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Allopurinol for women in pregnancy for neuroprotection of the fetus (Protocol)

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[Intervention Protocol]

Allopurinol for women in pregnancy for neuroprotection of the fetus

Kathryn A Martinello[1,2], Emily Shepherd[3], Philippa Middleton[4], Caroline A Crowther[3,5]

[1]Department of Neonatal and Perinatal Medicine, The University of Adelaide, Women's and Children's Hospital, Adelaide, Australia. [2]Department of Neonatology, Institute for Women's Health, University College London, London, UK. [3]ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [4]Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Adelaide, Australia. [5]Liggins Institute, The University of Auckland, Auckland, New Zealand

Contact address: Kathryn A Martinello, Department of Neonatal and Perinatal Medicine, The University of Adelaide, Women's and Children's Hospital, 72 King William Road, Adelaide, South Australia, 5006, Australia. kathryn.martinello@adelaide.edu.au, kathryn.martinello@ucl.ac.uk.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of maternal allopurinol when used for neuroprotection of the fetus.

BACKGROUND

Description of the condition

Fetal brain injury - causes and consequences

Fetal brain injury is a major contributor to perinatal mortality and morbidity worldwide, with such injury being associated with a spectrum of neurosensory disabilities across the lifespan (Jensen 2003). While a number of causes of fetal brain injury have been recognised (including intrauterine infection, genetic factors and placental insufficiency), episodes of cerebral hypoxia, both acute and chronic, are pivotal in a high proportion of cases. Acute intrapartum hypoxic-ischaemic events are estimated to account for 1.2 million stillbirths, 717,000 neonatal deaths and 413,000 survivors with neurodevelopmental impairment worldwide each year (Lee 2013). Following hypoxia-ischaemia, a cascade of brain injury occurs in phases: early cell death, resulting from primary exhaustion of cellular energy stores, followed by a secondary phase of cell death (late neuronal damage), during reoxygenation and reperfusion (Rees 2011). Late neuronal damage is hallmarked by near complete mitochondrial energy production failure, oxidative stress, cytotoxic oedema, cell death and clinical deterioration (Jensen 2003; Rees 2011; Wassink 2014). Oxidative stress results from the overproduction of free radicals, which damage lipids, protein, and deoxyribonucleic acid (DNA). Fetuses and neonates, particularly when preterm, have deficient endogenous antioxidant capacity and high aerobic metabolic demand, increasing their susceptibility to oxidative neuronal injury (Tataranno 2015). Most of

the free radical production during reperfusion injury is dependent on xanthine-oxidase-mediated metabolism of hypoxanthine (to xanthine) (Tataranno 2015; Warner 2004). Substances that can prevent the formation of free radicals, or scavenge the free radicals produced, therefore have the potential to reduce brain injury and improve neurologic outcomes.

Description of the intervention

Allopurinol

Allopurinol is an inhibitor of the pro-oxidant enzyme xanthine-oxidase, and together with its active metabolite, oxypurinol, acts as a scavenger for toxic free radicals, and chelates non-protein-bound iron (Prickaerts 2014). Studies in experimental animal models, such as in rat pups, have shown that allopurinol can reduce the production of free radicals, and accordingly reduce the impact of hypoxia-reperfusion brain injury (Palmer 1990; Palmer 1993; Williams 1992). Randomised controlled trials in human, term, asphyxiated neonates have demonstrated improvements in outcomes related to perinatal brain injury with allopurinol administration, including in electrocortical brain activity and free radical formation (Van Bel 1998), and neurologic and neurodevelopmental outcomes at 12 or more months of age (Gunes 2007; Kaandorp 2012). Further randomised evidence has not, however, shown benefits for allopurinol when administered to severely asphyxiated human newborns, suggesting that beneficial effects may vary accordingly to degree of injury (Benders 2006). The relevant Cochrane Review 'Allopurinol for preventing mortality and morbidity in newborn infants with hypoxic-ischaemic encephalopathy' concluded that the data to determine clinically important benefits for allopurinol given to infants with hypoxic-ischaemic encephalopathy are to date, insufficient, and highlighted a need for larger trials in this area (Chaudhari 2012).

How the intervention might work

Allopurinol for fetal neuroprotection

It has been suggested that allopurinol may not be effective if administered 'too late' after an hypoxic event to offer neuroprotection. Evidence suggests that the majority of toxic free radical production associated with perinatal asphyxia occurs during the hypoxic in utero event, and to a greater extent, in the 30 to 60 minutes after birth with reoxygenation and reperfusion (Kaandorp 2012). There is thus increasing interest in the use of antenatally administered allopurinol, for providing fetal neuroprotection. Allopurinol could be used in the acute setting as a single/short course intravenous medication during labour, in the case of suspected fetal hypoxia, or as a regular oral medication throughout pregnancy, in the more chronic settings of prenatal malnutrition and intrauterine growth restriction. Allopurinol is known to cross the placenta, and animal studies have provided support for the maternal administration of allopurinol. In a rodent model, allopurinol has been shown to cross the placenta and reduce the production of free radicals (Kane 2013). In sheep models, maternal treatment with allopurinol during fetal asphyxia has been shown to reduce fetal neuronal damage (Kaandorp 2014) and markers of oxidative stress (Derks 2010; Masaoka 2005). More recently, allopurinol, given daily in the third trimester to pregnant sows, has been shown to have a protective effect on neuronal plasticity markers in low birthweight piglets (Prickaerts 2014).

Despite evidence revealing the potential for improved perinatal outcomes following maternal receipt of allopurinol during pregnancy/labour, concerns have been expressed surrounding its potential teratogenicity, mediated by the disruption of purine biosynthesis. While in a case series of 31 pregnant women exposed to allopurinol (for various indications, such as renal disease and gout) the absolute rate of congenital abnormalities was only as expected, one infant was born with severe malformations (including cleft lip and palate, renal hypoplasia, low-set ears, hearing deficit, micropenis, microphthalmia and bilateral cryptorchidism) (Hoeltzenbein 2013); this affected infant had a similar constellation of abnormalities to that of a previously reported allopurinol-exposed infant (Kozenko 2011). While further case series have reported safe use of allopurinol during pregnancy (Fazal 2013) caution has been recommended, particularly for use during the first trimester.

In light of current and emerging evidence, it is considered plausible that allopurinol may protect the human fetal brain against hypoxic-ischaemic brain injury. It is possible, however, that antenatal administration may be associated with adverse outcomes. It is important to assess whether maternally administered allopurinol (at times of known, suspected or potential fetal compromise) may offer fetal neuroprotection, and thus improve health outcomes associated with perinatal brain injury, without increasing the risk of harm.

Why it is important to do this review

Available animal and human evidence supports a fetal neuroprotective role for allopurinol, a xanthine-oxidase inhibitor, when administered to the mother. A collaboration of international neonatal neuroscientists recently rated allopurinol amongst the top five most promising experimental agents for both fetal and neonatal neuroprotection (Robertson 2012). A recent Cochrane Review concluded that there is currently insufficient data to determine whether allopurinol has clinically important benefits when administered to the compromised newborn, and highlighted the need for larger trials, assessing mortality and adverse long-term neurodevelopmental outcomes (Chaudhari 2012). It is now important to determine whether available evidence from human trials

of maternal antenatal administration of allopurinol can improve outcomes associated with perinatal brain injury, including mortality and neurosensory disabilities. This review will complement the existing Cochrane Reviews assessing antenatal administration of magnesium sulphate (Doyle 2009; Nguyen 2013), melatonin (Wilkinson 2016) and creatine (Dickinson 2014) for fetal neuroprotection.

OBJECTIVES

To assess the effectiveness and safety of maternal allopurinol when used for neuroprotection of the fetus.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published, unpublished and ongoing randomised, quasi-randomised and cluster-randomised controlled trials assessing maternal allopurinol for fetal neuroprotection. Cross-over trials will be excluded. We will include studies published as abstract only, provided there is sufficient information to allow us to assess study eligibility and risk of bias.

Types of participants

We will include any pregnant woman, regardless of whether the pregnancy was single or multiple, and regardless of the gestational age. This could include, for example, trials for women with acute intrapartum hypoxia-ischaemia, or in the setting of chronic fetal hypoxia-ischaemia and intrauterine growth restriction. This could also include pregnant women without actual/suspected fetal hypoxia with other pathology relevant to the intervention (ie gout).

Types of interventions

We will include all comparisons of allopurinol given to women, with a placebo or no treatment, or to an alternative agent aimed at providing fetal neuroprotection. We will include studies regardless of the route (i.e. oral or intravenous), timing, dose and duration of allopurinol administration. We will review intravenous and oral allopurinol together, as the oral bioavailability is nearly equivalent to intravenous (Breithaupt 1982). We will also include comparisons of different regimens for administration of allopurinol, that is, short- and long-term treatment courses (see subgroup analyses).

Types of outcome measures

Primary outcomes

For the infant/child

- Death or any neurosensory disability (this combined outcome recognises the potential for competing risks of death or survival with neurological problems) (at latest time reported)
- Death (defined as all fetal, neonatal or later death) (at latest time reported)
- Neurosensory disability (any of cerebral palsy, blindness, deafness, developmental delay/intellectual impairment) (at latest time reported) - see definitions below:
    - cerebral palsy: abnormality of tone with motor dysfunction (as diagnosed at 18 months or later)
    - blindness: corrected visual acuity worse than 6/60 in the better eye
    - deafness: hearing loss requiring amplification or worse
    - developmental delay/intellectual impairment: a standardised score less than minus one standard deviation (SD) below the mean

For the mother

- Any adverse effects severe enough to stop treatment

Secondary outcomes

For the fetus/neonate

- Fetal death
- Neonatal death
- Congenital abnormalities
- Gestational age at birth
- Birthweight (absolute and centile)
- Apgar score less than 7 at five minutes
- Active resuscitation via an endotracheal tube at birth
- Use of respiratory support (mechanical ventilation, continuous positive airways pressure or both)
- Seizures, either apparent clinically or detected by electroencephalographic recordings
- Hypoxic ischaemic encephalopathy (as defined by trialists)
- Neonatal encephalopathy (as defined by trialists)
- Any cortical, basal ganglia or white matter abnormality on brain imaging (magnetic resonance, computed tomography, or ultrasound)
- Intraventricular haemorrhage (including severity, as defined by trialists)
- Proven neonatal sepsis (as defined by trialists)

- Nectrotising enterocolitis (as defined by trialists)
- Abnormal neurological examination (as defined by the trialists, at a point earlier than 18 months of age)

For the mother

- Side effects and serious adverse events associated with treatment
- Women's satisfaction with treatment
- Mode of birth (normal vaginal birth, operative vaginal birth, caesarean section)

For the infant/child

- Cerebral palsy (any, and graded as severe: including children who are non-ambulant and are likely to remain so; moderate: including those children who have substantial limitation of movement; mild: including those children walking with little limitation of movement)
- Death or cerebral palsy
- Blindness
- Deafness
- Developmental delay/intellectual impairment (any, and classified as severe: a developmental quotient or intelligence quotient less than minus three SD below the mean; moderate: a developmental quotient or intelligence quotient from minus three SD to minus two SD below the mean; mild: a developmental quotient or intelligence quotient from minus two SD to minus one SD below the mean)
- Major neurosensory disability (defined as any of: moderate or severe cerebral palsy, legal blindness, neurosensory deafness requiring hearing aids, or moderate or severe developmental delay/intellectual impairment)
- Death or major neurosensory disability
- Growth assessments at childhood follow-up (weight, height, head circumference)

Use of health services

- Admission to intensive care unit for the mother
- Length of postnatal hospitalisation for the mother
- Admission to neonatal intensive care for the infant
- Costs of care for the mother or baby, or both

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.
The Register is a database containing over 24,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Cochrane Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.
Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).
In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the term 'allopurinol'.

Searching other resources

We will search the reference lists of retrieved studies.
We will not apply any language or date restrictions.

Data collection and analysis

We will use the following methods for assessing studies identified by the search.

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third review author.

We will create a PRISMA study flow diagram to map out the number of records identified, included and excluded (Liberati 2009).

Data extraction and management

We will design a purpose-built, electronic form to manage data extraction. The data extraction form will also include trial dates, sources of trial funding, and trialists' declarations of interest. For eligible studies, two review authors will extract the data using the agreed form. Discrepancies will be resolved through discussion or, if required, referred to a third review author. We will enter data into Review Manager 5 (RevMan 5) software (RevMan 2014) and check for accuracy. When information regarding any of the above is absent or unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses that we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as-treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest have been reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to affect the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

We will use the GRADE approach to evaluate the quality of the evidence, as outlined in the GRADE handbook (GRADE Working Group 2004). The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for specific outcomes. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. In this review we will use the GRADE approach to assess the following outcomes.

For the/infant/child

- Death or any neurosensory disability (this combined outcome recognises the potential for competing risks of death or survival with neurological problems) (at latest time reported)
- Death (defined as all fetal, neonatal or later death) (at latest time reported)
- Neurosensory disability (any of cerebral palsy, blindness, deafness, developmental delay/intellectual impairment) (at latest time reported)
- Congenital abnormalities
- Admission to neonatal intensive care
- Neonatal encephalopathy

For the mother

- Any adverse effects severe enough to stop treatment

We will use GRADEpro Guideline Development Tool (GRADEpro GDT 2015) to import data from RevMan 5 (RevMan 2014) in order to create a 'Summary of findings' table, which will present a summary of the intervention effect and a measure of quality according to the GRADE approach for each of the above outcomes.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised

trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multi-armed studies

We plan to include multi-armed trials, ensuring analyses are independent. If multi-armed trials are included, we will split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. Alternatively, we will combine groups to create a single pair-wise comparison.

Cross-over trials

We will exclude cross-over designs as these are unlikely to be a valid study design for Pregnancy and Childbirth Reviews.

Multiple pregnancies

As infants from multiple pregnancies are not independent, we plan to use cluster-trial methods in the analyses, where the data allows, and where multiples make up a substantial proportion of the trial population, to account for non-independence of variables (Gates 2004).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, that is, we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 (Higgins 2003) and Chi^2 statistics (Deeks 2017). We will regard heterogeneity as substantial if an I^2 statistic is greater than 30% and either the Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it (Sterne 2017).

Data synthesis

We will carry out statistical analysis using the RevMan 5 software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: that is, where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, we will present the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We will perform separate comparisons for those trials comparing allopurinol with no treatment or a placebo, and those comparing allopurinol with an alternative neuroprotective agent.
If we identify substantial heterogeneity, we will investigate it using subgroup analyses. We will perform subgroup analyses, where possible, for the following subgroups.

- Gestational age at commencement of allopurinol: less than 20 weeks' gestation versus 20 weeks' gestation or more
- Time of commencement of allopurinol: antenatal versus intrapartum
- Indication: routine supplementation/maternal indication versus for those deemed at risk or showing evidence of fetal hypoxia
- Dose: low dose ($\leq$ 100 mg daily) versus medium dose (> 100 and < 600 mg daily) versus high dose ($\geq$ 600 mg daily)

Subgroup analyses will be limited to the review's primary outcomes.

We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it. We will assess subgroup differences by interaction tests available within RevMan 5 (RevMan 2014. We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I^2 statistic value.

Sensitivity analysis

We will explore the effects of trial quality assessed by allocation concealment and random sequence generation (considering selection bias), by omitting studies rated as 'high risk of bias' (including quasi-randomised trials) or 'unclear risk of bias' for these components. We will investigate the effects of the randomisation unit (individual versus cluster) on the outcomes, and the impact of including studies with high levels of missing data. We will explore the effects of any assumptions made, such as the value of the ICC used for cluster-randomised trials. Sensitivity analyses will be limited to the primary outcomes.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Kathryn Martinello and Emily Shepherd drafted the first version of the protocol, with Philippa Middleton and Caroline Crowther making comments and contributing to the final draft.

DECLARATIONS OF INTEREST

Kathryn Martinello: Current (Sept 2015-) honorary research staff member with the Neonatal Neuroprotection Group, Institute for Women's Health, University College London, UK. This group investigates numerous neuroprotectants in a postnatal preclinical model of hypoxic-ischaemic encephalopathy, not including allopurinol. This group has, in the past, held a grant from Chiesi Pharmaceuticals for research into melatonin as a postnatal neuroprotectant.

Emily Shepherd: none known.

Philippa Middleton: none known.

Caroline Crowther: none known.

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