

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

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## 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 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). The condition occurs in 3.5-6/1000 live births. Treatments evaluated for this condition include hypothermia, magnesium sulphate, anticonvulsants, mannitol, dexamethasone, nicardipine, and caffeic acid phenethyl ester, but none has been effective.<sup>1-4</sup>

Treatment with hyperbaric oxygen has been used in China to treat a wide variety of conditions including hypoxic-ischaemic encephalopathy.<sup>5-7</sup> 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.<sup>8</sup> This systematic review investigates whether hyperbaric oxygen is clinically effective for the treatment of neonates born at term with hypoxic-ischaemic encephalopathy.

## Methods

We searched the Cochrane controlled trials register and database of systematic reviews, Medline, Embase, CINAHL, and HealthSTAR, to November 2004 using search terms covering hyperbaric oxygenation, neonate, hypoxic-ischaemic encephalopathy and brain injury. We also searched Chinese electronic databases and hand searched selected Chinese journals to July 2004 (see [bmj.com](http://bmj.com)).

We identified relevant studies by searching databases, scanning reference lists, and consulting experts. Publications in any language were eligible. We examined titles, abstracts, and keywords of citations for the terms for "hyperbaric oxygen therapy for neonatal hypoxic-ischaemic encephalopathy". 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 (>36 weeks' gestation) with hypoxic-ischaemic encephalopathy and a history of perinatal asphyxia. Outcomes included mortality and incidence of long term neurological sequelae. One reviewer assessed studies for inclusion. This was checked independently by a second reviewer. Both reviewers independently extracted data from the papers using a standardised form. No disagreements were encountered. We assessed the quality of the included trials using criteria of the York Centre for Reviews and Dissemination.<sup>9</sup> Analysis was mainly qualitative, with meta-analysis.

## 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 (see [bmj.com](http://bmj.com)) and 106 were excluded. All



Additional references w1-w20 are on [bmj.com](http://bmj.com)



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of the included trials were conducted in China and published in Chinese language medical journals.<sup>w1-w20</sup> The trials had between 40 and 198 patients. 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 (see bmj.com).

Seventeen of the 20 studies mentioned “random” in the methods section, but few other trial details were given. None of the randomised trials mentioned the method of sequence allocation or whether allocation was concealed. Treatment was allocated on an alternate basis in the other three studies.<sup>w6, w9, w11</sup> Only one trial mentioned blinding (of outcome assessment).<sup>w6</sup> No trials with losses to follow-up described reasons. The only trials with intention to treat analysis were those without losses to follow-up.

Not all outcomes were reported in each trial, but overall treatment with hyperbaric oxygen had a better outcome than the comparator (see bmj.com). Seven trials reported mortality (fig 1). Hyperbaric oxygen significantly reduced mortality in hypoxic-ischaemic encephalopathy (odds ratio 0.26, 95% confidence interval 0.14 to 0.46). Seven trials measured neurological sequelae (fig 2). Neurological sequelae were significantly reduced in neonates treated with hyperbaric oxygen compared with controls. (0.41, 0.27 to 0.61). Little heterogeneity was seen between the trials for both comparisons.

Adverse events were reported in only one trial—retrolental fibroplasia occurred in one case each in the intervention group and the control group at follow-up.<sup>w20</sup> Seven trials reported no adverse events, and the remainder did not mention adverse events.

## Discussion

The results of this systematic review suggest that treatment with hyperbaric oxygen may reduce mortality and neurological sequelae in term neonates with

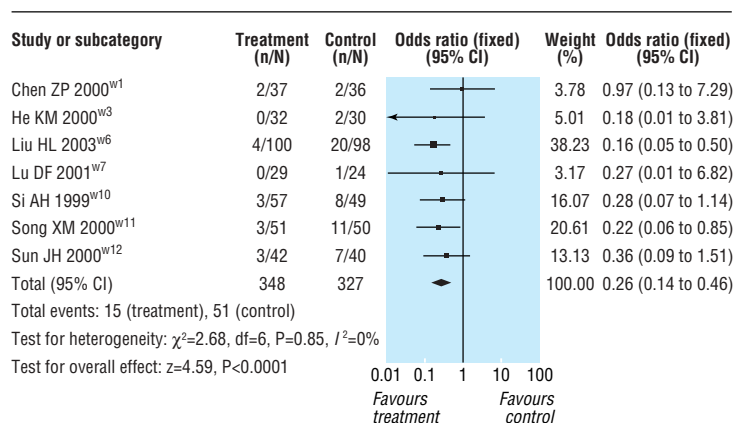


Fig 1 Effect of treatment with hyperbaric oxygen on mortality in hypoxic-ischaemic encephalopathy

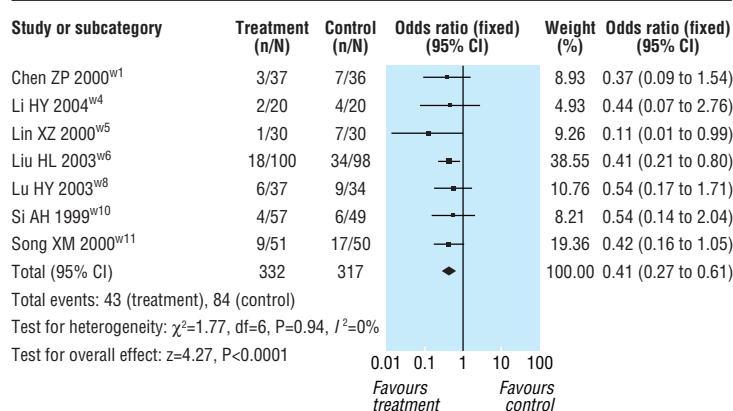


Fig 2 Effect of treatment with hyperbaric oxygen on neurological sequelae in hypoxic-ischaemic encephalopathy

hypoxic-ischaemic encephalopathy. Although this treatment is controversial, it has developed rapidly in China over the past decade and is widely used.

## 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. Little information was given on side effects such as retrolental fibroplasias.

## 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 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. The costs of providing this treatment could be high, but they might be outweighed by fewer neonatal deaths and reduced requirements

### 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

for specialist paediatric care. 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. 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.

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## Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study

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### Abstract

**Objective** To evaluate the association of environmental exposure to tobacco smoke from husbands and from work, as well as from family members in early life, with all cause mortality and mortality due to cancer or cardiovascular disease in Chinese women.

**Design** Ongoing prospective cohort study in Shanghai, China.

**Participants** Of 72 829 women who had never smoked, 65 180 women provided information on smoking by their husbands, and 66 520 women provided information on exposure to tobacco smoke at work and in early life from family members.

**Main outcome measures** All cause mortality and cause specific mortality with the main focus on cancer and cardiovascular disease. Cumulative mortality according to exposure status, and hazard ratios.

**Results** Exposure to tobacco smoke from husbands (mainly current exposure) was significantly associated with increased all cause mortality (hazard ratio 1.15, 95% confidence interval 1.01 to 1.31) and with increased mortality due to cardiovascular disease (1.37, 1.06 to 1.78). Exposure to tobacco smoke at work was associated with increased mortality due to cancer (1.19, 0.94 to 1.50), especially lung cancer (1.79, 1.09 to 2.93). Exposure in early life was associated with increased mortality due to cardiovascular disease (1.26, 0.94 to 1.69).

**Conclusions** In Chinese women, exposure to environmental tobacco smoke is related to moderately increased risk of all cause mortality and mortality due to lung cancer and cardiovascular disease.

### Introduction

The excess risk of coronary heart disease and lung cancer from environmental tobacco smoke is estimated at about 15-35%.<sup>1-3</sup> Studies on the relation between environmental tobacco smoke and mortality are few and most have limited statistical power.<sup>4 5</sup>

We used data from the Shanghai women's health study—an ongoing prospective cohort study—to examine the association of environmental tobacco smoke with mortality. The rate of smoking in Chinese men is high, but most Chinese women living in Shanghai do not smoke. For the causes of death, we focused on cancer, especially lung cancer, which is most closely related to tobacco smoke, and cardiovascular disease, particularly stroke, a leading cause of death and disability in China.

### Methods

#### Shanghai women's health study

Eligible women (n = 81 170) were aged 40-70 and lived in seven areas of urban Shanghai.<sup>6</sup> In total, 75 220 women (92.7%) completed the baseline survey, which included a face to face interview and a self administered questionnaire, from March 1997 to May 2000. Subsequently, 278 (0.4%) women outside the eligible age range were excluded, leaving 74 942 women in the baseline cohort. The cohort has been followed up every two years by face to face interviews. Data are also obtained from the Shanghai Cancer Registry and

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