Clinical effectiveness of treatment with hyperbaric oxygen for neonatal hypoxic-ischaemic encephalopathy: systematic review of Chinese literature

Zulian Liu, Tengbin Xiong, Catherine Meads

Abstract

Objectives To investigate the clinical effectiveness of treatment with hyperbaric oxygen for neonates with hypoxic-ischaemic encephalopathy. This treatment is frequently used in China but much less often in the West.

Data sources Western (Cochrane controlled trials register and database of systematic reviews, Medline, Embase, CINAHL, and HealthSTAR) and Chinese (China Hospital Digital Library, Chinese Medical Journal Network) databases and hand search of Chinese journals. No language restrictions.

Review methods Randomised or quasi-randomised controlled trials of treatment with hyperbaric oxygen compared with “usual care” in term neonates with hypoxic-ischaemic encephalopathy. Outcomes included mortality and long term neurological sequelae. Standardised forms were used to extract and compare data. Criteria of York Centre for Reviews and Dissemination were used to assess quality. Analysis was mainly qualitative but included meta-analysis.

Results 20 trials were found, mainly from Chinese sources. The reporting quality of trials was poor by Western (CONSORT) standards. Treatment with hyperbaric oxygen had better outcomes than the comparator in almost all trials. The odds ratios of the meta-analyses were 0.26 (95% confidence interval 0.14 to 0.46) for mortality and 0.41 (0.27 to 0.61) for neurological sequelae.

Conclusion Treatment with hyperbaric oxygen possibly reduces mortality and neurological sequelae in term neonates with hypoxic-ischaemic encephalopathy. Because of the poor quality of reporting in all trials and the possibility of publication bias, an adequately powered, high quality randomised controlled trial is needed to investigate these findings. The Chinese medical literature may be a rich source of evidence to inform clinical practice and other systematic reviews.

Introduction

Hypoxic-ischaemic encephalopathy is a severe complication of asphyxia that occurs before, during, or after birth. It can result in death or neurological damage, which can manifest in the short term (within 12-24 hours) as seizures, altered reflexes, or altered level of consciousness (or a combination), and in the longer term by developmental delay, epilepsy, mental retardation, or cerebral palsy (or a combination). Diagnosis is by a history of asphyxia that has caused acidemia, a low Apgar score, neurological damage, and the involvement of many organs. The condition is commonly graded as mild, moderate, or severe. Sarnat stages can be used to classify the neurological damage—stage I is least severe and stage III most severe. The condition occurs in 3.5-6/1000 live births, and the outcome is worse for more severely affected neonates. One case series of 38 births reported 14 deaths and 13 patients with a poor outcome. In another series of 42 survivors with moderate hypoxic-ischaemic encephalopathy followed up at one year, two were dead, 13 had cerebral palsy, one had another severe disability, four had mild developmental delay, and 22 had developed normally.7 Treatments evaluated for this condition include hypothermia, magnesium sulphate, anticonvulsants, mannitol, dexamethasone, nicardipine, and caffeic acid phenethyl ester, but none has been effective. Management usually consists of supportive care and keeping oxygen saturation at 95%.

Patients treated with hyperbaric oxygen inhale 100% oxygen inside a hyperbaric chamber that is pressurised to >0.1 MPa (megapascals). This treatment has been evaluated in the West for a wide range of conditions, including cerebral oedema, brain injuries, and cerebral palsy, but not for hypoxic-ischaemic encephalopathy.8–10 In Russia, hyperbaric oxygen has been used to treat neonatal injuries (fetal asphyxia), and this treatment is used for hypoxic-ischaemic encephalopathy in China, but apparently not in Hong Kong.11–13 Hyperbaric oxygen is usually given one to three times per day at 0.15-0.17 MPa for 60-120 minutes, with the aim of increasing oxygen in the tissues.14 The rationale for this treatment is that it may reverse local hypoxia, inhibit post-ischaemic vasoconstriction, and promote the formation of collagen matrix, which is essential for angiogenesis and restoration of blood flow to injured tissue.11,12 This systematic review investigates whether hyperbaric oxygen is clinically effective for the treatment of neonates born at term with hypoxic-ischaemic encephalopathy.

Methods

The protocol for this systematic review was developed as part of a masters degree in health technology assessment. The search strategy comprised a search of Western electronic databases and a search of Chinese databases and other sources. We searched the Cochrane controlled trials register and database of systematic reviews, Medline, Embase, CINAHL, and HealthSTAR up to November 2004 using search terms “hyperbaric oxygen”, “hyperbaric oxygenation”, “neonate(s)”, “newborn(s)”, “infant newborn(s)”, “hypoxic-ischemic”, “encephalopathy”, “encephalopathies”, “brain injury”, “brain injuries”, “brain damage”, “brain ischemia”, “hypoxia brain”, and “birth asphyxia”. We also searched a variety of Chinese electronic
Research

Table 1  Characteristics of 20 trials investigating treatment with hyperbaric oxygen in hypoxic-ischaemic encephalopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients*</th>
<th>Diagnostic criteria (severity*)</th>
<th>Baseline comparisons</th>
<th>Age at start of treatment</th>
<th>Treatment†</th>
<th>Usual care‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2000*</td>
<td>37</td>
<td>Ji Nan conference (I, II, and III)</td>
<td>No statistically significant difference in status of consciousness, convulsion, muscle tone, reflexes, or computed tomography results</td>
<td>2-5 days</td>
<td>NA</td>
<td>0.14-0.16 MPa (concentration=80%); 20 min/30 min/20 min; once a day ×10 days; 1-5 courses; not clear</td>
</tr>
<tr>
<td>Dong 2003‡</td>
<td>92</td>
<td>Han Zhou conference (NA)</td>
<td>No statistically significant difference in sex, age, status of asphyxia, or clinical symptoms</td>
<td>&lt;48 hours</td>
<td>&lt;24 hours</td>
<td>0.15-0.17 MPa; 15 min/30 min/20 min; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>He 2000‡</td>
<td>I: 4; II: 18; III: 10</td>
<td>Han Zhou conference (I, II, and III)</td>
<td>No statistically significant difference in birth weight, degree of asphyxia, or main clinical symptoms</td>
<td>&lt;72 hours</td>
<td>&lt;24 hours</td>
<td>0.15 MPa; 15 min/15 to 30 min; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>Li 2004‡</td>
<td>20</td>
<td>Hu and Jiang (I, III)</td>
<td>No statistically significant difference in birth weight, sex, age, or Apgar score</td>
<td>I and II: 15 hours to 7 days; III: &gt;7 days</td>
<td>NA</td>
<td>Not clear; not clear; 10 times; I and II=1-2 courses, III=3-5 courses; 10-15 days</td>
</tr>
<tr>
<td>Lin 2007‡</td>
<td>30</td>
<td>NA (I, II, and III)</td>
<td>No statistically significant difference in birth weight, sex, age, or clinical grade</td>
<td>NA</td>
<td>≤1 day</td>
<td>Not clear; not clear; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>Liu 2003§</td>
<td>II: 61; III: 39; III: 60; III: 38</td>
<td>Han Zhou conference (II and III)</td>
<td>No statistically significant difference in sex, birth weight, illness status, tachypnea, maternal age, social status, or family status</td>
<td>Within 24 days</td>
<td>Within 24 days</td>
<td>0.15-0.17 MPa; 15 min/30 min/20 min; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>Lu 2001‡</td>
<td>II: 19; III: 10</td>
<td>Han Zhou conference (I and II) and excluded cerebral haemorrhage)</td>
<td>No statistically significant difference in birth weight, gestational age, time starting treatment, or clinical grade</td>
<td>2-8 days</td>
<td>NA</td>
<td>0.12 MPa; 20 min/30 min/20 min; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>Lu 2003‡</td>
<td>37</td>
<td>Han Zhou conference (II and III; excluded cerebral haemorrhage)</td>
<td>No statistically significant difference in sex, birth weight, or degree of asphyxia and anoxia</td>
<td>≤48 hours after admission; stable if with cerebral haemorrhage</td>
<td>NA</td>
<td>0.16 MPa; 20 min/30 min/20 min; once a day ×10 days; II=2 courses, III=3 courses; not clear</td>
</tr>
<tr>
<td>Lu 1999‡</td>
<td>I: 15; II: 11; III: 6</td>
<td>Han Zhou conference (I, II, and III)</td>
<td>No statistically significant difference in sex, birth weight, status of asphyxia and anoxia, or clinical symptoms</td>
<td>&lt;48 hours</td>
<td>&lt;24 hours</td>
<td>0.15-0.17 MPa; 15 min/30 min/20 min; once a day ×10 days; not clear; not clear</td>
</tr>
<tr>
<td>Si 1999‡</td>
<td>I: 11; II: 27; III: 19</td>
<td>Han Zhou conference (II, II, and III; excluded those with brain malformation and severe decompensation)</td>
<td>No statistically significant difference in sex, birth weight and status of asphyxia.</td>
<td>&lt;48 hours after admission</td>
<td>NA</td>
<td>0.2 MPa; 20 min/60 min/20 min; once a day ×7 days; not clear; not clear</td>
</tr>
<tr>
<td>Song 2000§</td>
<td>51</td>
<td>Han Zhou conference (II and III)</td>
<td>No statistically significant difference in sex, birth weight, clinical grade, maternal age, and family status</td>
<td>NA</td>
<td>&lt;3 days</td>
<td>NA</td>
</tr>
<tr>
<td>Sun 2002‡</td>
<td>I: 21; III: 21</td>
<td>Ji Nan conference (I and III)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;3 days</td>
<td>NA</td>
</tr>
<tr>
<td>Sun 1998‡</td>
<td>I: 10; II: 18; III: 4</td>
<td>Ji Nan conference (I, II, and III; included complications of cerebral haemorrhage)</td>
<td>No statistically significant difference in various aspects including symptoms</td>
<td>NA</td>
<td>NA</td>
<td>0.14 MPa (1.4 atm); 15 min/40 min/20 min; once a day ×7-10 days; not clear; not clear</td>
</tr>
<tr>
<td>Wang 2002‡</td>
<td>I: 15; II: 22; III: 11</td>
<td>Ji Nan conference (II and III; excluded cerebral haemorrhage from birth injury and malformation)</td>
<td>No statistically significant difference in sex, birth weight, or degree of asphyxia and anoxia</td>
<td>NA</td>
<td>&lt;2-3 days</td>
<td>0.14 MPa; 20 min/50 min/25 min; 7 days; I=1 course, II=2-3 courses, III=3-4 courses; 3-5 days</td>
</tr>
<tr>
<td>Wang 1999†</td>
<td>I: 14; III: 9</td>
<td>Han Zhou conference (II and III; excluded cerebral haemorrhage from birth injury and malformation)</td>
<td>No statistically significant difference in sex, birth weight, gestational age, or Apgar score</td>
<td>72 hours</td>
<td>NA</td>
<td>0.15-0.16 MPa (concentration=80%); 20 min/30 min/20 min; once a day ×5-6 days; not clear; not clear</td>
</tr>
</tbody>
</table>

*No of patients

†Intervention

‡Control

§Study No of patients

*Diagnostic criteria

†Baseline comparisons

‡Usual care

(1 All): http://www.bmj.com/ BMJ: first published as 10.1136/bmj.38776.731655.2F on 11 May 2006. Downloaded from http://www.bmj.com on 6 October 2023 by guest. Protected by copyright.
We identified relevant studies by searching electronic databases, scanning reference lists, and consulting experts in the specialty. Publications in any language were eligible. Reference lists were hand searched for further references. We examined titles, abstracts, and keywords of citations as given on the databases for the terms for “hyperbaric oxygen therapy for neonatal hypoxic-ischaemic encephalopathy”. Where possible, we obtained the full text of all potentially relevant citations.

The predetermined inclusion criteria were fully published randomised or quasi-randomised controlled trials of treatment with hyperbaric oxygen compared with “usual care” in full term neonates (more than 36 weeks’ gestation) with hypoxic-ischaemic encephalopathy and a history of perinatal asphyxia. We also accepted alternate allocation as quasi-randomised. Outcomes were mortality and incidence of long term neurological sequelae (developmental delay, epilepsy, mental retardation, or cerebral palsy, or a combination). One reviewer (ZL) assessed studies for inclusion and this was checked independently by a second reviewer (TX). Both reviewers independently extracted data from the papers using a standardised, predesigned data extraction form, and no disagreements were encountered. We assessed the quality of the included trials by using criteria of the York Centre for Reviews and Dissemination; we focused on randomisation, allocation concealment, presence of blinding, explanation of withdrawals, and presence or absence of intention to treat analysis.

We tabulated the characteristics and results of all the included studies; analysis was mainly qualitative. We carried out meta-analysis using Metaview 4.1 (Cochrane Collaboration Review Manager 4.1 software). We used fixed effects models when statistical heterogeneity was absent and random effects models when heterogeneity was present. Statistical heterogeneity was present if χ² values were greater than the degrees of freedom.

Results

We found six citations in Western databases, but none met the inclusion criteria. We identified 126 citations from the Chinese searches. Twenty trials met the inclusion criteria and 106 were excluded (59 had the wrong study design, 37 did not specify the term neonate, two had different interventions, and eight had different outcomes).35 All of the included trials were conducted in China and published in Chinese language medical journals. The
trials studied between 40 and 198 patients. Four different sets of criteria were used to diagnose hypoxic-ischaemic encephalopathy (see table 1). These sets are similar and the criteria used are an abnormal obstetric history of fetal anoxia and distress; asphyxia after birth resulting in a low Apgar score and disturbance of consciousness; change in muscle tone; and abnormal reflexes within 12 hours of birth. The severity of hypoxic-ischaemic encephalopathy varied and grading of severity was probably not applied uniformly across the trials. Trials used various doses of hyperbaric oxygen and some had additional treatments, such as antioxidants and neurotrophic agents in each arm. Populations and the delivery of hyperbaric oxygen varied and grading of severity was probably not applied uniformly across the trials. Trials used various doses of hyperbaric oxygen and some had additional treatments, such as antioxidants and neurotrophic agents in each arm. Populations and the delivery of hyperbaric oxygen varied and grading of severity was probably not applied uniformly across the trials. Trails used various doses of hyperbaric oxygen and some had...
Fibroplasia occurred in one case each in the intervention group.

Geneity was seen between the trials for both comparisons.

Oxygen compared with controls (0.41, 0.27 to 0.61). Little heterogeneity was significantly reduced in neonates treated with hyperbaric oxygen.

Mortality in hypoxic-ischaemic encephalopathy (odds ratio 0.26, 95% confidence interval 0.14 to 0.46). Seven trials reported mortality (fig 2). Hyperbaric oxygen significantly reduced mortality in hypoxic-ischaemic encephalopathy.

Only seven trials included because order of birth was considered to be a random event. Selection bias may have been more prominent in these studies, but because of the uniformly poor methodological quality of reporting this could not be determined. Only one trial mentioned blinding (of outcome assessment).

No trials with losses to follow-up described reasons for the losses. The only trials with intention to treat analysis were those without losses to follow-up. Figure 1 shows quality factors.

The results of this systematic review suggest that treatment with hyperbaric oxygen may reduce mortality and neurological sequelae in term neonates with hypoxic-ischaemic encephalopathy. Hyperbaric oxygen has been used to treat various conditions for several decades and has been used in neonates. Although this form of treatment is controversial, it has developed rapidly in China over the past decade and is widely used there.

**Limitations**

Trial reports were of poor quality according to the criteria of the York Centre for Reviews and Dissemination, were not written to CONSORT standards, and lacked many details. Publication bias is a possibility as studies with negative results may not have been published. The 20 trials differed greatly in terms of the severity and status of the condition, exposure to hyperbaric oxygen, time to treatment and other baseline characteristics, and the measurement of outcomes. In addition, little information was given on side effects such as retrolental fibroplasia.

**Implications**

An adequately powered, high quality, randomised controlled trial is needed to investigate the effectiveness of hyperbaric oxygen in term neonates with hypoxic-ischaemic encephalopathy. If the effectiveness of this treatment is confirmed, this will have two adverse events, and the remainder did not mention adverse events (table 2).

### Discussion

The results of this systematic review suggest that treatment with hyperbaric oxygen may reduce mortality and neurological sequelae in term neonates with hypoxic-ischaemic encephalopathy. Hyperbaric oxygen has been used to treat various conditions for several decades and has been used in neonates. Although this form of treatment is controversial, it has developed rapidly in China over the past decade and is widely used there.

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main implications. Firstly, the treatment of hypoxic-ischaemic encephalopathy will change radically in the West and hyperbaric oxygen chambers will be required in all special care baby units. Secondly, evidence of the effectiveness of this treatment came from Chinese sources that are not routinely searched when systematic reviews are carried out in the West. It is not known at present how much useful evidence will be found once researchers start to look. This may also be true for evidence collected in Russia. To determine whether the inclusion of Chinese and Russian trials would reinforce or change the conclusions of systematic reviews, Chinese and Russian trials of interventions should be reviewed and the results compared with currently available systematic reviews. In future, it may become general policy to check these databases, so systematic review groups would need reviewers skilled in these languages who also have access to the relevant databases and journals.

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Contributors: ZL conducted the original systematic review submitted for the masters degree in full. TX checked the inclusions and duplicate data extraction. CM supervised the original systematic review, wrote the journal article from it, and is guarantor.

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What is already known on this topic
Hypoxic-ischaemic encephalopathy is a severe complication of asphyxia before, during, or after birth and occurs in 3.5–6/1000 live births

Current treatment in the West consists mainly of best supportive care

Hyperbaric oxygen is commonly used in China to treat this condition

What this study adds
This systematic review of 20 Chinese trials found that treatment with hyperbaric oxygen reduced mortality and neurological sequelae such as epilepsy, mental retardation, and cerebral palsy, but in all trials reporting of methods was poor and publication bias is a possibility

A high quality randomised controlled trial is needed to investigate and confirm the effectiveness of this treatment