

Hyperbaric oxygen for term newborns with hypoxic ischemic encephalopathy (Protocol)

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[Intervention Protocol]

Hyperbaric oxygen for term newborns with hypoxic ischemic encephalopathy

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Editorial group: Cochrane Neonatal Group.

Publication status and date: New, published in Issue 8, 2011.

Citation: Xiong T, Li H, Zhao J, Dong W, Qu Y, Wu T, Mu D. Hyperbaric oxygen for term newborns with hypoxic ischemic encephalopathy. *Cochrane Database of Systematic Reviews* 2011, Issue 8. Art. No.: CD009248. DOI: 10.1002/14651858.CD009248.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this review is to determine the effects of therapeutic HBO (with or without hypothermia) on death and long-term neurodevelopmental disabilities in term newborn infants with HIE. Furthermore, the short-term medical effects and side effects of HBO will be studied.

Primary comparisons:

1. HBO versus supportive care;
2. HBO versus hypothermia therapy;
3. HBO plus hypothermia versus hypothermia alone;
4. HBO plus erythropoietin versus erythropoietin alone.

Subgroup analyses were planned on the basis of:

1. severity of HIE (mild, moderate, severe) ([Sarnat 1976](#); [Finer 1981](#));
2. the therapeutic time window, by timing of commencement of the intervention (< 6 hours versus 6 hours to 7 days versus > 7 days);
3. the peak pressure of HBO (< 2 ATA versus > 2ATA);
4. the number of courses of HBO (single course versus multiple courses).

BACKGROUND

Description of the condition

Perinatal asphyxia is caused by lack of oxygen (hypoxia) or lack of perfusion (ischemia), or both, to various organs of the fetus or the newborn. Perinatal asphyxia can occur in utero, during labor and delivery, or in the postnatal period. Estimates of the incidence of perinatal asphyxia vary from one to eight per 1000 live births (van Handel 2007). The World Health Organization has estimated that perinatal asphyxia is the cause of 23% of mortality in the neonatal period and 8% of global child mortality at the age of less than five years (Bryce 2005).

In the neonate, hypoxic ischemic encephalopathy (HIE) is characterized by clinical and laboratory evidence of acute or subacute brain injury due to perinatal asphyxia. The cause of HIE is not always obvious; HIE is not a single disease entity but a condition resulting from diverse causes that manifest as signs of brain injury (Higgins 2006). Moderate or severe hypoxic ischemic encephalopathy (HIE) caused by perinatal asphyxia affects 0.5 to 1 per 1000 live births (Jacobs 2007). HIE is one of the main causes of disabilities in infants born at term. Fifteen per cent to 20% of affected newborns will die during the postnatal period and an additional 25% will sustain permanent clinical deficits (Ferriero 2004). Deficits include functional motor deficits (cerebral palsy, which is a non-progressive motor or postural disorder originating in early life), cognitive deficits (mental retardation or subnormal intellectual function resulting in impaired language skills, learning, executive functions or social ability), and auditory impairment (Gonzalez 2006; Jiang 2008). Historically, treatment has been limited to supportive intensive care (Roka 2008). Recently, trials of therapeutic mild hypothermia treatment in infants with moderate to severe HIE has proven effective in reducing death and serious developmental disability (Jacobs 2007; Kirpalani 2007).

Description of the intervention

Hyperbaric oxygen (HBO) therapy is defined by the Undersea and Hyperbaric Medical Society as a treatment in which a patient is placed in a treatment chamber and intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than sea level (a pressure greater than 1 atmosphere absolute (ATA), where 1 ATA = 750 mm Hg = 0.1 MPa). The roots of HBO therapy can be traced to over three centuries ago, when Henshaw built the first hyperbaric chamber (Gill 2004). HBO is regarded as the only treatment for decompression sickness and arterial gas embolism and has been approved by the Undersea and Hyperbaric Medical Society for a variety of other medical conditions (Gill 2004).

HBO therapy has been identified as a promising therapy for ischemic injury to the central nervous system. In experimental animal models of neonatal hypoxic ischemic brain injury, HBO

therapy has been demonstrated to improve neurological outcome (Matchett 2009). In 1963, HBO therapy was applied in resuscitation of the newborn with perinatal asphyxia (Hutchison 1963). Further exploratory studies have been performed since that time. There is a concern that excessive oxygen may cause retinopathy of prematurity or bronchopulmonary dysplasia, leading some investigators to recommend against the use of HBO in neonates (Yang 2008). However, hyperbaric oxygen has been used to treat newborns with neonatal HIE in clinical studies in China. The time window of HBO is still controversial. In clinical studies, HBO is usually initiated within one to seven days after birth, administered one to three times per day at 0.15 to 0.17 MPa for 60 to 120 minutes, and continued for one to four courses of treatment (Liu 2006).

How the intervention might work

The mechanisms of HBO therapy are not completely understood. HBO therapy has been reported to improve brain injuries in different cerebral regions, including the cortex (Wang 2009a), white matter (Wang 2007a), and hippocampus (Liu 2007; Bai 2008; Wang 2008), after hypoxia ischemia. Hypoxia during asphyxia leads to impairment of mitochondrial function, energy failure, accumulation of purine derivatives, and increased generation of reactive oxygen species. After ischemia, the resultant hypoxia leads to a vicious cycle of events including reduced energy metabolism, brain edema and elevated intracranial pressure that can ultimately result in cell death (Chang 1999; Littlejohns 2005; Stiefel 2005; Van Putten 2005). The application of HBO is based on the theory that inhalation of oxygen at increased atmospheric pressure might produce a marked elevation of oxygen partial pressure in arterial blood and thus improve oxygen tension in the hypoxic brain (Nighoghossian 1997; Calvert 2007).

Recent studies have demonstrated that neuronal death occurs in two phases following hypoxic ischemic insult. In the first phase, there may be immediate 'primary neuronal death' that is related to cellular hypoxia with exhaustion of the cellular high energy stores (primary energy failure) immediately after the insult (Jacobs 2007). Hyperbaric oxygen can produce a marked elevation of oxygen partial pressure in the arterial blood and thus improve the oxygen tension in the hypoxic brain.

After a latent period of at least six hours, the secondary phase of 'delayed neuronal death' begins. The mechanisms of delayed neuronal death include hyperemia, cytotoxic edema, mitochondrial failure, accumulation of excitotoxins, cellular apoptosis, nitric oxide synthesis, free radical damage, and cytotoxic actions of activated microglia. In several animal models, HBO therapy has been demonstrated to reduce these processes. In a rat brain injury model, HBO treatment significantly increased brain tissue partial pressure of oxygen (PO₂) after injury and restored the mitochondrial redox potential (a measure of mitochondrial function) by four hours (Daugherty 2004). In seven-day old rat pups subjected

to unilateral carotid artery ligation, HBO therapy restored the levels of adenosine triphosphate (ATP) and phosphocreatine and increased the utilization of energy, ultimately leading to a reduction in brain injury (Calvert 2007a). Hyperbaric oxygen preconditioning provides brain protection against hypoxic ischemic (HI) insult via inhibition of neuronal apoptosis pathways (Li 2008). In a middle cerebral artery occlusion rat model, HBO therapy prevented apoptosis and promoted neurological function and the opening of the mitochondrial ATP-sensitive potassium channel (Lou 2006), inhibited neutrophil infiltration in the injured brain, decreased inflammation (Atochin 2000; Miljkovic-Lolic 2003), reduced basal lamina degradation, and preserved the integrity of the blood-brain barrier after cerebral ischemia (Veltkamp 2006). In a rat traumatic brain injury model, the application of HBO during the early phase significantly diminished intracranial pressure elevation and decreased the mortality level (Rogatsky 2005). In neonatal rats with intrauterine hypoxic ischemic brain damage, early HBO treatment can increase synaptic transmission efficiency, improve central nervous electrophysiological conduction velocity, and reduce neuronal death (Chen 2009).

In a clinical trial, Zhou and colleagues investigated the roles of HBO in antioxidant capacity in neonates with HIE (Zhou 2008). They found that the serum superoxide dismutase (SOD) level increased and serum levels of malondialdehyde (MDA), nitric oxide (NO) and nitric oxide synthetase (NOS) decreased significantly after HBO therapy. The antioxidant capacity increases with increasing HBO pressure in neonates with HIE.

Advances in the understanding of stem cell biology may lead to promising approaches for rescue therapy in developing brains (Ferriero 2002). HBO promotes the proliferation of neural stem cells in hypoxic ischemic brain damaged (HIBD) neonatal rats (Wang 2007). HBO also promotes cortical migration and differentiation of endogenous neural stem cells in neonatal rats with HIBD (Wang 2009a). HBO can promote the differentiation of implanted human neural stem cells into neurons in neonatal rats following HIBD (Bai 2008).

A potential reason for the failure of developing new therapy for HIE in newborns is that animal studies involving a mature nervous system are extrapolated to the neonatal brain and further translated to clinical trials (Ferriero 2002). In this assumption, the therapeutic time window is limited to a few hours (such as six hours) after the event. In fact, it is clear that neuropathological changes evolve over weeks for the developing nervous system. There is a wide therapeutic window of opportunity in the developing nervous system (Ferriero 2002). Delayed administration (96 hours after the insult) of HBO treatment still reduces HIBD in neonatal rats. With increasing courses of HBO treatment, the inhibition of apoptosis and neuronal protection gradually increased (Wang 2009).

HBO treatment plays a role in regulating genes and the protein expression of neurons that might be neuroprotective. The genes and proteins regulated by HBO include factors associated with stress

responses, transport, neurotransmission, signal transduction, and transcription factors (Chen 2009b). In addition, HBO therapy leads to activation of ion channels (Mrcic-Pelcic 2004), up-regulation of SOD (Freiberger 2006) and decreased caspases (Li 2008; Chen 2009a), suppression of p38 mitogen activated protein kinase (Yamashita 2009), and activation of Wnt signalling (Wang 2007), which might affect neuroprotection.

Why it is important to do this review

There is a growing body of research in the use of HBO for hypoxic ischemic injury. On the one hand, the protective effects of HBO for the treatment of hypoxic ischemic injury have been demonstrated most extensively in experimental animal models and in some clinical trials. On the other hand, the following potential side effects of HBO have been reported; HBO might lead to the formation of oxygen radical species (Narkowicz 1993) resulting in consumption of antioxidants (Kot 2003; Bader 2007) and reduction in antioxidant enzyme activity (Benedetti 2004), ultimately causing lipid peroxidation (Benedetti 2004; Muth 2004) and DNA damage (Muth 2004; Groger 2005; Hauser 2006;).

Complications and side effects of HBO treatment include barotrauma to the ear, round window blowout, 'sinus squeeze', visual refractive changes, numb fingers, dental problems, claustrophobia, seizures, and pulmonary oxygen toxicity, although these effects are either very rare or are only temporary (Phillips 2005). HBO treatment seems to be the proverbial 'double-edged sword' in cerebral hypoxic ischemic insults. In clinical studies, the therapeutic time window, pressure, timing, dosing intervals, and courses of HBO treatment in HIE vary amongst trials. Therefore, it is important to review the available evidence to evaluate the effectiveness and safety of HBO treatment for neonates with HIE and to determine the optimal therapeutic parameters of HBO treatment.

A systematic review of HBO for neonatal HIE performed in 2006 reported that treatment with hyperbaric oxygen possibly reduces mortality and neurological sequelae in term neonates with HIE (Liu 2006). However, there are several limitations to this paper. First, the inconsistent diagnostic criteria for HIE may lead to heterogeneity among the included studies. Second, the included trials may be of poor quality since the design and methods of the trials are not clear; this needs to be clarified by phone or mail. Third, for the included 20 trials the severity of HIE, exposure time to HBO treatment, and other baseline characteristics were not consistent. Finally, no trials of negative results were found, which means publication bias is possible or the searching strategy should be improved. Therefore, it is necessary to perform this systematic review, searching for all the randomised controlled trials of HBO therapy for neonates with HIE, to summarize currently available evidence. Additional randomised controlled clinical trials have now been completed.

OBJECTIVES

The objective of this review is to determine the effects of therapeutic HBO (with or without hypothermia) on death and long-term neurodevelopmental disabilities in term newborn infants with HIE. Furthermore, the short-term medical effects and side effects of HBO will be studied.

Primary comparisons:

1. HBO versus supportive care;
2. HBO versus hypothermia therapy;
3. HBO plus hypothermia versus hypothermia alone;
4. HBO plus erythropoietin versus erythropoietin alone.

Subgroup analyses were planned on the basis of:

1. severity of HIE (mild, moderate, severe) (Sarnat 1976; Finer 1981);
2. the therapeutic time window, by timing of commencement of the intervention (< 6 hours versus 6 hours to 7 days versus > 7 days);
3. the peak pressure of HBO (< 2 ATA versus > 2ATA);
4. the number of courses of HBO (single course versus multiple courses).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials, cluster trials will be included. Studies completed but unpublished and studies reported only as abstracts will be included. No language restrictions will be applied.

Types of participants

Inclusion criteria

1. Newborn infants: term neonates (> 37 weeks) with postnatal age of 28 days or less.
2. Evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria:
 - a) Apgar score of five or less at five or 10 minutes;
 - b) mechanical ventilation or resuscitation at 10 minutes;
 - c) cord pH < 7.1, or an arterial pH < 7.1, or base deficit of 12 or more within 60 minutes of birth.

3. Evidence of encephalopathy according to Sarnat staging (Sarnat 1976):

- a) stage 1 (mild): hyperalertness, hyperreflexia, dilated pupils, tachycardia, absence of seizures;
 - b) stage 2 (moderate): lethargy, hyperreflexia, miosis, bradycardia, seizures, hypotonia with weak suck and Moro reflex;
 - c) stage 3 (severe): stupor, flaccidity, small midposition pupils which react poorly to light, decreased stretch reflexes, hypothermia and absent Moro reflex.
4. No major congenital abnormalities or syndromes recognizable at birth.

Types of interventions

Included trials will investigate all forms of HBO therapy, regardless of initial time, duration, frequency and pressure of treatment. HBO treatment can be given alone or in combination with another medical treatment such as hypothermia. HBO intervention will be compared with no HBO treatment at normothermia or hypothermia.

Types of outcome measures

Primary outcomes

1. Infant mortality (death at 28 days and at 12 months).
2. Long-term (> 18 months) major neurodevelopmental disabilities among all participants or survivors (cerebral palsy, developmental delay (Bayley or Griffith assessment more than 2 SD below the mean), or intellectual impairment (IQ more than 2 SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification).

Secondary outcomes

1. Potential adverse effects of HBO during treatment period and after the treatment period:
 - a) traumatic injury to the ears, nasal sinuses, or lungs from the compression or expansion of gas pressure (barotrauma);
 - b) seizures (post-treatment);
 - c) retinopathy (retrolental fibroplasia): acute retrolental fibroplasia (any stage of retrolental fibroplasia during the weeks after birth, observed by direct or indirect ophthalmoscopic examination), and severe retrolental fibroplasia (Stage 3 or greater);
 - d) bronchopulmonary dysplasia: oxygen dependency (oxygen > 21% or positive pressure, or both) at 28 days postnatal age with or without compatible clinical and radiographic changes.
2. Short-term medical effects of HBO (early indicators of a neurodevelopmental outcome after HBO therapy):
 - a) Thompson neurological scores (Thompson 1997) or Sarnat scores (Sarnat 1976; Finer 1981);
 - b) Neonatal Behavioral Neurological Assessment (NBNA) score (Bao 1993);

- c) severity of electroencephalogram (EEG) abnormality:
 - i) severe: isoelectric or burst-suppression pattern,
 - ii) moderate: low voltage or discontinuous background,
 - iii) mild: electrographic seizures, dysmaturity;
- d) incidence and severity of seizures (and number of anticonvulsants);
- e) basal ganglia, thalami, posterior limb of internal capsule or white matter injury, parasagittal neuronal necrosis on magnetic resonance imaging (MRI) (at day 7);
- f) days to full sucking feeds.

Search methods for identification of studies

Electronic searches

The standard search strategy of the Cochrane Neonatal Review Group, as outlined in *The Cochrane Library*, will be used. No language restrictions will be applied.

1. We will search the Cochrane Central Register of Controlled Trials (*The Cochrane Library*), MEDLINE on Ovid (1950 to 2011), EMBASE (1980 to 2011).
2. The Cochrane Neonatal Specialized Register will be searched. This register contains reports of trials identified from regular searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE.
3. WHO International Clinical Trials Registry Platform and Clinical Trials Registries will be searched for ongoing studies.
4. ISI Web of Knowledge (1969 to 2011).
5. DORCTHIM (Database of Randomised Controlled Trials in Hyperbaric Medicine) at www.hboevidence.com (from inception to 2010). DORCTHIM was compiled from an unfocused search of PubMed using “hyperbaric oxygenation” as a MESH term, along with handsearching of primarily hyperbaric journals since first publication and checking references in identified RCTs.
6. Five major Mainland Chinese academic literature databases will also be searched using keywords in Chinese: CNKI (China National Knowledge Infrastructure) (1979 to 2010), VIP (Wei Pu Information) (1989 to 2011), Wang Fang Data (1980 to 2011), CMCI (Chinese Medical Citation Index) (1994 to 2011), CBM (Chinese Biologic Medical database) (1978 to 2011).
7. Searching from the China Hyperbaric Oxygen Medicine Information Center (1980 to 2011).

The following search strategy that uses a combination of controlled vocabulary, subjects terms, and free text terms will be used for MEDLINE and adapted for other databases.

1. For HIE the following subject headings and text words will be used:
 Asphyxia (explode) [MeSH heading] OR Hypoxic Ischemic Encephalopathy (explode) [MeSH heading] OR hypoxic isch* OR cerebral hypoxic isch* OR hypoxia brain OR encephalopathy OR cerebral ischemia OR cerebral hypoxia OR perinatal asphyxia OR

perinatal hypoxic ischemic encephalopathy OR perinatal hypoxic ischemia encephalopathy

2. For neonates the following subject headings and text words will be used:

Infant, Newborn (explode) [MeSH heading] OR infan* OR newborn* OR new-born* OR baby OR babies OR neonat* OR child OR boy* OR girl*

3. For hyperbaric oxygen treatment the following subject headings and text words will be used:

Hyperbaric Oxygenation (explode) [MeSH heading] OR Hyperbaric oxygen OR HBO OR HBOT

We will combine 1 AND 2 AND 3, then combine the results with the highly sensitive search strategy for RCTs.

Searching other resources

We will handsearch selected journals and conference proceedings and contact known experts in the field to identify additional published or unpublished trials.

Data collection and analysis

Selection of studies

We will assess all published articles identified as potentially relevant by the literature search. Abstracts retrieved from the search will be read independently by Tao Xiong and Jing Zhao to identify all trials that meet the inclusion criteria. If needed, full text articles will then be retrieved and reviewed. Differences in opinion will be resolved by a third review author (Dezhi Mu) and discussion among the review authors will be carried out. If the details of the primary trials are not clear, the trial authors will be contacted for clarification.

Data extraction and management

We will design a form to extract data. Two review authors (Tao Xiong, Jing Zhao) will independently extract, assess, and code all available data for each study using a specially designed data extraction form. If it is necessary, additional information and clarification of published data will be requested from the authors of individual trials. Review Manager software (RevMan 5.0) will be used to enter all the data, by Tao Xiong; Jing Zhao will check it.

Assessment of risk of bias in included studies

Risk of bias in included studies will be assessed by two review authors using the recommended tool of The Cochrane Collaboration. This tool is a domain-based evaluation, which involves the assessment and presentation of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. We will consider the

relative importance of different domains, then judge which domains are most important in the current review. Finally, summary assessments of the risk of bias will be made (Higgins 2009).

Measures of treatment effect

We will calculate relative risk (RR) with its 95% confidence interval (CI) for dichotomous data. We will calculate the risk difference (RD) with 95% CI and the number needed to treat (NNT). We will express continuous data as mean difference (MD) and the 95% confidence interval (CI).

Unit of analysis issues

As detailed in Section 16.3 of the Cochrane Handbook for Systematic Reviews of Interventions, particular biases in cluster-randomised trials include: (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; (iv) incorrect analysis; and (v) comparability with individually randomised trials. One way to avoid unit-of-analysis errors in cluster-randomised trials is to conduct the analysis at the same level as the allocation, using a summary measurement from each cluster. In the case of a neonatal intensive care unit (NICU)-cluster trial, we will look for evidence of adjustments at the level of each neonate as well as each allocated neonatal unit. Alternatively, we may use statistical methods based on a 'multilevel model', a 'variance components analysis', or 'generalized estimating equations (GEEs)' to determine whether the method used is appropriate. Effect estimates and their standard errors from correct analyses of cluster-randomised trials may be meta-analysed using the generic inverse-variance method in RevMan (Higgins 2009). Crossover trials will be excluded.

Dealing with missing data

We will obtain data from the primary investigator, as feasible, for unpublished trials or when published data are incomplete. If this approach is unsuccessful, analyses will be restricted to available data. Evaluation of important numerical data such as screened, eligible, and randomised patients as well as intention-to-treat (ITT) and per-protocol (PP) populations will be carefully performed. Dropouts, missing at follow-up, and withdrawn study participants will be investigated. Issues of last-observation-carried-forward (LOCF), ITT and PP will be critically appraised and compared to the specification of primary outcome parameters and the power calculation. We will perform sensitivity analyses to assess how the overall results are affected with and without the inclusion of studies with significant dropout rates. For a particular outcome, if less than 70% of patients allocated to the treatments are reported on at the end of the trial, the data will not be used as they are considered to be too prone to bias.

Assessment of heterogeneity

We plan to use a fixed-effect model if there is no evidence of significant heterogeneity between studies. The Chi² test (if $P \leq 0.10$, substantial or considerable heterogeneity is present) will be employed to determine whether there is statistically significant heterogeneity. The degree of statistical heterogeneity will be assessed by examining the I² statistic (if $I^2 \geq 50\%$, substantial or considerable heterogeneity is present). Trials will be explored to investigate possible explanations for heterogeneity. If heterogeneity is identified among a group of studies, we will check the data and again explore the reasons for heterogeneity. When there is heterogeneity that cannot readily be explained, we may divide the studies into subgroups if they have an appropriate basis.

Assessment of reporting biases

Overcoming, detecting, and correcting for publication bias is still problematic. Publication bias will be tested using funnel plots, or other corrective analytical methods, depending on the number of clinical trials included in the systematic review. The funnel plot should be seen as a generic means of displaying small-study effects. Asymmetry could be due to publication bias or to a relationship between trial size and effect size. Therefore, true heterogeneity in intervention effects is just one cause of funnel plot asymmetry; we will not pay too much attention to its asymmetry (Egger 1997; Higgins 2009).

Data synthesis

If more than one eligible trial is identified and there is sufficient homogeneity among the studies with respect to participants and reported outcomes, statistical analyses will be performed using the standard methods of the Neonatal Review Group, using the RevMan software with the fixed-effect model for meta-analysis. Categorical data will be presented as relative risk (RR) with 95% confidence interval (CI). The weighted mean difference (WMD) with 95% CI will be used for outcomes measured on a continuous scale. The number needed to treat (NNT) will be presented, as appropriate.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis on the basis of the following issues:

1. severity of HIE (mild, moderate, severe) (Sarnat 1976; Finer 1981);
2. the therapeutic time window, timing of commencement of intervention (< 1 day versus 1 to 5 days versus > 5 days);
3. the peak pressure of HBO (< 2 ATA versus > 2ATA);
4. the number of courses of HBO (single course versus multiple courses).

Sensitivity analysis

Sensitivity analyses will be performed based on missing data and study quality.

In the case of missing data, we will employ sensitivity analyses using different approaches to imputing missing data.

If appropriate, we will also conduct 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.

ACKNOWLEDGEMENTS

The Cochrane Neonatal Review Group has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

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* Indicates the major publication for the study

HISTORY

Protocol first published: Issue 8, 2011

CONTRIBUTIONS OF AUTHORS

Tao Xiong is responsible for all aspects of the protocol, contributed to the design, development and revision.

Jing Zhao is responsible for developing the search strategy.

Wenbin Dong and Yi Qu provided support for the background part of the protocol.

Honghao Li provided support with a methodological perspective.

Taixiang Wu works as a co-supervisor, at both protocol and review stage.

Dezhi Mu is responsible for revising the protocol and is supervising the progress of the whole review.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, China.
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External sources

- Chinese Cochrane Center, West China Hospital of Sichuan University, China.