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

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CRD summary
This review assessed the effectiveness of hyperbaric oxygen treatment in neonates with hypoxic-ischaemic encephalopathy. It concluded that oxygen treatment may reduce mortality and neurologic sequelae, but trial reports were of poor quality and a large randomised controlled trial is needed. The review was well-conducted and these conclusions, based on the Chinese literature, seem reliable.

Authors' objectives
To investigate the clinical effectiveness of hyperbaric oxygen treatment for neonates with hypoxic-ischaemic encephalopathy.

Searching
Western and Chinese data sources were searched. For Western literature, MEDLINE, EMBASE, CINAHL, HealthSTAR, the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews were searched up to November 2004. For Chinese literature, the authors searched the China Hospital Digital Library, CMJ Network and the bibliographical database from the China Hyperbaric Oxygen Medicine Information Centre, and handsearched two paediatric journals. The search terms were reported. Reference lists were also checked and experts were contacted. Studies published in full in any language were eligible.

Study selection
Study designs of evaluations included in the review
Randomised or quasi-randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of hyperbaric oxygen treatment compared with usual care were eligible for inclusion. Where reported, treatment in the included studies ranged from 0.12 to 0.2 megapascals over various durations of increasing, stable and decreasing pressure, but was mostly given once daily for 10 days.

Participants included in the review
Studies of full-term neonates (more than 36 weeks' gestation) with hypoxic-ischaemic encephalopathy and a history of perinatal asphyxia were eligible for inclusion. Different criteria were used to diagnose hypoxic-ischaemic encephalopathy.

Outcomes assessed in the review
The outcomes specified by the inclusion criteria were mortality and long-term neurological sequelae. Long-term neurological sequelae were developmental delay, epilepsy, mental retardation, cerebral palsy, or a combination of these.

How were decisions on the relevance of primary studies made?
One reviewer assessed studies for inclusion; a second reviewer independently checked this process.

Assessment of study quality
Study validity was assessed by considering randomisation, allocation concealment, blinding, explanation of withdrawals, and use of intention-to-treat analysis, using the criteria of the Centre for Reviews and Dissemination at the University of York.

The authors did not state how many reviewers performed the validity assessment.
Data extraction
Two reviewers independently extracted the data using a predesigned form and there were no disagreements. The outcomes extracted were the total effectiveness rate (as measured by the individual studies), mean days to recovery, length of follow-up and number of losses to follow-up, numbers of deaths and long-term neurological sequelae, and adverse events. The odds ratios (OR) and 95% confidence intervals (CIs) for each study were calculated for mortality and neurological sequelae.

Methods of synthesis
How were the studies combined?
Meta-analyses of mortality and neurological sequelae were conducted using fixed-effect models in the absence of statistical heterogeneity or random-effects models in the presence of statistical heterogeneity. Other results were synthesised narratively.

How were differences between studies investigated?
Statistical heterogeneity was assessed using a chi-squared test and the I-squared statistic.

Results of the review
Twenty studies (n=1,855) were included: 17 randomised trials (n=1,494) and 3 quasi-randomised trials (n=361). The numbers of patients in each trial ranged from 40 to 198.

All of the included trials were conducted in China and published in Chinese medical journals. Quality aspects were poorly reported as, although most mentioned the word 'random', none reported the method of randomisation or if allocation was concealed. Only one trial reported blinding and none gave reasons for any loss to follow-up. The only trials with intention-to-treat analyses were those with no losses to follow-up.

Hyperbaric oxygen treatment resulted in statistically significant reductions in both mortality (OR 0.26, 95% CI: 0.14, 0.46; based on 7 trials) and neurological sequelae (OR 0.41, 95% CI: 0.27, 0.61; based on 7 trials). No heterogeneity was observed for either outcome (I-squared 0%). Adverse events were reported by 8 trials, of which seven reported that there were no adverse events and one reported retrolental fibroplasias in two neonates (one intervention and one control).

The authors stated that, overall, treatment with hyperbaric oxygen had a better outcome than the comparator in the 20 included studies.

Authors' conclusions
Treatment with hyperbaric oxygen may reduce mortality and neurological sequelae in term neonates with hypoxic-ischaemic encephalopathy. Given the poor quality of reporting and risk of publication bias, an adequately powered, high-quality RCT is needed to investigate these findings.

CRD commentary
This review had a clearly defined objective and predetermined inclusion criteria that addressed eligible study designs, interventions, participants and outcomes. The search strategy seemed appropriate, although only studies published in full were included and unpublished material appeared not to have been sought; this can introduce publication bias into the review. Study quality was assessed using relevant criteria for RCTs and the authors concluded that the trial reports were of poor quality. However, independent verification of this was not possible as quality aspects were summarised overall rather than for each trial. Two reviewers independently selected studies and extracted the data, which minimises the risk of errors and bias.

The meta-analyses of the two outcomes for which data were available both used fixed-effect models, which was appropriate given that there was little statistical heterogeneity. This was a well-conducted review and the authors'
conclusions are likely to be reliable. Since all of the evidence included in the review was from China, where this treatment is frequently used, the findings may not be applicable to other countries where it is not in standard use.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that an adequately powered, high-quality RCT of the effectiveness of hyperbaric oxygen in term neonates with hypoxic-ischaemic encephalopathy is needed. Future systematic reviews should also consider searching Chinese and possibly Russian literature, as the evidence found in this review came from Chinese sources that are not routinely searched by Western researchers.

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