Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia

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There was no evidence to suggest that anticonvulsants prior to development of seizures in asphyxiated term newborns to prevent death, seizures or subsequent severe neurodevelopmental disabilities was successful. Hence, routine use of anticonvulsants in asphyxiated term infants, in the absence of seizures, cannot be recommended.

RHL Commentary by Saloojee H

1. EVIDENCE SUMMARY

This review examines the value of early use (prior to the development of seizures) of anticonvulsants to the newborn in preventing death, seizures, or subsequent severe neurodevelopmental disability in asphyxiated term newborns. Nine randomized controlled trials (RCTs) were identified of which two were excluded. However, the remaining seven trials were considered by the reviewers to be of insufficient methodological quality and size to confirm any evidence of benefit. A meta-analysis of five of these trials comparing barbiturates with conventional therapy following perinatal asphyxia also failed to show any difference in death or disability rates.

An unpublished randomized study, performed in 1987 in South Africa, was not included in the review (1). This study compared the administration of both phenobarbitone (20 mg/kg of body weight) and dexamethasone (2 mg/kg of body weight daily intramuscularly for three days) with no intervention in 56 infants (1). No difference in mortality or neurodevelopmental status at 12 months was found between the two groups. The results concur with this review’s conclusion.

The reviewers’ task was complicated by the paucity of suitable studies and the different anticonvulsants and controls being compared. Most RCTs identified in the systematic review were methodically weak - deficiencies included lack of blinding, allocation concealment and placebo control. The available studies also differed in their definition of asphyxia, study outcomes, period after birth when the intervention was offered and definition of study outcomes. Furthermore, the number of children contributing to the meta-analysis on mortality and developmental delay was small, only 228 and 77, respectively.

On the basis of this review, routine use of anticonvulsants in asphyxiated term infants, in the absence of seizures, cannot be recommended.

The search strategy was appropriate. Hand searching of abstracts was limited to European and American paediatric conference proceedings, resulting in the omission of at least one relevant abstract from a conference in a developing country. Trials have been analysed appropriately.
2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

Asphyxia is a common perinatal event, particularly in developing countries where it accounts for about 21% of all neonatal deaths (2). Reported incidence figures for asphyxia range from two to 27 per 1000 deliveries depending on location, period and criteria used to define asphyxia. The subsequent development of an encephalopathy is a more reliable indicator of the occurrence of a severe asphyxial event. Again, rates vary with an incidence of 4-9/1000 births in under-resourced settings, and 1-4/1000 in developed country settings. Seizures rates vary widely in asphyxia studies, probably reflecting the stringency of study entry criteria. Seizures were reported in 13-82% of infants in the studies included in this review. Furthermore, there is some evidence that both mortality and morbidity following asphyxia may be higher in under-resourced settings (3,4). For example, a 65% neurodevelopmental disability rate at 12 months of age was reported in South African infants with moderate encephalopathy (Grade 2 HIE) as compared to a 20-25% rate in studies from developed countries (4).

2.2. Feasibility of the intervention

The administration of an anticonvulsant, particularly phenobarbitone, as a neuroprotective agent following severe perinatal asphyxia is an attractive option in poorer settings. Phenobarbitone is available, affordable and can be administered intravenously or intramuscularly in almost any setting. Nevertheless, its use as a neuroprotective agent is uncommon in most centres and the results of this review should strengthen the argument for its continued non-use.

2.3. Applicability of the results of the Cochrane Review

While all the studies reviewed were conducted in developed countries, there is no reason to believe that the conclusion is not relevant to less developed settings. Anticonvulsants (mainly phenobarbitone) are widely used in under-resourced settings. However, they are provided as treatment for neonatal convulsions rather than as a primary neuroprotective strategy, as reviewed here.

Perinatal asphyxia rates remain stubbornly high in under-resourced settings. In the absence of easily implementable preventive strategies, the use of a simple, once-off, post-insult intervention is appealing. Thus, the lack of evidence for anticonvulsant therapy - a cheap and relatively safe intervention is disappointing.

It is possible that benefits of neuroprotective strategies following perinatal asphyxia may be greater in under-resourced settings. Mortality and disability rates following asphyxia are higher here (3, 4) since specialized supportive care, which may restrict further neurological damage in these infants, is often limited.

In a retrospective case-control study done in Nigeria, early (within one hour following resuscitation and prior to the onset of signs of hypoxic-ischaemic encephalopathy) administration of low-dose (10mg/kg of body weight) phenobarbital to term infants with perinatal asphyxia was associated with a threefold increase in the incidence of subsequent seizures compared to controls, and consequently a trend towards increased mortality (5). There was no clear explanation for this worse outcome. There may be a risk of respiratory depression associated with the use of phenobarbitone. Data on the increased risk of mortality with the use of a single dose of 20 mg/kg of body weight of phenobarbitone in childhood cerebral malaria is suggestive of this risk (6).

2.4. Implementation of the intervention
The review argues against the implementation of the intervention.

### 2.5. Research

Despite the negative results of the review there may be a case for carrying-out, particularly in developing countries, a randomized controlled trial with larger number of asphyxiated infants addressing substantive outcome measures.

Many potential agents are currently being explored as rescue therapies after asphyxial insult. These include free radical inhibitors and scavengers, excitatory amino acid antagonists, calcium channel blockers, nitric oxide synthase inhibitors and moderate hypothermia. It is unlikely that a single 'magic-bullet' agent will effectively stop the complex cascades of injury associated with asphyxia. Combining therapies with synergistic effects may allow smaller, less toxic doses of drugs to be used with potentially greater success.

I believe that there is limited merit in examining the benefits of anticonvulsants alone in future studies. Instead, large, randomized, controlled, multicentre, multi-country trials where different combinations of potential neuroprotective therapies are tested would be preferable. In this context, phenobarbitone warrants consideration for inclusion as one agent in a multi-combination study arm, e.g. combined with hypothermia.

Attention should focus on managing encephalopathic infants more appropriately. Unfortunately, most recommendations in this area are 'expert-based' rather than evidence based. Current practices commonly used in managing asphyxiated infants that require evidence of effectiveness include fluid restriction, head elevation, routine use of antibiotics and criteria for treating established seizures.

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### References


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