Systematic review of therapy after hypoxic-ischaemic brain injury in the perinatal period

Whitelaw A

Authors' objectives
To evaluate randomised controlled trials (RCTs) of interventions for full-term infants developing hypoxic-ischaemic encephalopathy (HIE).

Searching
MEDLINE, the Cochrane Library and the Cochrane Controlled Trials Register were searched using the following search terms: 'asphyxia neonatorum', 'birth asphyxia', 'hypoxia', 'encephalopathy', 'convulsions', 'seizures', 'brain damage', 'mannitol', 'dexamethasone', 'glucocorticosteroid', 'steroid', 'barbiturate', 'phenobarbital', 'oxygen free radical', 'free radical', 'allopurinol', 'calcium channel blocker', 'glutamate antagonist', 'NMDA blocker', 'magnesium', 'nicardipine', 'nimodipine', 'lidoflazine', 'hypothermia', 'cooling', 'naloxone' and 'endorphin', combined with 'newborn infant'. Articles in any language were considered. The author also contacted other researchers in this area for additional relevant data.

Study selection
Study designs of evaluations included in the review
RCTs with a comparison control group were included. Randomisation was the preferred source of the control group.

Specific interventions included in the review
Any intervention given with the object of reducing brain injury and disability was considered. The type of interventions included were: interventions to reduce cerebral oedema, e.g. mannitol and glucocorticosteroids; anticonvulsants; calcium-channel blockers; interventions aimed at glutamate receptors, e.g. magnesium sulfate; and interventions that reduce free radical damage, e.g. allopurinol; hypothermia; and endorphin antagonists.

Participants included in the review
The participants were full-term newborn infants of gestational age greater than 36 weeks, who were at risk of encephalopathy and disability or were already showing signs of encephalopathy.

Outcomes assessed in the review
The primary outcomes were death and disability. Secondary outcomes including the extent of brain injury on scanning were also relevant.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The author does not report a method for assessing validity. The included trials were assessed using four methodological criteria: avoidance of selection bias, avoidance of performance bias, avoidance of attrition bias, and avoidance of detection bias.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. There were no tables presented showing the data extracted in the review; it is therefore not possible to state what categories of extraction were used by the author.
Methods of synthesis
How were the studies combined?
The majority of the studies were combined in a narrative review, although the author states that three of the barbiturate trials were included in a meta-analysis. Individual odds ratios and 95% confidence intervals were calculated for each trial, but a pooled statistical result was not reported; only a narrative conclusion was presented for these trials. The method of meta-analysis was not reported.

How were differences between studies investigated?
The author does not report a method for assessing any heterogeneity in the included studies.

Results of the review
The author states that 5 RCTs were included in the review, although there appears to be a discrepancy between the numbers of studies reported in the abstract and discussed in the review. There appears to be 15 studies discussed in some detail in the review:

2 studies of mannitol (1 uncontrolled study and 1 case series),
2 studies of dexamethasone,
3 RCTs comparing prophylactic barbiturate therapy with no routine anticonvulsant therapy,
1 RCT of phenobarbitone versus phenytoin,
1 RCT of chloral hydrate versus diazepam,
1 study of calcium-channel blockers (nicardipine),
1 phase I study of magnesium sulphate,
1 RCT on the use of allopurinol to reduce free radical damage,
1 RCT on salvia miltiorrhiza versus citicoline, and
1 case series and 1 RCT on hypothermia.

There were methodological problems with all of the included trials. The review of barbiturate prophylaxis showed no statistically significant effect on death or disability.

One trial of allopurinol showed short-term benefits, but was too small to test death or disability.

One small trial of hypothermia found no adverse effects, but was too small to examine death or disability.

To date, no adequate trials of dexamethasone, calcium-channel blockers, magnesium sulphate or naloxone have been completed. Pilot studies in infants have demonstrated the risks of magnesium sulfate and calcium-channel blockers.

Authors' conclusions
The author states that no intervention can be recommended for the treatment of neonatal HIE on the basis of consistent randomised trial evidence. It is unlikely that calcium-channel blockers and magnesium will be of use, since better evidence from animal models and clinical studies has shown a very real risk of hypotension in the babies most at risk. Allopurinol and hypothermia have emerged as two potential interventions: there has been good support from animal models, and pilot clinical neonatal trials have shown promise.

CRD commentary
The author clearly stated the research question and the inclusion and exclusion criteria. The literature search appeared to be thorough, and covered several databases with no language restrictions. The author also tested for publication bias and found no evidence for additional missed studies.

The quality of the included studies was formally assessed but not reported, apart from summaries of quality provided in the discussion of each intervention. The author did not report how the articles were selected or who performed the selection, validity assessment, and data extraction. The data extraction was not reported in tables, but the narrative discussion of the included studies made it clear which studies were included in the analysis and results of this review. The abstract reported that five RCTs were included in the review; this number does not match the number of studies discussed in the review, whether RCTs or any other study design.

The majority of the studies were combined in a narrative review with no assessment of possible differences between them. The results of a meta-analysis of three of the trials reported only individual odds ratios and 95% confidence intervals for each trial, and not the pooled results. The conclusion, i.e. no intervention should be recommended, appears to follow from the results, but the review could have presented the data and results in a clearer format.

**Implications of the review for practice and research**

**Practice:** The author did not state any implications for practice.

**Research:** The author states that allopurinol and possibly salvia miltiorrhizae deserve to be investigated further to determine whether they could have a role in neonatal HIE.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.