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

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This record should be cited as:
Evans DJ, Levene MI, Tsakmakis M. Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD001240. DOI: 10.1002/14651858.CD001240.pub2.

This version first published online: 18 July 2007 in Issue 3, 2007.
Date of most recent substantive amendment: 08 March 2007

ABSTRACT

Background
Seizures are common following perinatal asphyxia and may exacerbate secondary neuronal injury by increasing cerebral metabolic demand, causing fluctuations in oxygenation and perfusion, and triggering the release of excitatory neurotransmitters. Anticonvulsant therapy has been used in infants with perinatal asphyxia in order to prevent seizures. However, long term anticonvulsant therapy may lead to inhibition of brain development. Therefore, the routine use of anticonvulsant therapy to prevent seizures following perinatal asphyxia needs to be evaluated.

Objectives
To assess the effect of administering anticonvulsants to infants of 37 weeks gestation or more following perinatal asphyxia on death or subsequent severe neurodevelopmental disability and/or the prevention of seizures.

Search strategy
Relevant randomised controlled trials were identified using a combination of electronic database searches, hand searches and a search of the Cochrane Controlled Trials Registry.

Selection criteria
All randomised or quasi-randomised controlled clinical trials that reported data comparing the following outcomes: mortality, neurodevelopmental disability, neonatal seizures and adverse events, following anticonvulsant therapy in term infants (37 weeks or more) compared to controls (with or without placebo) following perinatal asphyxia.

Data collection and analysis
Methodological quality and validity of studies were assessed without consideration of the results. Data relevant to the outcome were extracted and analysed.

Main results
Seven randomised or quasi-randomised controlled trials that met the selection criteria were included. No studies were of sufficient methodological quality and size to demonstrate a valid, clinically significant change in the risk of mortality or severe neurodevelopmental disability. A meta-analysis combining five studies comparing barbiturates with conventional therapy following perinatal asphyxia demonstrated no difference in risks of death, severe neurodevelopmental disability, or the combined outcome of death or severe neurodevelopmental disability.

Authors' conclusions
At the present time, anticonvulsant therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures. Any future studies should be of sufficient size to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability.

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PLAIN LANGUAGE SUMMARY

It is unclear whether giving anticonvulsants to newborn babies soon after possible birth asphyxia at term is safe and effective. More studies are needed.

Seizures (or convulsions) are common following birth asphyxia. These seizures may worsen the brain injury. In theory, anticonvulsant medication given to babies soon after possible birth asphyxia may improve outcome by preventing seizures and protecting the brain. Anticonvulsant drugs are not without side effects and there are concerns that they might impair brain development. The studies included in this review involved relatively small numbers of babies and few studies assessed developmental outcome. At present, there is insufficient information on which to base recommendations about the effectiveness of giving anticonvulsants to newborn babies soon after possible birth asphyxia.

BACKGROUND

Throughout the world, perinatal asphyxia remains an important cause of perinatally acquired brain injury in full term infants. In technically developed countries, the incidence of death or severe neurological impairment following perinatal asphyxia is 0.5 - 1.0 per 1000 live births (Finer 1981; Levene 1985; Thornberg 1995). In developing countries, perinatal asphyxia appears to be more common (al-Alfry 1990; Airede 1991; Boo 1991; Kinoti 1993; Singh 1991). Although follow up programmes are not well developed in these countries, it is likely that perinatal asphyxia produces a huge burden of world-wide disability.

During perinatal asphyxia, hypoxia and ischaemia cause primary neuronal injury because of cell necrosis (Hossman 1983). Neonatal resuscitation results in improved oxygenation and reperfusion, which lead to delayed, or secondary, neuronal injury. The mechanisms believed to be important in this secondary phase of neuronal injury include oxygen free radical production (McCord 1985), intracellular calcium entry (Siesjo 1992) and apoptosis (Buttke 1994).

Seizures are a common feature of Hypoxic-Ischaemic Encephalopathy (HIE) (Sarnat 1976). Seizures can substantially increase central nervous system (CNS) metabolic demand (Younkin 1986), cause the release of excitatory neurotransmitters such as glutamate (McDonald 1990), lead to fluctuations in systemic arterial pressure (Clozel 1985) and result in hypoxia and hypercapnea. Therefore, seizures themselves may cause further neuronal injury following asphyxia.

The potential benefits of preventing further neuronal injury associated with seizures following asphyxia has prompted the widespread use of anticonvulsants, and barbiturates in particular, for the prevention of seizures. In addition to their anticonvulsant activity, barbiturates are known to decrease CNS metabolic rate when given in high doses (Nilsson 1971), reduce calcium entry post-ischaemia and scavenge free radicals (Demopoulos 1977). These actions may potentially attenuate the cascade of damaging processes initiated following hypoxic-ischaemic insults, thereby reducing secondary neuronal injury. For these reasons, barbiturates have been used prophylactically (whether or not the infant has seizures) following perinatal asphyxia in neonates, although long-term therapy in animals leads to inhibition of brain growth and development.

OBJECTIVES

To determine the effect of administering anticonvulsant therapy on death or subsequent severe neurodevelopmental disability and/or the prevention of seizures in infants 37 weeks gestation or more following perinatal asphyxia.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All published, unpublished and ongoing randomised or quasi-randomised trials with reported data comparing the specified outcomes in asphyxiated term infants given anticonvulsants with outcomes in controls with or without placebo.

Types of participants

Neonates, of 37 or more completed weeks of gestation, following perinatal asphyxia. Perinatal asphyxia was considered a clinical diagnosis, characterised by signs of fetal distress, depression at birth, neonatal encephalopathy or other signs of multi-organ dysfunction. The presence or absence of seizures before trial entry was not a required inclusion criterion.

Types of intervention

Anticonvulsants administered in the early neonatal period (within the first seven days of life) with the intention of preventing neuronal injury following perinatal asphyxia or the intention of preventing seizures.

Types of outcome measures

Primary outcome: death or severe neurodevelopmental disability assessed at greater than, or equal to, 12 months of age. Severe neurodevelopmental disability was defined as any one or combination

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of the following: cerebral palsy, developmental delay (DQ < 70), blindness.

Secondary outcomes: seizure control in the neonatal period; childhood epilepsy; hypotensive episodes following administration of anticonvulsant; reported adverse events. Seizures were either apparent clinically or detected by electro-encephalographic recordings.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

See Neonatal Review Group search strategy. The specific search strategy for MEDLINE and the Cochrane Controlled Trials Registry as given below. The abstracts of the Society for Pediatric Research and European Society for Pediatric Research, published in the Journal of Pediatric Research were searched from January 1980 to January 2007. Cited references from retrieved articles were searched for additional studies. Abstracts and letters to the editor were reviewed to identify randomised controlled trials which had not been published. Editorials, indicating expert opinion, were reviewed to identify any further studies, not already included in the review.

1. MEDLINE Search

Dates: 1966 - Nov 2006

Strategy

#1 explode 'Asphyxia-Neonatorum' / all subheadings
#2 asphyx$
#3 hypox$ ADJ ischaemi$
#4 hypox$ ADJ ischemi$
#5 encephalopath$
#6 #1 or #2 or #3 or #4 or #5
#7 explode 'Anticonvulsants-' / all subheadings
#8 anticonvuls$
#9 explode 'Seizures-' / all subheadings
#10 convulsi$
#11 seiz$
#12 #7 or #8 or #9 or #10 or #11
#13 #6 and #12

This output was combined with the search filter for randomised controlled trials (see Appendix 5c of the Cochrane Handbook).

2. Cochrane Controlled Trials Registry Search

Date: Issue 3, 2006

Strategy (Update Software)

#1 ASPHYXIA-NEONATORUM*:ME
#2 ASPHYX*
#3 HYPOX*
#4 ENCEPH*
#5 (((#1 or #2) or #3) or #4)
#6 ANTICONVULSANTS*:ME
#7 SEIZURES*:ME
#8 CONVULSI*
#9 SEIZ*
#10 ANTICONVULS*
#11 ((((#6 or #7) or #8) or #9) or #10)
#12 (#5 and #11)

METHODS OF THE REVIEW

The primary reviewer screened the title and abstract of studies identified by the above search strategy. Both primary and a secondary reviewer re-screened the full text of the report of each study identified as of potential relevance. Studies meeting any of the pre-specified inclusion criteria were included. Studies were evaluated for inclusion and methodological quality without consideration of results. Reviewers were not blinded to authorship, institution or journal.

The methodological quality of the various components of the study design known to be important in minimising bias were scored separately by reviewers before a consensus was obtained. The components were those relating to the following sources of potential bias, namely: selection, performance, attrition and detection.

Selection bias (Allocation concealment - Section 6 of the Cochrane Handbook):
A = adequate, B = can't tell / unclear, C = not used / inadequate.

Performance bias (blinding of caretakers to the intervention):
A = adequate, B = can't tell / unclear, C = not used / inadequate.

Attrition bias (post-randomisation exclusions and loss to follow-up):
A: < 5% loss, B: 5 - 9.9% loss, C: 10 - 20% loss, D: > 20% loss or unable to calculate because of lack of data.

Detection bias (blinding of outcome assessment):
A: Double blind, neither investigator nor participant (parent or guardian) knew, or was likely to correctly identify, treatment allocation.
B: Single blind, either investigator or participant knew, or was likely to correctly identify, treatment allocation.
C: No blinding. Includes studies where effects, or side effects, of treatment meant that it was likely that the treatment allocation could be correctly identified in a significant proportion (>20%) of participants.
D: Can't tell.

The treatment effects of individual trials were examined by comparing groups allocated to the treatment under study

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(prophylactic anticonvulsant therapy versus placebo or standard treatment, that is anticonvulsants for the treatment of seizures). Data relating to the primary and secondary outcomes (described above) were compared. Where relevant and if possible, relative risk (RR) and risk difference (RD) were calculated for dichotomous data and weighted mean difference (WMD) for continuous data, with 95% confidence intervals (CI) for all analyses. Analysis of outcome data was by intention to treat. Where relevant, meta-analyses was performed using the fixed effects "assumption free" model. Where relevant and if possible, heterogeneity between trial results was examined using the I-squared test for dichotomous outcomes.

Subgroup analyses were performed according to the types of anticonvulsants administered. Subgroup analyses according to (a) the grade of Hypoxic-Ischaemic Encephalopathy and (b) the presence or absence of seizures were only be performed where the data allowed grouping according to characteristics measured before trial entry (as both grade of Hypoxic-Ischaemic Encephalopathy and seizure rates are likely to be affected by anticonvulsant therapy).

DESCRIPTION OF STUDIES

Nine randomised or quasi-randomised controlled trials using neonatal anticonvulsive therapy following perinatal asphyxia were identified.

Two of these studies were excluded. Ruth 1988 randomised very low birthweight infants to receive phenobarbital or placebo following birth; perinatal asphyxia was not an eligibility criterion. Wilkinson 1989 compared four anticonvulsants in a randomised control trial. The anticonvulsants were used for treatment (not prophylaxis) of electro-encephalographically apparent seizures of any aetiology, not exclusively perinatal asphyxia. Infants were a mixture of term and premature neonates. It was not possible to extract the data relating only to term infants following asphyxia.

The characteristics of participants, interventions and outcomes of the remaining seven studies are given in the table: Characteristics of Included Studies. Five studies compared a barbiturate with conventional therapy (Goldberg 1986; Hall 1998; Ruth 1991; Singh 2004; Vargas-Origel 2004), Vela 1987 compared phenobarbital with phenytoin and Kuzemko 1972 compared chloral hydrate with diazepam. The clinical definition of perinatal asphyxia was vague in Kuzemko 1972. Three studies recorded neurodevelopmental outcome beyond one year of age: Goldberg 1986; Hall 1998 and Ruth 1991. The remaining studies only reported short-term neonatal outcomes (deaths, abnormal neurological status and seizures within the neonatal period): Kuzemko 1972; Vela 1987; Singh 2004 and Vargas-Origel 2004.

METHODOLOGICAL QUALITY

Selection

All studies used formal randomisation, although the method was only stated in Hall 1998. Only Hall 1998 used adequate allocation concealment. No attempt at concealment was made in Kuzemko 1972 and the method of concealment was unclear in Goldberg 1986; Vela 1987; Ruth 1991; Singh 2004 and Vargas-Origel 2004 .

In the studies by Kuzemko 1972 and Singh 2004, randomisation resulted in unequal numbers of infants being allocated to the two groups (17 allocated to chloral hydrate versus 11 allocated to diazepam treatment and 25 allocated to phenobarbital versus 20 allocated to control, respectively.). No adequate explanation for this imbalance is evident.

Performance

No study used a placebo. Only in the studies by Vela 1987 and Kuzemko 1972 were the neonatal clinicians, responsible for the care and assessment of neonatal outcomes, blind to study group.

Potential bias arising from co-intervention remains a possibility in the five studies that did not use caretaker blinding: Goldberg 1986; Hall 1998; Ruth 1991; Singh 2004 and Vargas-Origel 2004. In Goldberg 1986, 14 infants in the group treated with thiopental and 12 infants in the control group received phenobarbital for the treatment of clinical seizures. Hall 1998 compared phenobarbital with conventional treatment for the prevention of seizures following asphyxia. The control group received a mean of 27 mg/kg of phenobarbital as treatment for seizures, compared to a mean of 39 mg/kg in the experimental group. The incidence of seizures was greater in the control group, compared to the phenobarbital group, and this may have led to the control group requiring more anticonvulsants for treatment (a downstream treatment effect). The clinicians caring for the infants were aware of treatment allocation, however, and may have had a lower threshold to diagnose and treat clinical seizures in the control group (co-intervention bias). In Vargas-Origel 2004, 3 out of 36 infants in the control group received phenobarbital for the treatment of seizures: additional phenobarbital was needed in 2 out of 37 infants in the experimental group. In Ruth 1991 and Singh 2004, the numbers of infants treated with additional anticonvulsants were not stated.

Attrition

There was a post-randomisation loss of 23% in the study by Hall 1998, 13% in Kuzemko 1972, 3% in Goldberg 1986 and 0% in Vela 1987; Singh 2004 and Vargas-Origel 2004. There were no data to calculate attrition in Ruth 1991.

Detection

Only three studies had blind assessment of outcome; only one of these (Goldberg 1986) assessed outcomes outside the neonatal

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period. Vela 1987 utilised a double-blind study design. Kuzemko 1972 used an independent clinician to administer the medications and the neonatal staff responsible for assessment were blind to study group allocation. Goldberg 1986 used a blinded outcome assessment at 1-3 years but the high incidence of hypotension in the experimental group may have led to the shorter term outcomes, such as clinical seizures, being recorded without the clinician being blind.

RESULTS

None of the studies reported data to enable analyses according to subgroups other than type of anticonvulsant.

BARBITURATES VS. CONTROL (Comparison 01):

Death (before neurodevelopmental assessment by 3 years) (Outcome 01.01):

There was no significant difference in mortality rates between experimental and control groups reported in the five studies comparing barbiturates with standard therapy (Goldberg 1986; Hall 1998; Ruth 1991; Singh 2004; Vargas-Origel 2004). The meta-analysis, combining results from these studies, also showed no significant difference in mortality rates (typical RR 1.13, 95% CI 0.59, 2.17).

Severe neurodevelopmental disability in survivors examined (Outcome 01.02):

There was no significant difference in the rates of severe neurodevelopmental disability between experimental and control groups reported in the three studies comparing barbiturates with standard therapy and reporting this outcome (Goldberg 1986; Ruth 1991; Hall 1998). The meta-analysis, combining results from these studies, also showed no significant difference in rates of severe neurodevelopmental disability (typical RR 0.61, 95% CI 0.30, 1.22).

Death or severe neurodevelopmental disability (Outcome 01.03):

Only one study demonstrated a significant reduction in the relative risk of the combined outcome of severe neurodevelopmental disability or death in infants treated with phenobarbital (RR = 0.30, 95% CI 0.10 to 0.93; Hall 1998), although the significant post-randomisation loss, potential for co-intervention bias and unblinded outcome assessment raise concerns about the validity of these findings. The other two studies that reported both death and neurodevelopmental outcomes showed no difference in the risk of the combined outcome of severe neurodevelopmental disability or death, when comparing barbiturates with standard therapy (Goldberg 1986 and Ruth 1991). The meta-analysis, combining results from these three studies, also showed no significant difference in the risk of the combined outcome of death or severe neurodevelopmental disability (typical RR 0.78, 95% CI 0.49, 1.23).

PHENOBARBITAL VS. CONTROL (Comparison 02):

Seizures within neonatal period (Outcome 02.01):

Two studies compared Phenobarbital versus control and reported the rates of seizures within the neonatal period (Hall 1998; Vargas-Origel 2004); neither reported any significant difference in rates. The seizures rates were relatively low in both groups in the study by Vargas-Origel 2004, reflecting the fact that only a small proportion of infants enrolled had moderate or severe HIE.

IQ in survivors at 6 years of age (Outcome 02.02):

There was no significant difference in the IQ of survivors at six years of age, treated with phenobarbital or control as neonates (Ruth 1991).

Hypotension requiring inotropes (Outcome 02.03):

Singh 2004 stated that side effects of phenobarbital (hypotension, respiratory depression or excessive sleepiness) were not seen during the study. Vargas-Origel 2004 reported arterial pressures two hours after trial entry and there was no significant difference in values between those infants given prophylactic phenobarbital and those in the control group.

THIOPENTONE VS. CONTROL (Comparison 03):

Goldberg 1986 compared Thiopentone versus control and reported the proportions of infants suffering from seizures within three days of age and at three days of age.

Seizures within 3 days of age (Outcome 03.01):

No significant difference reported (Goldberg 1986).

Seizures at 3 days of age (Outcome 03.02):

No significant difference reported (Goldberg 1986).

Hypotension requiring inotropes (Outcome 03.03):

Goldberg 1986 reported an increase in the relative risk of neonatal hypotension, requiring inotropic support, associated with thiopental therapy, although this was not significant (RR = 1.76, 95% CI 0.98 to 3.16).

PHENOBARBITAL VS. PHENYTOIN (Comparison 04):

Seizures within the first 7 days of age (Outcome 04.01):

Vela 1987 reported similar rates of seizures occurring within the first week, when comparing Phenobarbital with Phenytoin.

CHLORAL HYDRATE VS. DIAZEPAM (Comparison 05):

Seizures beyond 3 days of age (Outcome 05.01):

Kuzemko 1972 did not find any significant difference in the proportions of infants with seizures occurring beyond three days of age, in infants treated with either Chloral Hydrate or Diazepam after birth.

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DISCUSSION

Perinatal asphyxia remains an important cause of death and neurodevelopmental disability. In this review, seven randomised controlled trials of anticonvulsants for preventing mortality and morbidity in full term infants with perinatal asphyxia were identified. It is disappointing that all the studies reporting mortality and neurodevelopmental disability are small in number (n < 40) and only one study assessed neurodevelopment blind to allocated intervention. Currently, there is little evidence from these studies to suggest that treatment with anticonvulsants following perinatal asphyxia in term infants leads to improvement in these outcomes.

Asphyxia also leads to seizure activity, which, in turn, may further compromise neuronal recovery. Seizures within the neonatal period is an outcome reported by most studies in this review. There is little evidence that treatment with anticonvulsants soon after an episode of perinatal asphyxia significantly reduces the subsequent seizure burden. It also remains to be established whether prevention of such seizure burden would represent a significant clinical achievement, i.e. whether reducing seizure activity will be translated into improvements in rates of death or severe neurodevelopmental disability.

No uniform definition of perinatal asphyxia was used between studies. This is because, in the absence of a valid and practical single marker of an hypoxic-ischaemic insult (with the potential to cause significant cerebral injury), the definition of perinatal asphyxia will remain clinical. Studies should strive towards a common clinical definition and endeavour to collect data relating to the markers in the neonatal period known at present to be associated with a poor neurodevelopmental outcome (e.g. magnetic resonance imaging, EEG data, etc.). It is also important for future research to identify other early and reliable markers associated with greatest risk of asphyxial cerebral injury, in order that potential neuroprotective strategies, commenced soon after birth, can be assessed in future studies.

AUTHORS' CONCLUSIONS

Implications for practice

At the present time, anticonvulsant therapy to term infants in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures.

Implications for research

Any future studies should be of high quality: randomised control trials with allocation, performance and outcome assessment blinding. Such studies should be of sufficient size, with minimal attrition, to have the power to detect clinically important reductions in mortality and severe neurodevelopmental disability, as the primary outcome measures. Potential adverse effects, such as hypotension following barbiturate therapy, should be prospectively defined and reported. The relatively low incidence of perinatal asphyxia is such that there is a need for collaborative effort in order to mount such future studies.

POTENTIAL CONFLICT OF INTEREST

None

ACKNOWLEDGEMENTS

The authors wish to acknowledge the help given by Dr Eduardo Moya (for translation of Vela 1987) and Dr Maria Juarez (for translation of Vargas-Origel 2004).

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- University of Leeds UK
- North Bristol NHS Trust UK

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TABLES

Characteristics of included studies

Study	Goldberg 1986
Methods	RCT: assignment "using list of random numbers" Controlled trial. No placebo. Sources of potential bias: Selection: B; Performance: C; Attrition: B, 2 patients (1 patient each group) lost to neurodevelopmental follow up (6%); Detection: C (neonatal outcomes), B (assessment at 1-3y).
Participants	Term infants with severe perinatal asphyxia. Criteria: signs of hypoxic-ischaemic encephalopathy and requiring mechanical ventilation within first hour of life; plus two of the following: perinatal distress (abnormal fetal heart pattern or requiring prolonged neonatal resuscitation); Apgar score below 5 at 5 minutes; base deficit greater than 16 mEq/l within first hour of life. At trial entry: n=17 (experimental); n=15 (control).
Interventions	Experimental: Thiopental 15 mg/kg IV over 30 minutes, then 10 mg/kg/h for 90 minutes, 5 mg/kg/h for 60 minutes, 3 mg/kg/h for 8 hours, 1.5 mg/kg/h for 6 hours and 0.75 mg/kg/h for 6 hours. Control: conventional therapy (phenobarbitone or phenytoin for clinically evident seizures).
Outcomes	Hypotension requiring inotropes. Hypotension defined by attending clinician, based upon normative data. Clinically apparent seizure activity over the first three days of life. Death before neurodevelopmental assessment. Neurodevelopmental assessment at 1-3 years of age (Bayley). Severe neurodevelopmental defined as Bayley <68.

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Characteristics of included studies (*Continued*)

Notes	Co-intervention: 14 experimental and 12 control infants received phenobarbitone for seizures.
Allocation concealment	B – Unclear

Study	**Hall 1998**
Methods	RCT. Sealed envelope randomisation. Controlled trial. No blinding. No placebo. Sources of potential bias: Selection: A; Performance: C; Attrition: D, 9 patients (23% post randomisation loss): 5 experimental, 4 control; Detection: D.
Participants	Term infants with severe perinatal asphyxia. Asphyxia defined by one of following criteria: initial arterial pH below 7.0 with base deficit above 15 mEq/l; Apgar score less than 4 at 5 minutes; no spontaneous respiratory effort before 10 minutes of life. At trial entry: n=20 (experimental); n=20 (control).
Interventions	Experimental: Phenobarbitone 40 mg/kg, IV over 60 minutes, administered after trial entry. Control: Standard therapy (phenobarbitone given in order to treat clinical seizures).
Outcomes	Number of infants with clinically evident seizures. Death before neurodevelopmental assessment. Neurodevelopmental assessment at 3 years of age (Gessell, Bayley, or Stanford-Binet). Appropriate definitions of severe neurodevelopmental disability.
Notes	Co-intervention: control group received mean of 27 mg/kg of phenobarbitone in first 24 hours, compared to a mean of 39 mg/kg in the experimental group.
Allocation concealment	A – Adequate

Study	**Kuzemko 1972**
Methods	RCT: Randomised. Prescription and administration of medication independent of assessment. Sources of potential bias: Selection: C; Performance: A; Attrition: C, 4 infants (13% post randomisation loss), 2 patients each group. Detection: A.
Participants	Term infants with cerebral irritability. Vague case definition. At trial entry: n=17 (Chloral Hydrate); n=11 (Diazepam).
Interventions	Chloral Hydrate 80 mg 6 hourly for 24-72 hours. Diazepam 1 mg 6 hourly for 24-72 hours.
Outcomes	Clinical seizures persisting beyond 3 days of life.
Notes	Short-term (neonatal) outcomes.
Allocation concealment	C – Inadequate

Study	**Ruth 1991**
Methods	RCT: unclear methods of randomisation, allocation concealment, blinding and use of placebo. Sources of potential bias: Selection: B; Performance: B; Attrition: D (no data); Detection: D.

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Characteristics of included studies (*Continued*)

Participants	Term infants with severe asphyxia (Apgar score less than 4 at 5 minutes or requiring mechanical ventilation beyond 30 minutes of life). At trial entry: n=21 (experimental); n=17 (control).
Interventions	Experimental: Phenobarbitone 30 mg/kg IV before 4 hours of age, a further 15 mg/kg 4 hours following first dose, followed by 5 mg/kg/day for 5 days. Control: conventional therapy.
Outcomes	Death before neurodevelopmental assessment. Neurodevelopmental assessment: Disability stated as cerebral palsy. Cognitive assessment at 6 years of age (WISC-r), expressed as IQ.
Notes	Co-intervention: not stated.
Allocation concealment	B – Unclear

Study	**Singh 2004**
Methods	RCT: assigned by computer-generated random numbers. No blinding. No placebo. Sources of potential bias: Selection: B; Performance: C; Attrition: A (nil); Detection: C.
Participants	Infants >33 weeks with Apgar <6 at 1 min plus fetal distress (fetal bradycardia or meconium-stained liquor or cord arterial pH<7.16) plus abnormality of tone and conscious level within 6 hours. At trial entry: n=25 (experimental); n=20 (control).
Interventions	Experimental: Phenobarbital 20 mg/kg IV within 6 hours of life. Control: standard therapy (no placebo).
Outcomes	Death, neurologically abnormal at discharge, CSF levels of malondialdehyde, superoxide dismutase, glutathione peroxidase and plasma levels of vitamins A and E.
Notes	Although the participants included infants below 37 weeks gestation, the study was included in this review as the majority of infants were near-term (>35 weeks). Co-intervention: not stated. The study reported mainly short term (neonatal) outcomes; only death was considered as an outcome for this review.
Allocation concealment	B – Unclear

Study	**Vargas-Origel 2004**
Methods	RCT. Unstated method of randomisation. Controlled trial. No blinding. No placebo. Sources of potential bias: Selection: B; Performance: C; Attrition: A (nil); Detection: C.
Participants	Infants >=37 weeks with one of the following: (a) umbilical arterial pH<=7.00 within 15min of life, (b) Base Deficit >=15mmol/l, (c) Apgar <3 at 5min, (d) no spontaneous respiration within first 10min. At trial entry: n=37 (Phenobarbital); n=36 (control).
Interventions	Experimental: Phenobarbital 40 mg/kg, IV over 60 minutes, administered within first hour of age. Control: Standard therapy (phenobarbital given in order to treat clinical seizures).
Outcomes	Death, Sarnat grade of HIE, number of infants with clinical seizures.
Notes	Short-term (neonatal) outcomes. Co-intervention: 5/36 infants in control group given Phenobarbital (mean dose 26mg/kg, mean time 9.2 hours. Experimental group given Phenobarbital 40mg/kg (mean time 0.88 hours). Infants in the trial had a relatively low rate of HIE grade II or III (12% overall: 11% experimental, 14% control).
Allocation concealment	B – Unclear

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Study	Vela 1987
Methods	RCT: randomisation procedure not clear, double-blind, controlled study. Sources of potential bias: Selection: B; Performance: A; Attrition: A (nil); Detection: A.
Participants	Term infants with perinatal asphyxia, defined as three of the following criteria: multiple late fetal heart rate decelerations, fetal bradycardia for >20 minutes, meconium-stained liquor, Apgar score of less than 8 at 5 minutes, requiring mechanical ventilation, requiring IV bicarbonate therapy. At trial entry: n=9 (Phenobarbitone); n=8 (Phenytoin).
Interventions	Phenobarbitone 12mg/kg IM, followed by 6 mg/kg/day for 7 days. Phenytoin 12mg/kg IM, followed by 6 mg/kg/day for 7 days.
Outcomes	Clinical seizures within the first 7 days.
Notes	Short-term (neonatal) outcomes.
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Ruth 1988	Eligibility criteria did not include evidence of perinatal asphyxia Infants < 1500g eligible and randomised to phenobarbitol or placebo for prevention of potential complications of 'unrecognised' asphyxia.
Wilkinson 1989	Anticonvulsants were used for treatment (not prevention) of electro-encephalographically apparent seizures of any aetiology, not exclusively perinatal asphyxia. Infants were a mixture of term and premature neonates. It was not possible to extract the data relating only to term infants following asphyxia.

ANALYSES

Comparison 01. Barbiturates vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death (before neurodevelopmental assessment by 3 years)	5	228	Relative Risk (Fixed) 95% CI	1.13 [0.59, 2.17]
02 Severe neurodevelopmental disability in survivors examined	3	77	Relative Risk (Fixed) 95% CI	0.61 [0.30, 1.22]
03 Death or severe neurodevelopmental disability	3	110	Relative Risk (Fixed) 95% CI	0.78 [0.49, 1.23]

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Comparison 02. Phenobarbital vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Seizures within neonatal period	2	113	Relative Risk (Fixed) 95% CI	0.72 [0.42, 1.23]
02 IQ in survivors at 6 years of age	1	30	Weighted Mean Difference (Fixed) 95% CI	-3.00 [-21.57, 15.57]
03 Hypotension requiring inotropes	2	118	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 03. Thiopentone vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Seizures within 3 days of age	1	32	Relative Risk (Fixed) 95% CI	1.03 [0.74, 1.44]
02 Seizures at 3 days of age	1	32	Relative Risk (Fixed) 95% CI	1.06 [0.40, 2.77]
03 Hypotension requiring inotropes	1	32	Relative Risk (Fixed) 95% CI	1.76 [0.98, 3.16]

Comparison 04. Phenobarbital vs. phenytoin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Seizures within the first 7 days of age	1	17	Relative Risk (Fixed) 95% CI	0.89 [0.07, 12.00]

Comparison 05. Chloral hydrate vs. diazepam

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neonatal seizures beyond 3 days of age	1	28	Relative Risk (Fixed) 95% CI	0.32 [0.03, 3.16]

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Asphyxia Neonatorum [*drug therapy; mortality]; Infant, Newborn; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

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

Authors Evans DJ, Levene MI, Tsakmakis M

Contribution of author(s) David Evans and Malcolm Levene conducted the original review in 1999 and update in 2001. For the most recent update, Maria Tsakmakis implemented the search and arranged for translation of papers. DE and MT appraised the new studies and DE updated the analyses and text of the review.

Issue protocol first published 1998/3

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Review first published	1998/3
Date of most recent amendment	21 May 2007
Date of most recent SUBSTANTIVE amendment	08 March 2007
What's New	This review updates the existing review "Anticonvulsants for preventing mortality and morbidity in full term newborns with perinatal asphyxia", first published in The Cochrane Library, Issue 3, 1998 and updated in Issue 2, 2001 (Evans 1998, Evans 2001). Our search was updated in January 2007. Two additional studies have been incorporated in the review since 2001.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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DOI	10.1002/14651858.CD001240.pub2
Cochrane Library number	CD001240
Editorial group	Cochrane Neonatal Group
Editorial group code	HM-NEONATAL

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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Barbiturates vs. control, Outcome 01 Death (before neurodevelopmental assessment by 3 years)

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

Comparison: 01 Barbiturates vs. control

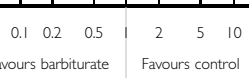
Outcome: 01 Death (before neurodevelopmental assessment by 3 years)

Study	Barbiturates n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goldberg 1986	5/17	3/15		23.0	1.47 [0.42, 5.14]
Hall 1998	2/20	4/20		28.9	0.50 [0.10, 2.43]
Ruth 1991	5/21	3/17		24.0	1.35 [0.37, 4.86]
Singh 2004	5/25	3/20		24.1	1.33 [0.36, 4.92]
× Vargas-Origel 2004	0/37	0/36		0.0	Not estimable
Total (95% CI)	120	108		100.0	1.13 [0.59, 2.17]

Total events: 17 (Barbiturates), 13 (Control)

Test for heterogeneity chi-square=1.33 df=3 p=0.72 I^2 =0.0%

Test for overall effect z=0.36 p=0.7



Analysis 01.02. Comparison 01 Barbiturates vs. control, Outcome 02 Severe neurodevelopmental disability in survivors examined

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

Comparison: 01 Barbiturates vs. control

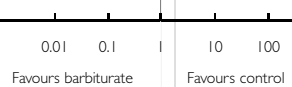
Outcome: 02 Severe neurodevelopmental disability in survivors examined

Study	Barbiturate n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goldberg 1986	5/11	6/11		41.7	0.83 [0.36, 1.94]
Hall 1998	1/13	6/12		43.4	0.15 [0.02, 1.10]
Ruth 1991	3/16	2/14		14.8	1.31 [0.25, 6.76]
Total (95% CI)	40	37		100.0	0.61 [0.30, 1.22]

Total events: 9 (Barbiturate), 14 (Control)

Test for heterogeneity chi-square=3.25 df=2 p=0.20 I^2 =38.5%

Test for overall effect z=1.40 p=0.2



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Analysis 01.03. Comparison 01 Barbiturates vs. control, Outcome 03 Death or severe neurodevelopmental disability

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

Comparison: 01 Barbiturates vs. control

Outcome: 03 Death or severe neurodevelopmental disability

Study	Barbiturate n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Goldberg 1986	10/17	9/15		38.1	0.98 [0.55, 1.74]
Hall 1998	3/20	10/20		39.9	0.30 [0.10, 0.93]
Ruth 1991	8/21	5/17		22.0	1.30 [0.52, 3.24]
Total (95% CI)	58	52		100.0	0.78 [0.49, 1.23]
Total events: 21 (Barbiturate), 24 (Control)					
Test for heterogeneity chi-square=4.53 df=2 p=0.10 I^2 =55.9%					
Test for overall effect z=1.08 p=0.3					

Analysis 02.01. Comparison 02 Phenobarbital vs. control, Outcome 01 Seizures within neonatal period

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

Comparison: 02 Phenobarbital vs. control

Outcome: 01 Seizures within neonatal period

Study	Phenobarbital n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hall 1998	9/20	14/20		77.5	0.64 [0.37, 1.13]
Vargas-Origel 2004	4/37	4/36		22.5	0.97 [0.26, 3.60]
Total (95% CI)	57	56		100.0	0.72 [0.42, 1.23]
Total events: 13 (Phenobarbital), 18 (Control)					
Test for heterogeneity chi-square=0.35 df=1 p=0.55 I^2 =0.0%					
Test for overall effect z=1.22 p=0.2					

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Analysis 02.02. Comparison 02 Phenobarbital vs. control, Outcome 02 IQ in survivors at 6 years of age

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

Comparison: 02 Phenobarbital vs. control

Outcome: 02 IQ in survivors at 6 years of age

Study	Phenobarbital N	Phenobarbital Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Ruth 1991	16	108.00 (21.00)	14	111.00 (29.50)		100.0	-3.00 [-21.57, 15.57]
Total (95% CI)	16		14			100.0	-3.00 [-21.57, 15.57]

Test for heterogeneity: not applicable

Test for overall effect z=0.32 p=0.8

Analysis 02.03. Comparison 02 Phenobarbital vs. control, Outcome 03 Hypotension requiring inotropes

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

Comparison: 02 Phenobarbital vs. control

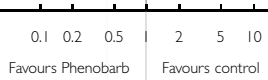
Outcome: 03 Hypotension requiring inotropes

Study	Phenobarbital n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Singh 2004	0/25	0/20		0.0	Not estimable
× Vargas-Origel 2004	0/37	0/36		0.0	Not estimable
Total (95% CI)	62	56		0.0	Not estimable

Total events: 0 (Phenobarbital), 0 (Control)

Test for heterogeneity: not applicable

Test for overall effect: not applicable



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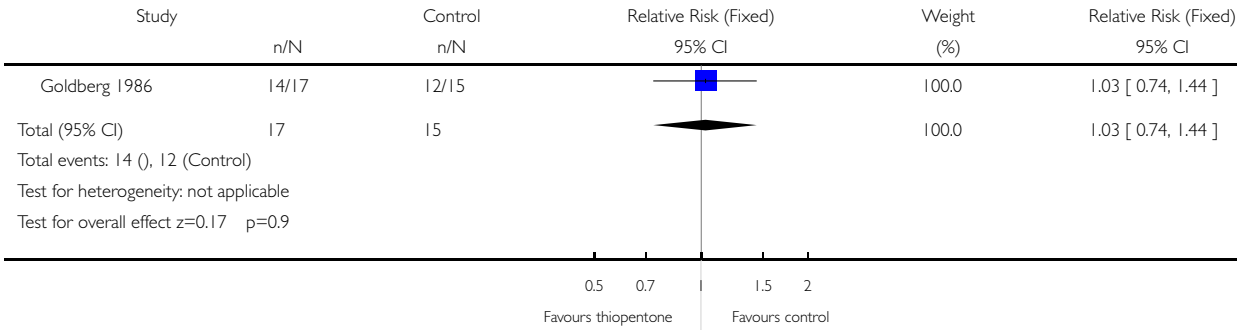
Analysis 03.01. Comparison 03 Thiopentone vs. control, Outcome 01 Seizures within 3 days of age

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

Comparison: 03 Thiopentone vs. control

Outcome: 01 Seizures within 3 days of age

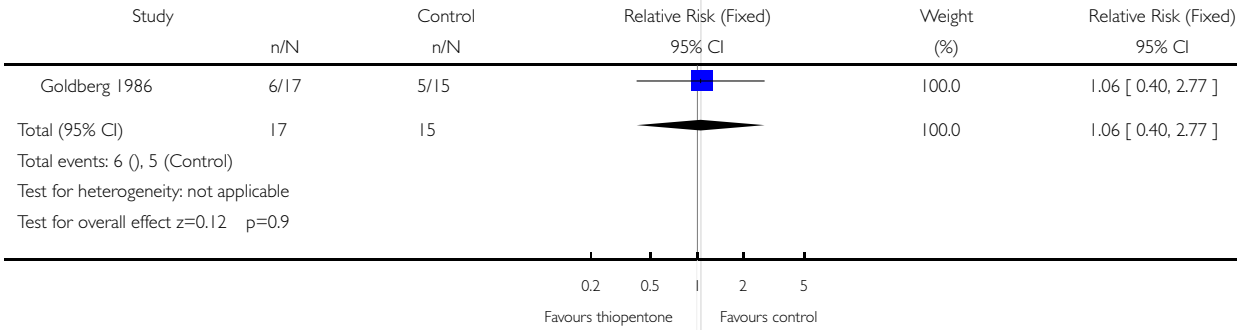


Analysis 03.02. Comparison 03 Thiopentone vs. control, Outcome 02 Seizures at 3 days of age

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

Comparison: 03 Thiopentone vs. control

Outcome: 02 Seizures at 3 days of age



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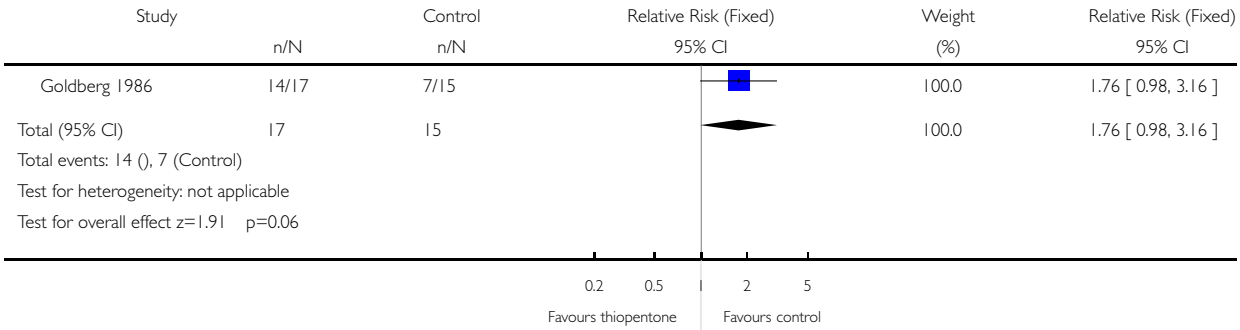
Analysis 03.03. Comparison 03 Thiopentone vs. control, Outcome 03 Hypotension requiring inotropes

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

Comparison: 03 Thiopentone vs. control

Outcome: 03 Hypotension requiring inotropes

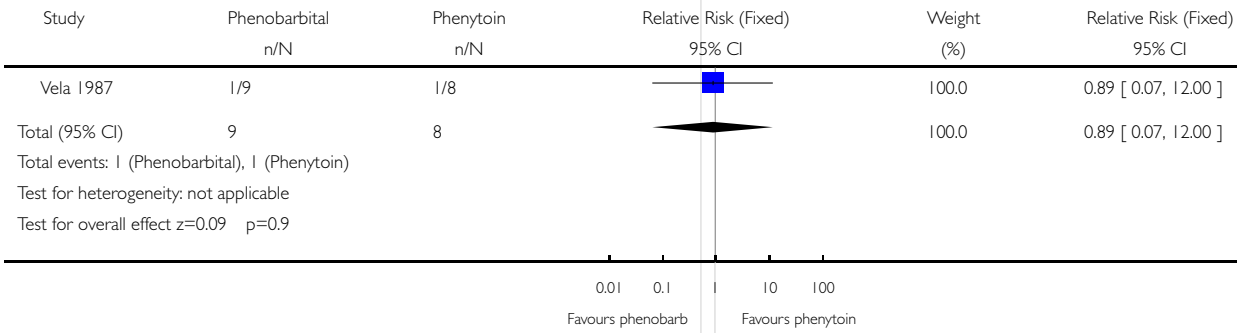


Analysis 04.01. Comparison 04 Phenobarbital vs. phenytoin, Outcome 01 Seizures within the first 7 days of age

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

Comparison: 04 Phenobarbital vs. phenytoin

Outcome: 01 Seizures within the first 7 days of age



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Analysis 05.01. Comparison 05 Chloral hydrate vs. diazepam, Outcome 01 Neonatal seizures beyond 3 days of age

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

Comparison: 05 Chloral hydrate vs. diazepam

Outcome: 01 Neonatal seizures beyond 3 days of age

Study		Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Kuzemko 1972	1/17	2/11		100.0	0.32 [0.03, 3.16]
Total (95% CI)	17	11		100.0	0.32 [0.03, 3.16]
Total events: 1 (), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					

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