischaemic cerebral infarction within 2 weeks and greater than 20 severity score out of 100 on a graded neurological scale designed to test for deficits in the areas supplied by the internal carotid artery No contraindications to HBOT or unstable medical conditions

**Hyperbaric oxygen therapy for acute ischaemic stroke (Review)**

**Anderson 1991** (Continued)

Interventions	Both groups received standard measures in neurological intensive care and vitamin E 400 mg 8-hourly during compression period Control: sham therapy on air at 1.5 ATA for 60 minutes within 6 hours of enrolment, then every 8 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 4 months
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not clear
Allocation concealment (selection bias)	High risk	Not mentioned in the text and may not have been done
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants lost to final follow-up and all accounted for in the text
Selective reporting (reporting bias)	Unclear risk	No protocol report available for checking
Other bias	Unclear risk	Mortality reported as ITT, but not clear for other outcomes Recruited some participants relatively late—up to 2 weeks

**Hong 2008**

Methods	RCT
Participants	86 young inpatients with ischaemic stroke
Interventions	Routine treatment versus routine treatment plus HBOT
Outcomes	Nerve function deficit score, effectiveness of HBOT and routine therapy
Notes	Abstract only with very little detail and no clear explanation of the results given

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given; "randomly divided into two groups"

**Hong 2008** (Continued)

Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding appears unlikely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information in the paper
Selective reporting (reporting bias)	Unclear risk	No information in the paper and no protocol available for checking
Other bias	Unclear risk	Too little information available

**Imai 2006**

Methods	RCT
Participants	Adults with acute embolic stroke (within 48 hours) in the MCA territory. Diagnosis with neurological signs, MRI findings; excluded if they received fibrinolytic treatment or had a seizure
Interventions	Both groups received standard care. Intervention group received HBOT at 2.0 ATA for 60 minutes daily for 7 days and a free-radical scavenger, edaravone 30 mg iv, before and after each HBOT session
Outcomes	Death, unfavourable outcomes by mRS, adverse events of otalgia and cerebral haemorrhage, median NIHSS scores
Notes	Methodology not well elucidated. Used combination of HBOT and free-radical scavenger

**Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	No details of methods; "patients were randomised"
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention of any attempt at blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up to 90 days
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Unclear risk	No indication of other bias



**Li 1998**

Methods	RCT
Participants	86 patients with cerebral infarction divided into 2 groups of 43 each
Interventions	Control group received 'Salvia Miltirrhiza Co,' and HBOT group received the same therapy plus daily treatment of breathing 100% oxygen at 2.0 ATA for 120 minutes for 10 days
Outcomes	Cerebral blood flow, EEG, haemorrheology and SOD
Notes	No outcomes relevant to this review reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'Were randomly divided'
Allocation concealment (selection bias)	Unclear risk	No mention of this
Blinding (performance bias and detection bias) All outcomes	High risk	No mention but unlikely in this trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results for all participants reported
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Unclear risk	No evidence of other bias

**Nighoghossian 1995**

Methods	RCT
Participants	34 adults (21 men) with ischaemic cerebral infarction confirmed by CT and presenting within 24 hours of onset of neurological deficit suggestive of MCA 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 participants 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 Participants were withdrawn from protocol if they deteriorated to coma or did not tolerate therapy (7 in total: 4 control, 3 HBOT)
Outcomes	Graded neurological examination on 3 scales: Orgogozo (100 to 0), Trouillas (0 to 10) and Rankin Disability Scale Orgogozo was calculated at baseline; all were calculated at 6 months and at 1 year Adverse effects of HBOT

**Hyperbaric oxygen therapy for acute ischaemic stroke (Review)**

**Nighoghossian 1995** (Continued)

Notes —

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, probably true
Allocation concealment (selection bias)	High risk	No mention in the text—probably not done
Blinding (performance bias and detection bias) All outcomes	Low risk	No indication of blinding but sham therapy employed, suggesting that at least participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants did not reach final follow-up and were accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Low risk	No indication of other bias

**Peng 2003**

Methods	RCT using coin toss
Participants	Adults 30 years of age and older with cerebral infarction within the past 7 days, diagnosed using a 1995 conference consensus guideline. Excluded if contraindication to HBOT or already on medication that affected free-radical production
Interventions	Both groups received standard pharmacological treatment (no details); HBOT group received 10 daily treatments at 2.3 ATA breathing 100% oxygen for 80 minutes
Outcomes	Serum nitric oxide, SOD, MDA and a clinical neurological deficit score. Clinical efficacy also estimated but meaning of this measure not clear
Notes	Text translated by Dr Ting Liu

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation described as by coin toss, so probably reliably random
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding

**Hyperbaric oxygen therapy for acute ischaemic stroke (Review)**

**Peng 2003** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information available
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Low risk	No evidence of other bias

**Rusyniak 2003**

Methods	RCT stratified by time from onset to enrolment (0 to 12 hours and 12 to 24 hours)
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 participants scored less than 23 points on the NIHSS No contraindications to HBOT, previous infarct within 3 months or evidence of potentially serious cardiac arrhythmia
Interventions	Control: sham therapy on oxygen 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, mRS and Glasgow Outcome Scale calculated at 90 days Mortality Adverse effects of HBOT
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used sealed envelopes
Allocation concealment (selection bias)	Low risk	Described in the text
Blinding (performance bias and detection bias) All outcomes	Low risk	Both participants and outcome assessors unaware of allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 participants did not reach final follow-up; 4 of these were not accounted for
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Low risk	—

**Sansone 1997**

Methods	RCT reported in abstract
Participants	17 participants (9 allocated to HBOT, 8 allocated to control) with a mean age of 61 years and presenting within 24 hours of CT-demonstrated infarction in middle or anterior cerebral arterial territory
Interventions	Control: sham treatment of breathing air without pressurisation HBOT: 100% oxygen at 1.5 to 1.8 ATA for 60 minutes once daily for 8 to 10 days
Outcomes	Neurological recovery score (10 = no disability, 0 = dead) at 6 months and at 12 months
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors state that participants were randomly assigned
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment—probably did not happen
Blinding (performance bias and detection bias) All outcomes	Low risk	Sham therapy arm suggests blinding for participants and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Mean and SD were given without number of participants
Selective reporting (reporting bias)	Unclear risk	No protocol was available for checking
Other bias	Unclear risk	This small trial may not have completed recruitment at reporting

**Yang 2003**

Methods	RCT of HBOT versus 'standard therapy'
Participants	80 participants with ischaemic stroke proven by CT or MRI within 72 hours of the event
Interventions	All participants received standard medical therapy including vasodilators, anticoagulants and 'nerve cell protectant' HBOT: 38 participants received 100% oxygen for 80 minutes daily at 2 ATA for 10 days Control: 32 participants received standard therapy only
Outcomes	Neurological recovery was measured on a scale.  <ol style="list-style-type: none"> <li>1. Cure: recovery to at least a self-caring state</li> <li>2. Obvious effect: main symptoms resolved and self-caring to some extent</li> <li>3. Effective: some evidence of recovery</li> <li>4. No effect: no evidence of recovery</li> </ol>
Notes	Unusual outcome measure

**Yang 2003** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were described as 'divided randomly'
Allocation concealment (selection bias)	High risk	No mention of allocation concealment—probably did not happen
Blinding (performance bias and detection bias) All outcomes	High risk	No evidence of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	10 missing participants unaccounted for
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Unclear risk	Short report with relatively little detail

**Yang 2004**

Methods	RCT with 3 treatment arms
Participants	120 participants with ischaemic stroke proven by CT or MRI within 72 hours of admission Had to be first event CVA, conscious and co-operative and accompanied by neurological deficits
Interventions	All participants received standard medical therapy and were enrolled in rehabilitation programmes as appropriate for this institution HBOT: 60 minutes treatment at 2.0 ATA breathing 100% oxygen once daily for a total of 20 treatments Control: standard therapy only  1 arm received a direct intravascular oxygen injection of 250 mL of oxygen twice daily: these participants were not included in this meta-analysis
Outcomes	Neurological deficit Fugl-Meyer motor assessment Barthel Index of activities of daily living
Notes	—

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors state that participants were randomly assigned
Allocation concealment (selection bias)	High risk	No mention of allocation concealment, so probably not done
Blinding (performance bias and detection bias)	Unclear risk	Single blinding (participant), but not clear whether this applied to HBOT/non-HBOT comparators—a sham therapy is not described

**Hyperbaric oxygen therapy for acute ischaemic stroke (Review)**

**Yang 2004** (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No protocol available for checking
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No obvious biases

**Zhao 2008**

Methods	RCT with a third control group of normal individuals
Participants	112 participants with acute cerebral infarction
Interventions	Routine treatment group received routine drug treatment and rehabilitation exercise. HBO group received the same routine therapy plus HBO treatment at 2.0 ATA for 60 minutes plus 30 minutes of slow depressurisation to 1.0 ATA, once each day for a total of 10 days
Outcomes	Serum levels of soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule, soluble E-selectin and matrix metalloproteinase-9 were detected by enzyme-linked immunosorbent assay
Notes	No outcomes of interest were reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No details. Participants "were recruited and randomized to a HBO group ( $n = 50$ ) and a routine treatment group ( $n = 62$ )." Large difference in the size of groups reduces our confidence in this process
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No mention, but unlikely in this study unless stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers contributing to final outcome not given
Selective reporting (reporting bias)	Unclear risk	No protocol available for checking
Other bias	Unclear risk	No clear indication of other biases

ADL: activities of daily living  
 ATA: atmosphere absolute  
 CT: computerised tomography  
 CVA: cerebrovascular accident  
 EEG: electroencephalography

HBOT: hyperbaric oxygen therapy  
 ITT: intention-to-treat  
 iv: intravenous  
 MCA: middle cerebral artery  
 MDA: malondialdehyde  
 MRI: magnetic resonance imaging  
 mRS: modified Rankin Scale  
 NIHSS: National Institutes of Health Stroke Scale  
 RCT: randomised controlled trial  
 SD: standard deviation  
 SOD: serum superoxide dismutase

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

Study	Reason for exclusion
<a href="#">Belokurov 1988</a>	Review only, not focused on stroke
<a href="#">Boschetti 1970</a>	Not a comparative study
<a href="#">Chen 2007</a>	Both arms received HBOT
<a href="#">Chen 2012</a>	Not an RCT
<a href="#">Chen 2013</a>	Pseudo-randomised study
<a href="#">Dong 2005</a>	Not all participants had confirmed ischaemic stroke ('ischemic cerebrovascular disease')
<a href="#">Efrati 2013</a>	RCT with delayed treatment control arm but included participants 6 to 36 months after both ischaemic and haemorrhagic stroke
<a href="#">Efuni 1987</a>	Not an RCT, non-random controls
<a href="#">Elinsky 1984</a>	Not an RCT, non-random controls
<a href="#">Gusev 1990</a>	Not an RCT, case series only
<a href="#">Heyman 1966</a>	Non-randomised and mixed aetiologies
<a href="#">Holbach 1979</a>	RCT, all participants received HBOT
<a href="#">Kaasik 1988</a>	Not an RCT
<a href="#">Kazantseva 2005</a>	Not an RCT
<a href="#">Kazantseva 2006</a>	Abstract only, not identified as an RCT
<a href="#">Lebedev 1983</a>	Not a randomised study
<a href="#">Oshima 1990</a>	Non-random comparative study, no results given
<a href="#">Pan 1996</a>	Abstract only, no relevant outcomes reported, probably not RCT
<a href="#">Pravdenkova 1983</a>	Not a randomised study
<a href="#">Pravdenkova 1984</a>	Not a randomised study

Study	Reason for exclusion
<a href="#">Sarno 1972a</a>	Not an RCT, case series only
<a href="#">Sarno 1972b</a>	Did not study acute stroke
<a href="#">Soodan 1992</a>	Not an RCT
<a href="#">Vila 2005</a>	Not an RCT and not involving acute stroke
<a href="#">Xia 1995</a>	Dose of HBOT lower than inclusion criteria (1.1 ATA)
<a href="#">Xing 2007</a>	All groups received HBOT
<a href="#">Yang 2002</a>	A study about haemorrhagic stroke only
<a href="#">Zhang 2000</a>	Not a randomised study

ATA: atmosphere absolute

HBOT: hyperbaric oxygen therapy

RCT: randomised controlled trial

### Characteristics of ongoing studies [ordered by study ID]

#### [Michalski 2008](#)

Trial name or title	Combination of systemic intravenous thrombolysis and hyperbaric oxygen therapy (HBOT) in acute ischemic stroke; a randomised single-blinded trial has started
Methods	Randomised single-blinded controlled trial
Participants	Acute stroke
Interventions	HBOT and thrombolysis
Outcomes	Infarct size, NIHSS, Barthel Index, mRS
Starting date	2008
Contact information	Michalski D, Kueppers-Tiedt L, Hobohm C, Schulz A, Wagner A, Schneider D Department of Neurology, University of Leipzig, Leipzig, Germany
Notes	

HBOT: hyperbaric oxygen therapy

mRS: modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

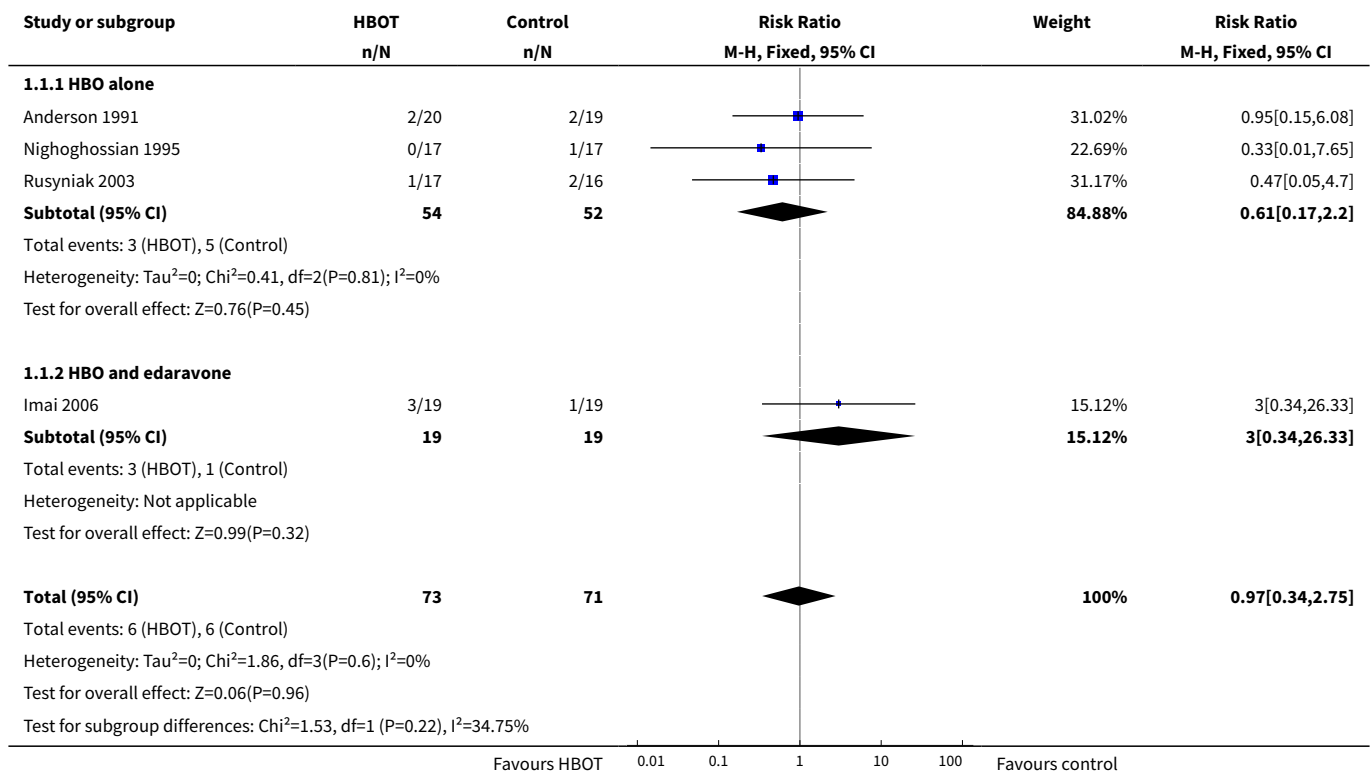
## DATA AND ANALYSES



**Comparison 1. Mortality**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at 3 to 6 months	4	144	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.34, 2.75]
1.1 HBO alone	3	106	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.17, 2.20]
1.2 HBO and edaravone	1	38	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.34, 26.33]

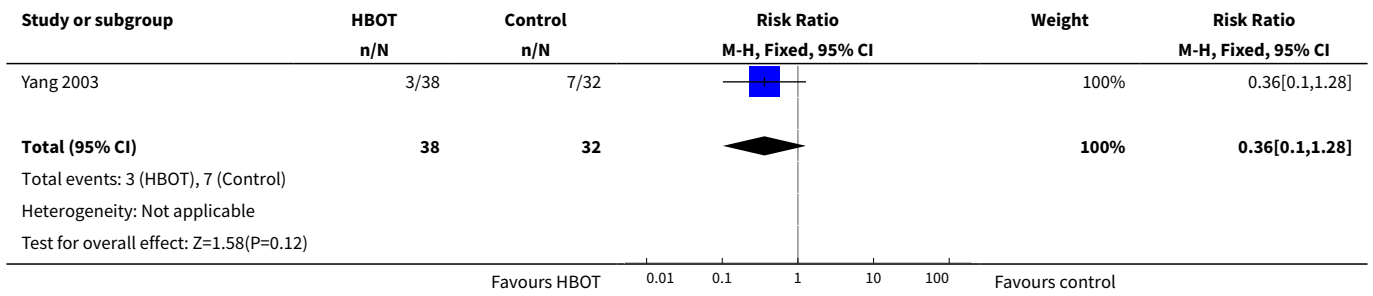
**Analysis 1.1. Comparison 1 Mortality, Outcome 1 Death at 3 to 6 months.**



**Comparison 2. Severe functional disability**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No effect of therapy—participants unable to care for themselves	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.28]

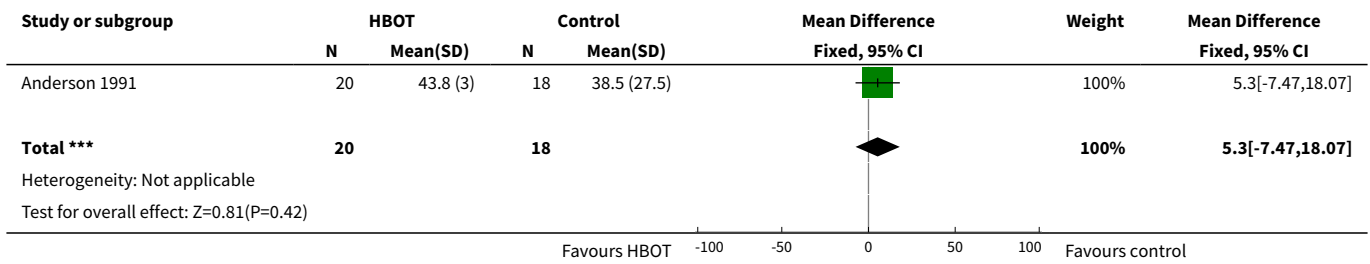
**Analysis 2.1. Comparison 2 Severe functional disability, Outcome 1 No effect of therapy—participants unable to care for themselves.**



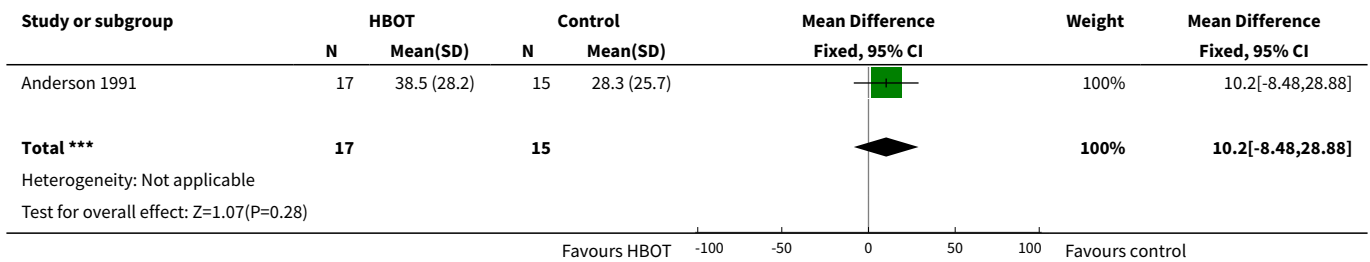
**Comparison 3. Functional scales**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean neurological score at day 5	1	38	Mean Difference (IV, Fixed, 95% CI)	5.30 [-7.47, 18.07]
2 Mean neurological score at week 6	1	32	Mean Difference (IV, Fixed, 95% CI)	10.2 [-8.48, 28.88]
3 Mean neurological score at 1 year	1	25	Mean Difference (IV, Fixed, 95% CI)	5.60 [-15.02, 26.22]
4 Mean Orgogozo score at 6 months	1	27	Mean Difference (IV, Fixed, 95% CI)	-18.20 [-41.62, 5.22]
5 Mean Orgogozo score at 1 year	1	27	Mean Difference (IV, Fixed, 95% CI)	-27.90 [-51.79, -4.01]
6 Mean Trouillas score at 6 months	1	20	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-4.16, 1.16]
7 Mean Trouillas score at 1 year	1	27	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-4.25, -0.15]
8 Mean Rankin score at 6 months	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.38, 0.18]
9 Mean Rankin score at 1 year	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.38, 0.18]
10 Mean neurological recovery score at 12 months	1	17	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-2.82, -1.58]
11 Neurological function deficit score at 3 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-5.63, -0.37]

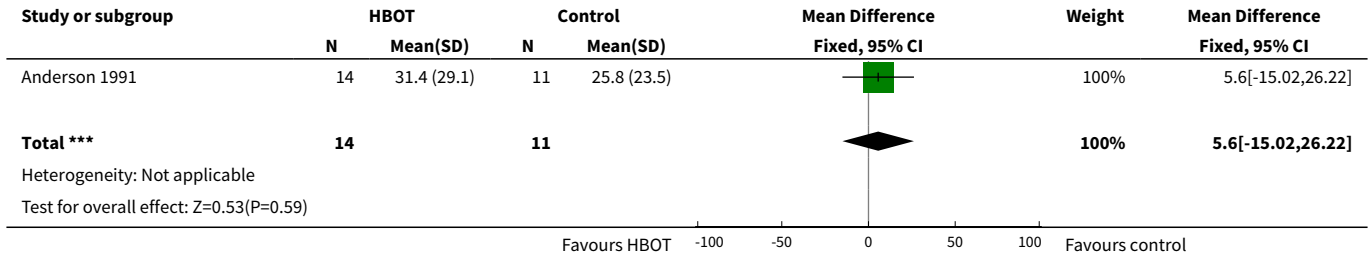
**Analysis 3.1. Comparison 3 Functional scales, Outcome 1 Mean neurological score at day 5.**



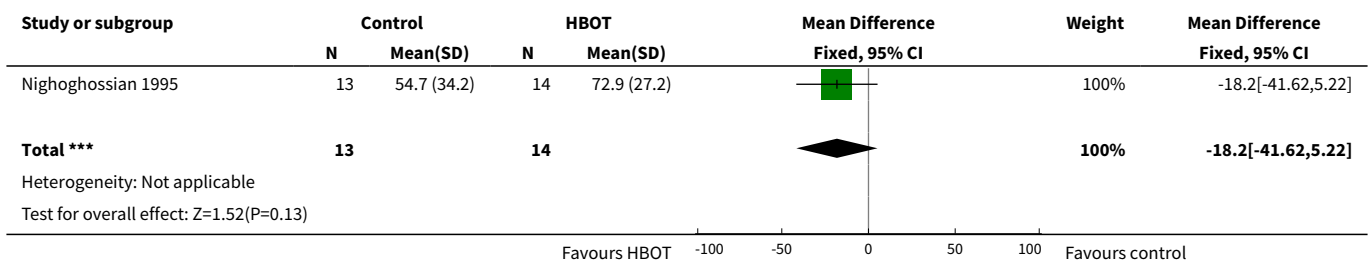
**Analysis 3.2. Comparison 3 Functional scales, Outcome 2 Mean neurological score at week 6.**



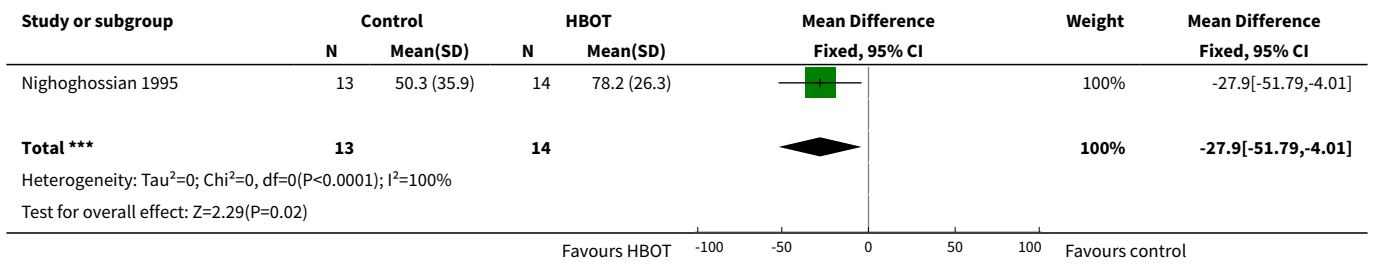
**Analysis 3.3. Comparison 3 Functional scales, Outcome 3 Mean neurological score at 1 year.**



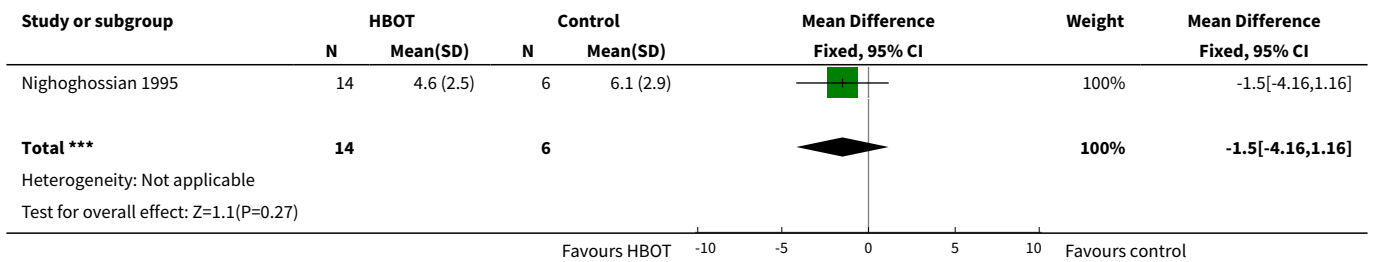
**Analysis 3.4. Comparison 3 Functional scales, Outcome 4 Mean Orgogozo score at 6 months.**



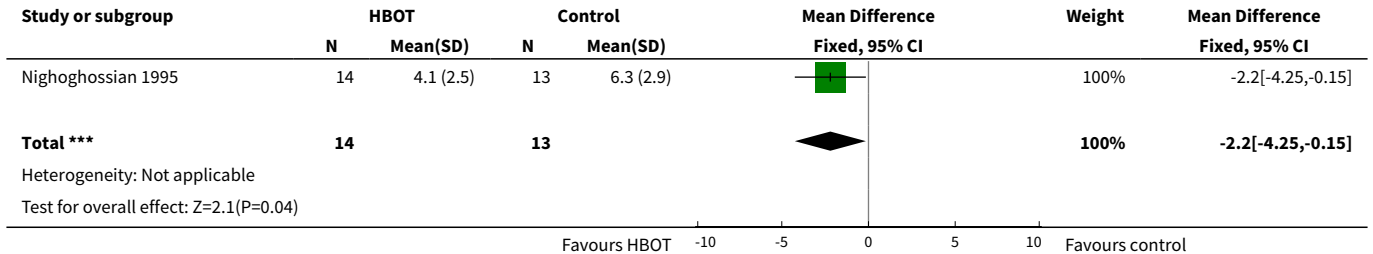
**Analysis 3.5. Comparison 3 Functional scales, Outcome 5 Mean Orgogozo score at 1 year.**



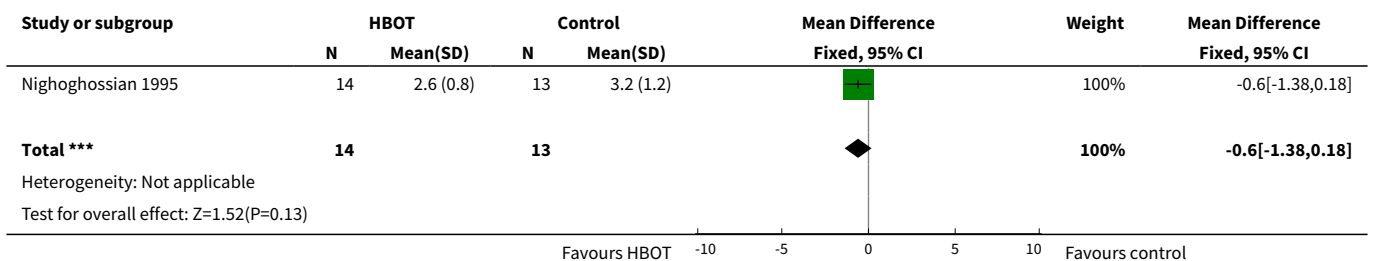
**Analysis 3.6. Comparison 3 Functional scales, Outcome 6 Mean Trouillas score at 6 months.**



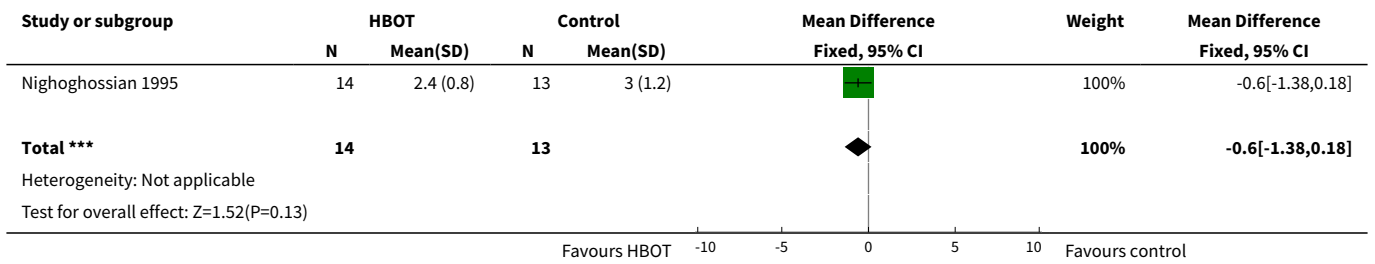
**Analysis 3.7. Comparison 3 Functional scales, Outcome 7 Mean Trouillas score at 1 year.**



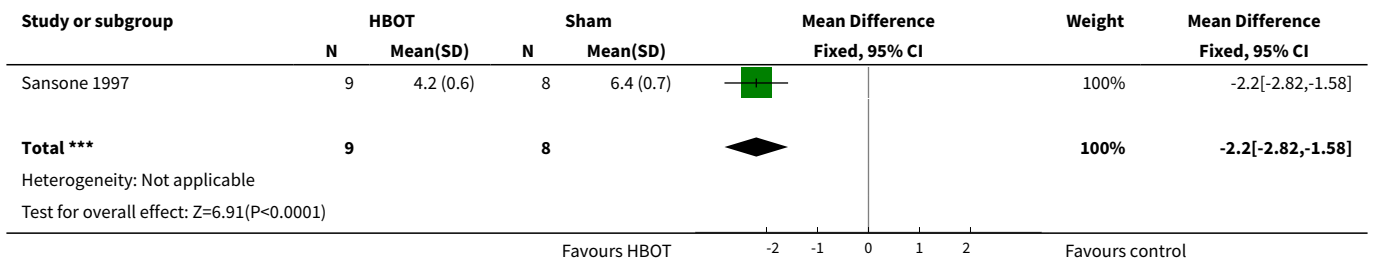
**Analysis 3.8. Comparison 3 Functional scales, Outcome 8 Mean Rankin score at 6 months.**



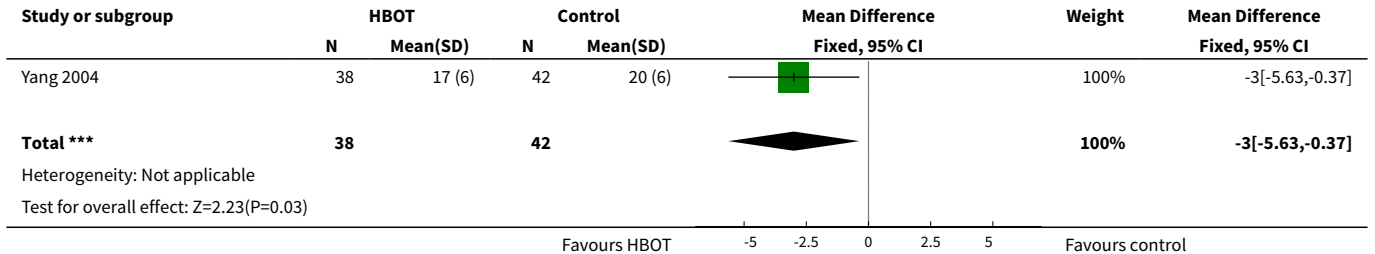
**Analysis 3.9. Comparison 3 Functional scales, Outcome 9 Mean Rankin score at 1 year.**



**Analysis 3.10. Comparison 3 Functional scales, Outcome 10 Mean neurological recovery score at 12 months.**



**Analysis 3.11. Comparison 3 Functional scales, Outcome 11 Neurological function deficit score at 3 weeks.**

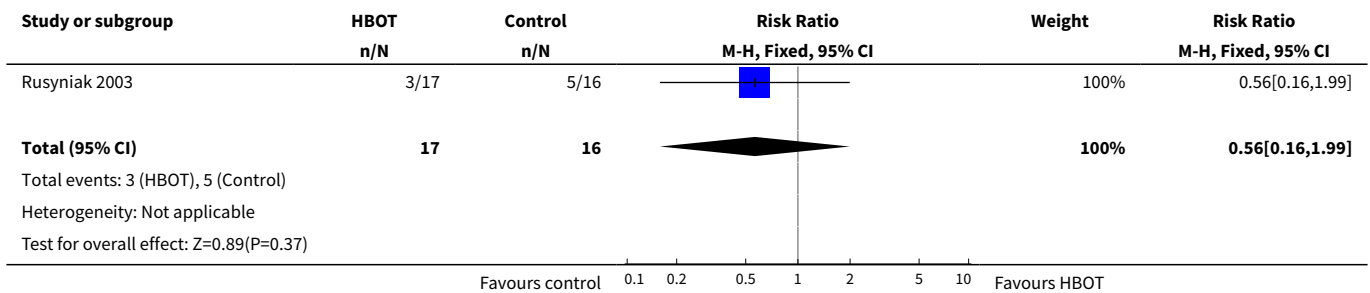


**Comparison 4. Deemed to have a good outcome**

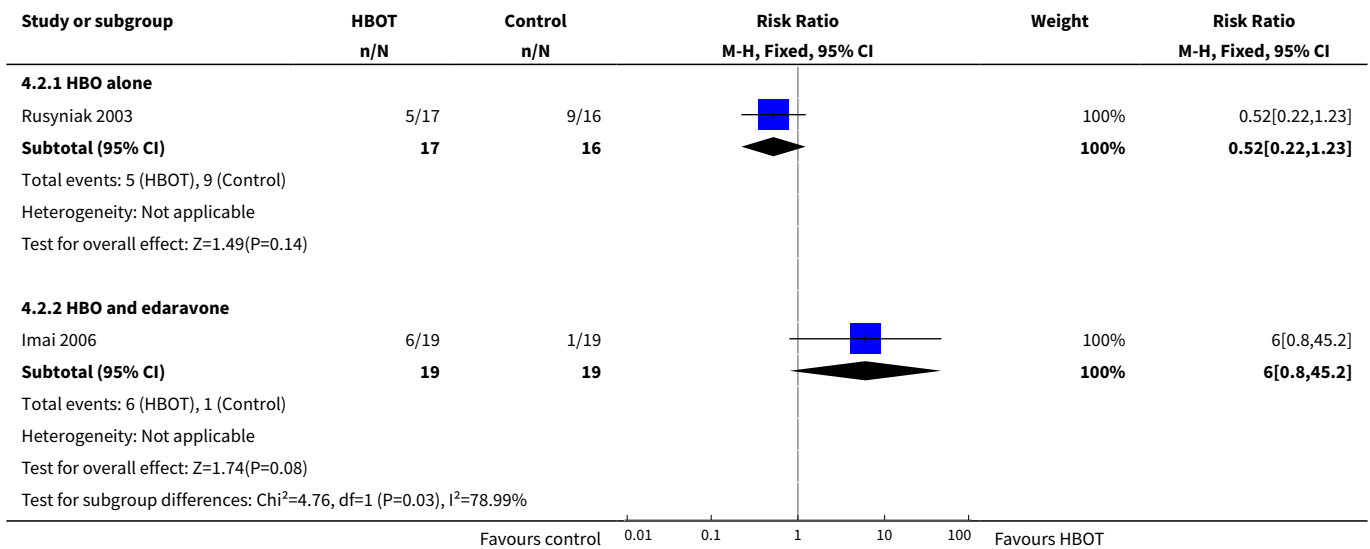
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NIHSS 0 or improved by 4 points at 24 hours	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.16, 1.99]
2 Modified Rankin score less than 2 at 90 days	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 HBO alone	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.23]
2.2 HBO and edaravone	1	38	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.80, 45.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Glasgow Outcome Score of 5	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.19]
4 NIHSS less than 2	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.24, 1.42]
5 Deemed cured and self-caring	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.64, 5.58]

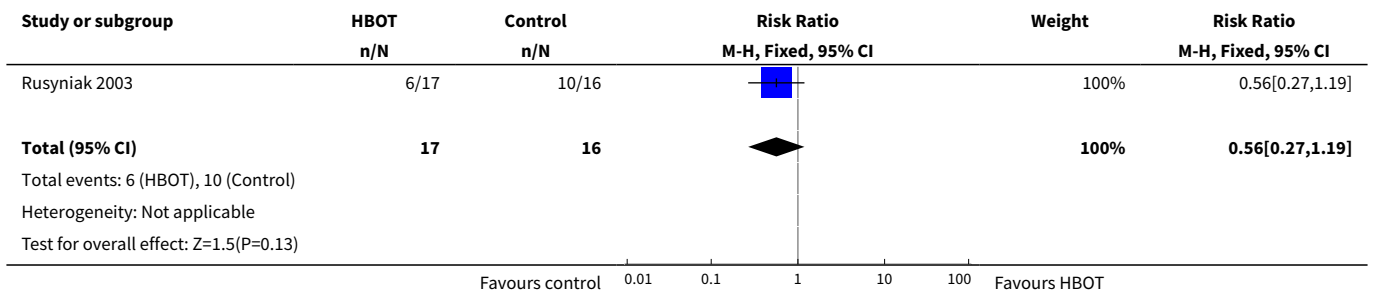
**Analysis 4.1. Comparison 4 Deemed to have a good outcome, Outcome 1 NIHSS 0 or improved by 4 points at 24 hours.**



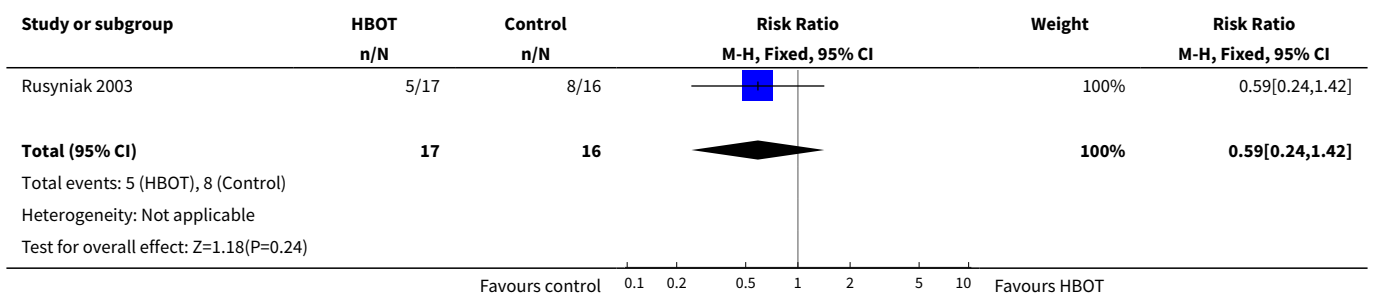
**Analysis 4.2. Comparison 4 Deemed to have a good outcome, Outcome 2 Modified Rankin score less than 2 at 90 days.**



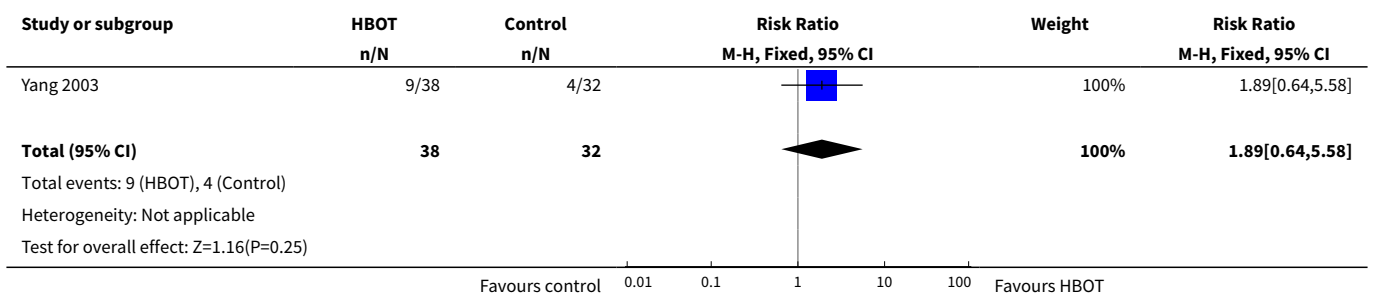
**Analysis 4.3. Comparison 4 Deemed to have a good outcome, Outcome 3 Glasgow Outcome Score of 5.**



**Analysis 4.4. Comparison 4 Deemed to have a good outcome, Outcome 4 NIHSS less than 2.**



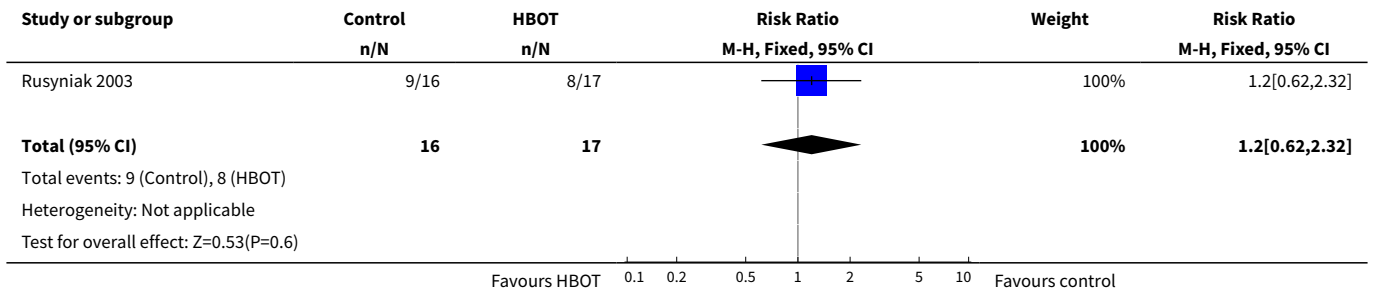
**Analysis 4.5. Comparison 4 Deemed to have a good outcome, Outcome 5 Deemed cured and self-caring.**



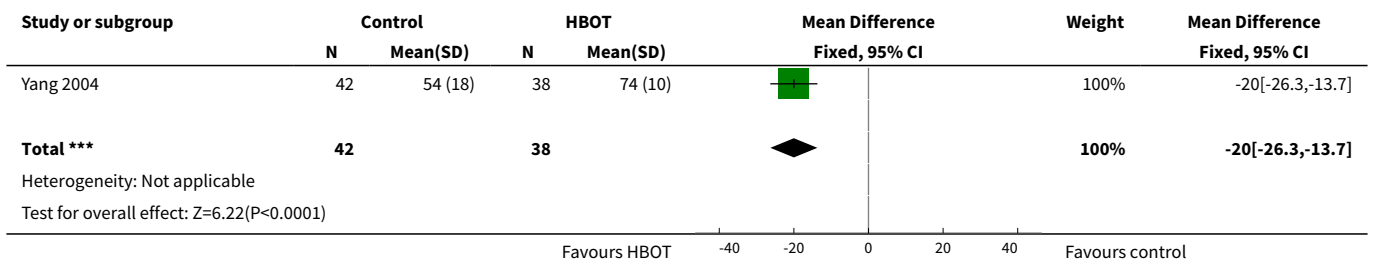
**Comparison 5. Activities of daily living**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Barthel Index 95 or 100 at 90 days	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.62, 2.32]
2 Mean Barthel Index at 3 weeks	1	80	Mean Difference (IV, Fixed, 95% CI)	-20.0 [-26.30, -13.70]

**Analysis 5.1. Comparison 5 Activities of daily living, Outcome 1 Barthel Index 95 or 100 at 90 days.**



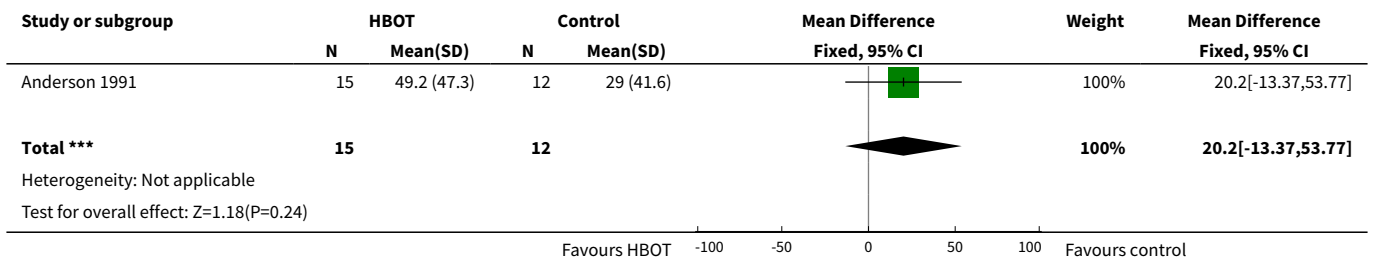
**Analysis 5.2. Comparison 5 Activities of daily living, Outcome 2 Mean Barthel Index at 3 weeks.**



**Comparison 6. Mean volume of infarct on CT**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean volume of infarct at 4 months	1	27	Mean Difference (IV, Fixed, 95% CI)	20.20 [-13.37, 53.77]

**Analysis 6.1. Comparison 6 Mean volume of infarct on CT, Outcome 1 Mean volume of infarct at 4 months.**

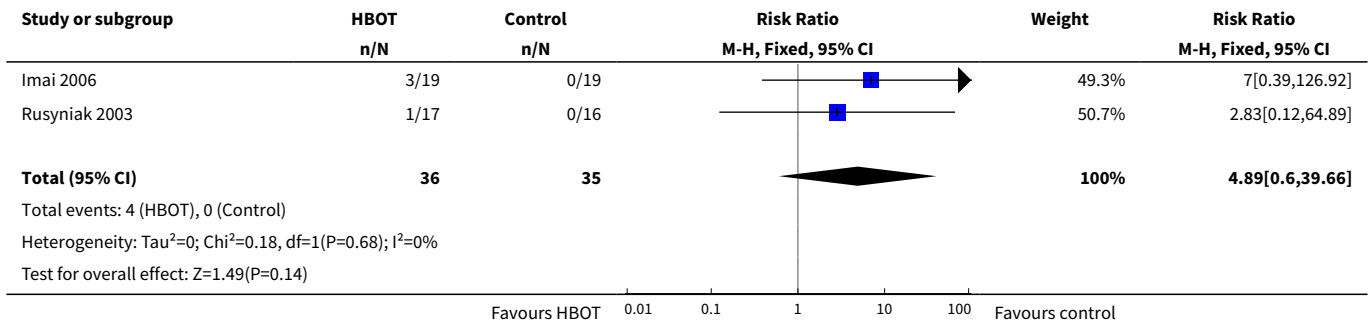




**Comparison 7. Adverse effects of therapy**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ear pain	2	71	Risk Ratio (M-H, Fixed, 95% CI)	4.89 [0.60, 39.66]

**Analysis 7.1. Comparison 7 Adverse effects of therapy, Outcome 1 Ear pain.**



**APPENDICES**

**Appendix 1. MEDLINE search strategy**

**MEDLINE (Ovid)**

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. ((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 or basilar artery or vertebral artery) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. Hyperbaric Oxygenation/
6. Oxygen Inhalation Therapy/
7. Oxygen/ae, tu
8. atmospheric pressure/
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. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 4 and 13
15. exp animals/ not humans.sh.
16. 14 not 15

The following line used to update the search:

17. limit 16 to ed=20080701-20140404

## Appendix 2. EMBASE search strategy

### EMBASE (Ovid)

1. stroke/ or cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/ or stroke unit/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. ((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 or basilar artery or vertebral artery) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. oxygen therapy/ or hyperbaric oxygen/
6. \*oxygen/
7. atmospheric pressure/
8. pressure chamber/
9. (hyperbar\$ or HBO\$).tw.
10. (high pressure oxygen or 100% oxygen).tw.
11. ((monoplace or multiplace) adj5 chamber\$).tw.
12. or/5-11
13. 4 and 12
14. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
15. 13 not 14

The following line used to update the search:

16. limit 15 to dd=20080701-20140404

## Appendix 3. CINAHL search strategy

### CINAHL (EBSCO)

- S1 .(MH "Cerebrovascular Disorders") OR (MH "Basal Ganglia Cerebrovascular Disease") OR (MH "Carotid Artery Diseases") OR (MH "Carotid Artery Thrombosis") OR (MH "Cerebral Ischemia+") OR (MH "Intracranial Arterial Diseases") OR (MH "Cerebral Arterial Diseases") OR (MH "Intracranial Embolism and Thrombosis+") OR (MH "Stroke") or (MH "Stroke Patients")
- S2 .TI ( isch#emi\* N6 (stroke\* or apoplex\* or cerebral vasc\* or cerebrovasc\* or cva or attack\* ) ) OR AB ( isch#emi\* N6 (stroke\* or apoplex\* or cerebral vasc\* or cerebrovasc\* or cva or attack\* ) )
- S3 .TI ( (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 or basilar artery or vertebral artery) N5 (isch?emi\* or infarct\* or thrombo\* or emboli\* or occlus\* or hypoxi\*) )
- S4 .AB ( (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 or basilar artery or vertebral artery) N5 (isch?emi\* or infarct\* or thrombo\* or emboli\* or occlus\* or hypoxi\*) )
- S5 .S1 OR S2 OR S3 OR S4
- S6 .(MH "Oxygen Therapy") OR (MH "Hyperbaric Oxygenation")
- S7 .(MH "Oxygen/AE/TU") OR (MH "Oxygenation")
- S8 .(MH "Atmospheric Pressure")
- S9 .TI ( hyperbar\* or HBO\* ) OR AB ( hyperbar\* or HBO\* )
- S10 .TI (high pressure oxygen or 100% oxygen) or AB (high pressure oxygen or 100% oxygen)
- S11 .TI ( ((monoplace or multiplace) N5 chamber\* ) ) OR AB ( ((monoplace or multiplace) N5 chamber\* ) )
- S12 .S6 OR S7 OR S8 OR S9 OR S10 OR S11
- S13 .S5 AND S12

The following lines to update the search:

- S14 .EM 200807-
- S15 .S13 AND S14

## Appendix 4. CENTRAL search strategy

- #1 [mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh ^"brain ischemia"] or [mh "brain infarction"] or [mh ^"hypoxia-ischemia, brain"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"carotid artery, internal, dissection"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh ^"infarction, anterior cerebral artery"] or [mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"] or [mh stroke] or [mh ^"vertebral artery dissection"]
- #2 isch\*mi\* near/6 (stroke\* or apoplex\* or cerebral next vasc\* or cerebrovasc\* or cva or attack\*):ti,ab

### Hyperbaric oxygen therapy for acute ischaemic stroke (Review)

- #3 (brain or cerebr\* or cerebell\* or vertebrobasil\* or hemispher\* or intracran\* or intracerebral or infratentorial or supratentorial or middle next cerebr\* or mca\* or "anterior circulation" or "basilar artery" or "vertebral artery") near/5 (isch\*mi\* or infarct\* or thrombo\* or emboli\* or occlus\* or hypoxi\*):ti,ab
- #4 #1 or #2 or #3
- #5 [mh ^"Hyperbaric Oxygenation"]
- #6 [mh ^"Oxygen Inhalation Therapy"]
- #7 [mh ^Oxygen/AE,TU]
- #8 [mh ^"atmospheric pressure"]
- #9 [mh ^"Atmosphere Exposure Chambers"]
- #10 (hyperbar\* or HBO\*):ti,ab
- #11 ("high pressure oxygen" or "100% oxygen"):ti,ab
- #12 ((monoplace or multiplace) near/5 chamber\*):ti,ab
- #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #14 #4 and #13

## WHAT'S NEW

Date	Event	Description
9 July 2014	New citation required but conclusions have not changed	Conclusions have not changed
9 July 2014	New search has been performed	We have included in the qualitative review one trial that was previously excluded and two new citations, all of which are randomised controlled trials (RCTs) but do not report any outcomes of interest. The review now includes 11 RCTs involving 705 participants. One new citation was added to the quantitative synthesis, but conclusions have not changed

## HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 3, 2005

Date	Event	Description
31 December 2008	New search has been performed	This review has been updated to 31 December 2008. We have included three new studies, but no substantial changes have been made to the conclusions. Six further studies previously awaiting classification have now been excluded
20 July 2008	Amended	This review has been converted to the new review format

## CONTRIBUTIONS OF AUTHORS

MH Bennett: conception of review, background, critical appraisal, hyperbaric medicine content expert, statistical analysis, co-author for description of studies and discussion.

S Weibel: 2014 update of search, critical appraisal, clinical epidemiology expert, co-author of 2014 update

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, text editor.

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## DECLARATIONS OF INTEREST

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

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Hyperbaric Oxygenation [mortality]; Brain Ischemia [complications] [mortality] [\*therapy]; Randomized Controlled Trials as Topic; Stroke [etiology] [mortality] [\*therapy]

### MeSH check words

Female; Humans; Male