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Xenon as an adjuvant to therapeutic hypothermia in near term and term newborns with hypoxic ischaemic encephalopathy (Protocol)

Rüegger CM, Davis PG, Cheong JL

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TABLE OF CONTENTS

[Intervention Protocol]

Xenon as an adjuvant to therapeutic hypothermia in near term and term newborns with hypoxic ischaemic encephalopathy

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ABSTRACT

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

To assess the effects of xenon as an adjuvant to therapeutic hypothermia on mortality and neurodevelopmental morbidity, and to ascertain clinically important side effects in newborn infants with HIE.

Secondary objectives will include early predictors of adverse outcome and assessment of potential side effects of xenon.

BACKGROUND

Description of the condition

Intrapartum asphyxia is the third leading cause of child death globally (Liu 2015). It is estimated that each year, over 0.7 million affected newborns die and 1.15 million develop acute disordered brain function known as hypoxic-ischaemic encephalopathy (HIE) (Lee 2013). HIE is one of the commonest causes of childhood neurodisability worldwide and results in a huge psychosocial and economic impact for families and society (Lawn 2014). Induced therapeutic hypothermia (body cooling) has emerged as an effective neuroprotective strategy in term and late preterm newborns suffering moderate to severe HIE. However, in the developed world half of the treated infants still die or face neurodevelopmental sequelae later in life (Jacobs 2013).

Human and animal studies have demonstrated that the basic cascade of brain injury related to hypoxic-ischaemic insults typically occurs in distinct phases (Hassell 2015); in the acute phase, the culmination of energy failure, acidosis, glutamate release, lipid peroxidation, and the toxic effect of nitric oxide leads to cell death via necrosis and activates apoptotic cascades (Ferriero 2004). After a partial recovery and a latent phase that lasts up to six hours, a secondary deterioration follows. This secondary phase is characterised by cytotoxic oedema, excitotoxicity, and secondary energy failure with nearly complete loss of mitochondrial activity

(Douglas-Escobar 2015). In newborns with moderate to severe HIE, this secondary phase of injury is typically associated with clinical deterioration and increased seizure activity. In magnetic resonance spectroscopy imaging (MRSI), which is the most accurate quantitative magnetic resonance biomarker in the neonatal period for prediction of neurodevelopmental outcome after HIE (Thayyil 2010), this secondary phase is generally accompanied by a second lactate elevation (Barkovich 1995). A tertiary phase involves active pathological processes occurring for months after a hypoxic-ischaemic insult, including late cell death, remodeling of the injured brain, and astrogliosis due to persistent inflammation and epigenetic changes (Fleiss 2012). It is this time following resuscitation, but before the secondary phase of injury, that allows for a potential window for neuroprotection or diminution of injury.

Description of the intervention

Xenon is an odourless, dense, noble gas that has been approved as an inhalational anaesthetic in adults. Xenon has a rapid onset of action via inhalation and is eliminated unchanged via the lungs within minutes when delivery is stopped. Upon administration, xenon rapidly decreases amplitude-integrated electroencephalogram (aEEG) background activity (Sabir 2016), which is consistent with clinical findings that demonstrate its anticonvulsant and electroencephalogram (EEG) suppressant effects in infants with HIE (Azzopardi 2013). Its potential as a neuroprotective agent, when inhaled at a subanaesthetic concentration of 50%, has been evaluated in small and large preclinical studies (Dingley 2006; Ma 2005). In animal models of moderate HIE, xenon significantly reduced brain injury and had an additive neuroprotective effect when combined with therapeutic hypothermia immediately after the insult (Chakkarapani 2010; Dingley 2008; Liu 2015; Thoresen 2009). This benefit was sustained with complete restoration of long-term functional outcomes and improved regional histopathology (Hobbs 2008).

The optimal timing, dose, and duration of inhaled xenon have not yet been established. Xenon has been shown to be neuroprotective in neonatal rats when administered before (Ma 2006), during (Ma 2005), and after a hypoxic insult (Dingley 2006). When administered immediately or within hours after a hypoxic-ischaemic event, xenon had a significant effect at concentrations of 40% ($Xe_{40\%}$) and greater (Ma 2005). When combined with therapeutic hypothermia in a hypoxic-ischaemic pig model, xenon was effective and safe in concentrations up to 70% and for as long as 24 hours (Chakkarapani 2010; Dingley 2008; Faulkner 2011). Although $Xe_{70\%}$ has been suggested to be more neuroprotective than $Xe_{50\%}$, most preclinical studies used concentrations $\leq$ 50% that induced sedation, allowed for the administration of substantial concentrations of oxygen, but did not result in respiratory depression (Dingley 2008).

In the field of adult critical care medicine, xenon's cardiovascular, analgesic, and safety profile has been thoroughly evaluated (Dingley 2001; Rossaint 2003; Sanders 2005). In the paediatric population, however, its safety has not yet been assessed systematically. In a piglet model of HIE that closely resembles perinatal asphyxia, xenon together with therapeutic hypothermia improved cardiovascular stability and reduced inotropic requirements (Chakkarapani 2012). There was no increased oxygen requirement, no cuffed tracheal tube complications, and no stridor or extubation delays either during or after xenon delivery (Chakkarapani 2010). Despite its favourable short-term safety profile, there is still considerable controversy around the lasting effect of anaesthetic agents on the developing brain in general (Sun 2010). Animal studies demonstrated that general anaesthetic agents produce accelerated apoptosis and cause adverse effects on cognition and behaviour (Jevtovic-Todorovic 2013; Andropoulos 2017). Xenon mainly acts by inhibiting the N-methyl-D-aspartate (NMDA) receptor, but in contrast to other inhalation anaesthetic agents, lacks dopamine-releasing properties and is not associated with an increase in neuroapoptosis (Faulkner 2011; Sabir 2013). A major disadvantage of xenon, however, is that it is difficult to use in clinical practice due to its scarcity (0.0087 ppm in air), high costs, and the need for closed-circuit delivery (including cuffed tubes) and recycling systems.

How the intervention might work

Xenon is an NMDA receptor antagonist which prevents postsynaptic binding of the excitatory neurotransmitter glutamate (Franks 1998). It competitively binds to the glycine site of the receptor (Dickinson 2007), by interacting with the aromatic ring of phenylalanine (Armstrong 2012). Xenon's neuroprotective properties have been demonstrated in cell culture (Petzelt 2003), in a rodent model of hypoxia-ischaemia (Dingley 2008; Hobbs 2008; Ma 2005; Thoresen 2009; Zhuang 2012), and in a neonatal pig model of global hypoxia-ischaemia (Chakkarapani 2010; Faulkner 2011). Apart from its blocking effect on NMDA receptors, additional neuroprotective mechanisms have been identified. Xenon activates two species of potassium channels including the inwardly rectifying K_{ATP} channel (Bantel 2010), and the two pore domain K^+channel (Gruss 2004); both of which have been linked to neuroprotection. Other actions include inhibition of the calcium/calmodulin dependent protein kinase II (Petzelt 2001), and activation of anti-apoptotic effectors Bcl-XL and Bcl-2 (Ma 2007). Furthermore, xenon increases the production of hypoxia-inducible factor 1alpha (HIF-1 alpha) and its downstream effectors erythropoietin, vascular endothelial growth factor, and glucose transporter 1 protein, which can interrupt the apoptotic pathway (Ma 2009). Through the inhibition of NMDA receptors and the reduction of apoptotic cell death, xenon is believed to exert most of its neuroprotective properties in the early and late phase of reperfusion injury.

Why it is important to do this review

Therapeutic hypothermia has been shown to be an effective therapy for neonatal HIE. However, the frequency of death and disability remains at about 50% in treated infants, necessitating the development of additional neuroprotective therapies. This is the first systematic review that will assess the evidence for xenon as an adjuvant to therapeutic hypothermia for newborns with HIE.

OBJECTIVES

To assess the effects of xenon as an adjuvant to therapeutic hypothermia on mortality and neurodevelopmental morbidity, and to ascertain clinically important side effects in newborn infants with HIE.

Secondary objectives will include early predictors of adverse outcome and assessment of potential side effects of xenon.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs that compare the use of inhaled xenon in combination with therapeutic hypothermia with therapeutic hypothermia alone.

Types of participants

1. Newborn infants of 35 weeks' gestation or greater with:
   i) evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria:
      a) Apgar score of five or less at 10 minutes;
      b) mechanical ventilation or resuscitation at 10 minutes;
      c) cord pH < 7.1, or an arterial pH < 7.1, or base deficit of 12 or more within 60 minutes of birth;
   ii) evidence of encephalopathy according to Sarnat staging (Finer 1981; Sarnat 1976):
      a) Stage 1 (mild): hyperalertness, hyperreflexia, dilated pupils, tachycardia, absence of seizures;
      b) Stage 2 (moderate): lethargy, hyperreflexia, miosis, bradycardia, seizures, hypotonia with weak suck, and Moro;
      c) Stage 3 (severe): stupor, flaccidity, small- to mid-position pupils that react poorly to light, decreased stretch reflexes, hypothermia, and absent Moro.
   iii) induced therapeutic hypothermia treatment (whole body or selective head cooling to 32°C to 34°C) initiated prior to six hours after birth;
   iv) no major congenital abnormalities recognisable at birth.

Types of interventions

Inhaled xenon (irrespective of the timing and the concentrations used) as an adjuvant to therapeutic hypothermia versus therapeutic hypothermia alone, based on the following prespecified definitions:

1. Therapeutic hypothermia:
   i) standard therapeutic hypothermia (whole body or selective head cooling to 32°C to 34°C initiated prior to six hours after birth) versus non-standard therapeutic hypothermia;
2. Xenon administration:
   i) irrespective of the timing (starting age and duration) and the concentrations used.

Types of outcome measures

Primary outcomes

The primary outcome measure will be death or long-term major neurodevelopmental disability in infancy (18 months to three years of age) defined as the following.

1. CP, graded according to the Gross Motor Function Classification System of Palisano 1997 for children two years and younger;
2. developmental delay (Bayley or Griffith assessment more than two standard deviations (SD) below the mean);
3. intellectual impairment (intelligence quotient (IQ) more than two SD below mean);
4. blindness (vision < 6/60 in both eyes);
5. sensorineural deafness requiring amplification.

Secondary outcomes

1. Death (all cause mortality to the latest follow-up examination);
2. major neurodevelopmental disability:
   i) in infancy (18 months to three years of age);
   ii) at school age (> five years);
3. each component of major neurodevelopmental disability in infancy (18 months to three years of age):
   i) CP, graded according to the Gross Motor Function Classification System of Palisano 1997 for children two years and younger;
   ii) developmental delay or intellectual impairment:

a) Bayley or Griffith assessment more than two SD below the mean or intellectual impairment (IQ more than two SD below mean);

b) neuromotor development (Bayley Scales of Infant Development - Psychomotor Development Index (BSID PDI)) assessed in survivors;

c) mental development (Bayley Scales of Infant Development - Mental Development Index (BSID MDI)) assessed in survivors;

iii) blindness vision (less than 6/60 in both eyes);

iv) sensorineural deafness requiring amplification;

4. cognitive and educational outcomes in survivors aged over five years old:

i) IQ and/or indices of educational achievement measured using a validated assessment tool including school examination results;

5. additional predictors of neurodevelopmental outcome:

i) severity of encephalopathy at enrolment (Sarnat staging) (Finer 1981; Sarnat 1976);

ii) severity of EEG abnormality at enrolment:

a) severe: isoelectric or burst-suppression pattern;

b) moderate: low voltage or discontinuous background;

c) mild: electrographic seizures, dysmaturity;

iii) seizures:

a) seizures during initial hospitalisation;

b) seizures or need for anticonvulsants at follow-up;

iv) magnetic resonance imaging (MRI) abnormalities during primary hospitalisation:

a) moderate or severe abnormalities in the basal ganglia or thalamus, severe white matter lesions or abnormalities in the posterior limb of the internal capsule, per Rutherford 2010 - see (Azzopardi 2008) assessed in the neonatal period;

6. potential adverse effects of xenon therapy during or immediately after administration:

i) heart rate:

a) sinus bradycardia (heart rate < 80 beats/minute);

b) sinus tachycardia (heart rate > 180/min);

c) prolonged QT interval;

d) major arrhythmia (requiring medical intervention or cessation of xenon therapy, or both);

ii) blood pressure:

a) hypotension (mean arterial pressure (MAP) < 40 mmHg);

b) need for inotrope support;

iii) respiratory impairment:

a) pneumonia;

b) pulmonary air leak;

c) pulmonary haemorrhage;

d) persistent pulmonary hypertension (PPHN) (diagnosed clinically or by echocardiogram);

iv) cuffed endotracheal tube complications:

a) extubation stridor;

v) skin rashes.

Search methods for identification of studies

We will conduct systematic searches for randomised controlled trials (RCTs) or quasi-RCTs and will consider only parallel-group trials. We will apply no language, publication year, or publication status restrictions.

Electronic searches

We will use the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group. We will undertake a comprehensive search of the following electronic sources.

We will use MESH terms and keywords to search the following:

- MEDLINE (1966 to current date);
- Embase (1966 to current date);
- Cochrane Library (most recent issue).

We will use keywords (to retrieve e-publications and items not indexed in MEDLINE):

- PubMed (1966 to current date).

Others:

- conference proceedings of the Perinatal Society of Australia and New Zealand (from 2005 to current date);
- conference proceedings of the Pediatric Academic Societies (from 2000 to current date).

The full search strategies for each database are included in Appendix 1. We will also screen the reference list of any cited articles.

Searching other resources

We will search clinical trial registries for ongoing and recently completed trials (e.g. ClinicalTrials.gov (clinicaltrials.gov) and the International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/).

Data collection and analysis

We will use the standard methods of the Cochrane Neonatal Review Group as described below.

Selection of studies

Two review authors (CR and JC) will independently search and identify eligible trials that meet the inclusion criteria using Covidence, which is an online screening and data extraction tool for Cochrane Reviews (Covidence 2017). They will first screen the titles and abstracts to identify potentially relevant citations, and

retrieve the full texts of all potentially relevant articles. They will independently assess the eligibility of the studies in accordance with the specified inclusion criteria. They will review studies for relevance based on study design, types of participants, interventions, and outcome measures. They will resolve any disagreements by discussion and, if necessary, by consulting a third review author (PD).

We will provide details of studies excluded from the review in the 'Characteristics of excluded studies' table along with the reasons for exclusion. We will contact the trial authors if the details of the primary trials are unclear.

Data extraction and management

Two review authors (CR and JC) will separately extract, assess, and code all data for each study using an online screening and data extraction tool for Cochrane Reviews (Covidence 2017). One review author (CR) will check exported data in Review Manager 5 (RevMan 5) software (RevMan 2014). A third review author will address any disagreements.

Assessment of risk of bias in included studies

Two review authors (CR and JC) will independently assess the risk of bias (as either low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

We will resolve disagreements by discussion or by consulting a third review author. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We will perform statistical analyses using standard methods of the Cochrane Neonatal Review Group. We will analyse the results of studies using RevMan 5 (RevMan 2014), and will present results as risk ratios (RRs), risk differences (RDs), number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) for categorical variables. We will use mean differences (MDs) for continuous variables. We will report the 95% confidence intervals (CI) on all estimates.

Unit of analysis issues

We will include all RCTs and quasi-RCTs. We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome.

Dealing with missing data

We will obtain data from the primary investigator, if feasible, for unpublished trials or when published data are incomplete.

Assessment of heterogeneity

We will assess statistical heterogeneity by examining the I^2 statistic, Higgins 2011, a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error. We will apply the I^2 statistic cutoffs and labels for heterogeneity as follows.

- Less than 25%: no heterogeneity;
- 25% to 49%: heterogeneity;
- 50% to 74%: moderate heterogeneity;
- $\geq$ 75%: high heterogeneity.

We will consider statistical heterogeneity to be substantial when the I^2 statistic value is greater than 50%. In addition, we will employ the Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine. We will explore clinical variation across studies by comparing the distribution of important participant factors among trials and trial factors (randomisation concealment, blinding of outcome assessment, loss to follow-up, treatment type, and co-interventions). We will consider a threshold P value of less than 0.1 as indicator of whether heterogeneity (genuine variation in effect sizes) is present.

Assessment of reporting biases

If we include 10 studies or more that investigate a particular outcome, we will use funnel plots to assess small study effects. Owing to several possible explanations for funnel plot asymmetry, we will interpret results carefully (Sterne 2011).

Data synthesis

If we identify more than one eligible trial and there is sufficient homogeneity among the included studies with respect to participants and reported outcomes, we will perform statistical analyses using the standard methods of the Cochrane Neonatal Review Group. We will use RevMan 5 software with the fixed-effect model for meta-analysis (RevMan 2014). We will present categorical data as relative risk (RR) with 95% CI. We will use standardised mean differences (SMDs) to combine trials that measure the same outcome using different methods. We will use the weighted mean difference (WMD) with 95% CI for outcomes measured on a

continuous scale. We will present the number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH), as appropriate.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

- Death (as above);
- major neurodevelopmental disability (as above);
- each component of major neurodevelopmental disability (as above).

Two review authors (CR and JC) will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from RCTs as high quality but downgrade the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro Guideline Development Tool (GRADEpro GDT 2015) to create a 'Summary of findings' table to report the quality of the evidence. The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect;
2. moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
3. low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
4. very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate.

Subgroup analysis and investigation of heterogeneity

We will plan subgroup analyses based on the following:

1. Severity of HIE:
   i) based on Sarnat score (Sarnat 1976; Finer 1981):
      a) mild versus moderate/severe;
   ii) based on electroencephalogram (EEG) or aEEG at baseline:
      a) mild (electrographic seizures, dysmaturity) versus moderate/severe (low voltage or discontinuous background/ isoelectric or burst-suppression pattern);
2. Xenon administration:
   i) concentration: < 30% versus ≥ 30%;
   ii) starting age: < six hours versus ≥ six hours after insult;
   iii) duration: < 12 hours versus ≥ 12 hours;
3. Gestational age:
   i) late preterm (35 0/7 through 36 6/7 gestational weeks) versus term infants (≥ 37 0/7 gestational weeks);
4. Quality of outcome assessment:
   i) high quality (≥ 18 months with formal psychological testing and review by developmental paediatrician for diagnosis of cerebral palsy (CP)) versus lower quality.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of the trials, and will ascertain whether or not studies at a high risk of bias overestimate the effect of treatment.

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None

REFERENCES

Additional references

Andropoulos 2017
Andropoulos DB, Greene MF. Anesthesia and developing brains - implications of the FDA warning. *New England Journal of Medicine* 2017;**376**(10):905–7.

Armstrong 2012
Armstrong SP, Banks PJ, McKitrick TJ, Geldart CH, Edge CJ, Babla R, et al. Identification of two mutations (F758W and F758Y) in the N-methyl-D-aspartate receptor glycine-binding site that selectively prevent competitive inhibition by xenon without affecting glycine binding. *Anesthesiology* 2012;**117**(1):38–47. [DOI: 10.1097/ALN.0b013e31825ada2e]

Azzopardi 2008
Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, et al. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. *BMC Pediatrics* 2008;**8**:17. [DOI: 10.1186/1471-2431-8-17]

Azzopardi 2013
Azzopardi D, Robertson NJ, Kapetanakis A, Griffiths J, Rennie JM, Mathieson SR, et al. Anticonvulsant effect of xenon on neonatal asphyxial seizures. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2013;**98**(5):F437–9. [DOI: 10.1136/archdischild-2013-303786]

Bantel 2010
Bantel C, Maze M, Trapp S. Noble gas xenon is a novel adenosine triphosphate-sensitive potassium channel opener. *Anesthesiology* 2010;**112**(3):623–30. [DOI: 10.1097/ALN.0b013e3181cf894a]

Barkovich 1995
Barkovich AJ, Westmark K, Partridge C, Sola A, Ferriero DM. Perinatal asphyxia: MR findings in the first 10 days. *AJNR. American Journal of Neuroradiology* 1995;**16**(3):427–38. [PUBMED: 7793360]

Chakkarapani 2010
Chakkarapani E, Dingley J, Liu X, Hoque N, Aquilina K, Porter H, et al. Xenon enhances hypothermic neuroprotection in asphyxiated newborn pigs. *Annals of Neurology* 2010;**68**(3):330–41. [DOI: 10.1002/ana.22016]

Chakkarapani 2012
Chakkarapani E, Thoresen M, Liu X, Walloe L, Dingley J. Xenon offers stable haemodynamics independent of induced hypothermia after hypoxia-ischaemia in newborn pigs. *Intensive Care Medicine* 2012;**38**(2):316–23. [DOI: 10.1007/s00134-011-2442-7]

Covidence 2017 [Computer program]
Veritas Health Innovation. Covidence. Version accessed 17 February 2017. Melbourne, Australia: Veritas Health Innovation, 2017.

Dickinson 2007
Dickinson R, Peterson BK, Banks P, Simillis C, Martin JC, Valenzuela CA, et al. Competitive inhibition at the glycine site of the N-methyl-D-aspartate receptor by the anesthetics xenon and isoflurane: evidence from molecular modeling and electrophysiology. *Anesthesiology* 2007;**107**(5):756–67. [DOI: 10.1097/01.anes.0000287061.77674.71]

Dingley 2001
Dingley J, King R, Hughes L, Terblanche C, Mahon S, Hepp M, et al. Exploration of xenon as a potential cardiostable sedative: a comparison with propofol after cardiac surgery. *Anaesthesia* 2001;**56**(9):829–35. [PUBMED: 11531666]

Dingley 2006
Dingley J, Tooley J, Porter H, Thoresen M. Xenon provides short-term neuroprotection in neonatal rats when administered after hypoxia-ischaemia. *Stroke* 2006;**37**(2):501–6. [DOI: 10.1161/01.STR.0000198867.31134.ac]

Dingley 2008
Dingley J, Hobbs C, Ferguson J, Stone J, Thoresen M. Xenon/hypothermia neuroprotection regimes in spontaneously breathing neonatal rats after hypoxic-ischaemic insult: the respiratory and sedative effects. *Anesthesia and Analgesia* 2008;**106**(3):916–23. [DOI: 10.1213/ane.0b013e3181618669]

Douglas-Escobar 2015
Douglas-Escobar M, Weiss MD. Hypoxic-ischaemic encephalopathy: a review for the clinician. *JAMA Pediatrics* 2015;**169**(4):397–403. [DOI: 10.1001/jamapediatrics.2014.3269]

Faulkner 2011
Faulkner S, Bainbridge A, Kato T, Chandrasekaran M, Kapetanakis AB, Hristova M, et al. Xenon augmented hypothermia reduces early lactate/N-acetylaspartate and cell death in perinatal asphyxia. *Annals of Neurology* 2011;**70**(1):133–50. [DOI: 10.1002/ana.22387]

Ferriero 2004
Ferriero DM. Neonatal brain injury. *New England Journal of Medicine* 2004;**351**(19):1985–95. [DOI: 10.1056/NEJMra041996]

Finer 1981
Finer NN, Robertson CM, Richards RT, Pinnell LE, Peters KL. Hypoxic-ischaemic encephalopathy in term neonates: perinatal factors and outcome. *Journal of Pediatrics* 1981;**98**(1):112–7. [DOI: 7452386]

Fleiss 2012
Fleiss B, Gressens P. Tertiary mechanisms of brain damage: a new hope for treatment of cerebral palsy?. *Lancet Neurology* 2012;**11**(6):556–66. [DOI: 10.1016/S1474-4422(12)70058-3]

Franks 1998
Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia?. *Nature* 1998;**396**(6709):324. [DOI: 10.1038/24525]

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. Version 14 September 2016. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Gruss 2004
Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP. Two-pore-domain K+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. *Molecular Pharmacology* 2004;**65**(2):443–52. [DOI: 10.1124/mol.65.2.443]

Hassell 2015
Hassell KJ, Ezzati M, Alonso-Alconada D, Hausenloy DJ, Robertson NJ. New horizons for newborn brain protection: enhancing endogenous neuroprotection. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2015;**100**(6):F541–52. [DOI: 10.1136/archdischild-2014-306284]

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hobbs 2008
Hobbs C, Thoresen M, Tucker A, Aquilina K, Chakkarapani E, Dingley J. Xenon and hypothermia combine additively, offering long-term functional and histopathologic neuroprotection after neonatal hypoxia/ischaemia. *Stroke* 2008;**39**(4):1307–13. [DOI: 10.1161/STROKEAHA.107.499822]

Jacobs 2013
Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with

hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD003311.pub3]

Jevtovic-Todorovic 2013
Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ, et al. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *British Journal of Anaesthia* 2013;**111**(2):143–51.

Lawn 2014
Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al. Every Newborn: progress, priorities, and potential beyond survival. *Lancet* 2014;**384**(9938):189–205. [DOI: 10.1016/S0140-6736(14)60496-7]

Lee 2013
Lee AC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatric Research* 2013;**74 Suppl 1**:50–72. [DOI: 10.1038/pr.2013.206]

Liu 2015
Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;**385**(9966):430–40. [DOI: 10.1016/S0140-6736(14)61698-6]

Ma 2005
Ma D, Hossain M, Chow A, Arshad M, Battson RM, Sanders RD, et al. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Annals of Neurology* 2005;**58**(2):182–93. [DOI: 10.1002/ana.20547]

Ma 2006
Ma D, Hossain M, Pettet GK, Luo Y, Lim T, Akimov S, et al. Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. *Journal of Cerebral Blood Flow and Metabolism* 2006;**26**(2):199–208.

Ma 2007
Ma D, Williamson P, Januszewski A, Nogaro MC, Hossain M, Ong LP, et al. Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. *Anesthesiology* 2007;**106**(4):746–53.

Ma 2009
Ma D, Lim T, Xu J, Tang H, Wan Y, Zhao H, et al. Xenon preconditioning protects against renal ischaemic-reperfusion injury via HIF-1alpha activation. *Journal of the American Society of Nephrology: JASN* 2009;**20**(4):713–20. [DOI: 10.1681/ASN.2008070712]

Palisano 1997
Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine and Child Neurology* 1997;**39**(4):214–23. [PUBMED: 9183258]

Petzelt 2001
Petzelt CP, Kodirov S, Taschenberger G, Kox WJ. Participation of the Ca(2+)-calmodulin-activated Kinase II in the control of metaphase-anaphase transition in human cells. *Cell Biology International* 2001;**25**(5):403–9.

Petzelt 2003
Petzelt C, Blom P, Schmehl W, Müller J, Kox WJ. Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. *Life Sciences* 2003;**72**(17):1909–18. [PUBMED: 12597990]

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rossaint 2003
Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, et al. Multicenter randomised comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003;**98**(1):6–13. [PUBMED: 12502972]

Sabir 2013
Sabir H, Bishop S, Cohen N, Maes E, Liu X, Dingley J, et al. Neither xenon nor fentanyl induces neuroapoptosis in the newborn pig brain. *Anesthesiology* 2013;**119**(2):345–57. [DOI: 10.1097/ALN.0b013e318294934d]

Sabir 2016
Sabir H, Wood T, Gill H, Liu X, Dingley J, Thoresen M. Xenon depresses aEEG background voltage activity whilst maintaining cardiovascular stability in sedated healthy newborn pigs. *Journal of the Neurological Sciences* 2016;**363**:140–4. [DOI: 10.1016/j.jns.2016.02.051]

Sanders 2005
Sanders RD, Ma D, Maze M. Xenon: elemental anaesthesia in clinical practice. *British Medical Bulletin* 2005;**71**:115–35. [DOI: 10.1093/bmb/ldh034]

Sarnat 1976
Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Archives of Neurology* 1976;**33**(10):696–705. [PUBMED: 987769]

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook. Introduction to GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed dd Month yyyy).

Sterne 2011
Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

Sun 2010
Sun L. Early childhood general anaesthesia exposure and neurocognitive development. *British Journal of Anaesthesia* 2010;**105**(Suppl 1):i61–8.

Thayyil 2010
Thayyil S, Chandrasekaran M, Taylor A, Bainbridge A, Cady EB, Chong WK, et al. Cerebral magnetic resonance biomarkers in neonatal encephalopathy: a meta-analysis. *Pediatrics* 2010;**125**(2):e382–95. [DOI: 10.1542/peds.2009-1046]

Thoresen 2009
Thoresen M, Hobbs CE, Wood T, Chakkarapani E, Dingley J. Cooling combined with immediate or delayed xenon inhalation provides equivalent long-term neuroprotection after neonatal hypoxia-ischemia. *Journal of Cerebral Blood Flow and Metabolism* 2009;**29**(4):707–14. [DOI: 10.1038/jcbfm.2008.163]

Zhuang 2012
Zhuang L, Yang T, Zhao H, Fidalgo AR, Vizcaychipi MP, Sanders RD, et al. The protective profile of argon, helium, and xenon in a model of neonatal asphyxia in rats. *Critical Care Medicine* 2012;**40**(6):1724–30. [DOI: 10.1097/CCM.0b013e3182452164]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategy

MEDLINE (Ovid)

1. Asphyxia neonatorum/
2. Hyoxia-Ischemia, Brain/
3. exp Anoxia/
4. exp Hypothermia, Induced/ OR hypothermia/
5. Xenon/
6. (birth or newborn* or neonat* or infan* or gestation* or near-term or term or perinatal or prematur* or pre-term or preterm or low-birth-weight or LBW or VLBW or ("35" adj5 week*) or ("36" adj5 week*) or ("37" adj5 week*) or ("38" adj5 week*) or ("39" adj5 week*) or ("40" adj5 week*) or ("41" adj5 week*) or ("42" adj5 week*) or ("43" adj5 week*) or ("44" adj5 week*)).af.
7. (2 or 3) and 4 and 5 and 6
8. 1 and 4 and 5
9. 7 or 8
10. exp animals/ not human*.sh
11. 9 not 10

Embase (Ovid)

1. (birth or newborn* or neonat* or infan* or gestation* or near-term or term or perinatal or prematur* or pre-term or preterm or low-birth-weight or LBW or VLBW or ("35" adj5 week*) or ("36" adj5 week*) or ("37" adj5 week*) or ("38" adj5 week*) or ("39" adj5 week*) or ("40" adj5 week*) or ("41" adj5 week*) or ("42" adj5 week*) or ("43" adj5 week*) or ("44" adj5 week*)).af.
2. hypoxic ischaemic encephalopathy/
3. exp asphyxia/
4. brain hypoxia
5. (neonatal adj asphyxial adj seizure*).tw,kw,hw.
6. xenon/
7. hypothermia/
8. induced hypothermia
9. (2 or 3 or 4) and 6 and (7 or 8) and 1
10. 5 and 6 and (7 or 8)
11. 9 or 10

12. exp ANIMAL/ not human*.sh.
13. 11 not 12

Cochrane Library (Wiley)

1. MeSH descriptor: [Asphyxia Neonatorum] this term only
2. Asphyxia* or Hypoxia or Hypoxic or Hypoxemia or Hypoxaemia or Ischemia or Ischaemia or Ischemic or Ischaemic or anoxia or anoxic (Word variations have been searched)
3. MeSH descriptor: [Hypoxia-Ischemia, Brain] this term only
4. MeSH descriptor: [Anoxia] explode all trees
5. MeSH descriptor: [Hypothermia, Induced] explode all trees
6. MeSH descriptor: [Hypothermia] this term only
7. Hypothermia or Cooling (Word variations have been searched)
8. MeSH descriptor: [Xenon] this term only
9. Xenon or Xe (Word variations have been searched)
10. (35 or 36 or 37 or 38 or 39 or 40 or 41 or 42) next week* (Word variations have been searched)
11. birth or newborn* or neonat* or infan* or gestation* or near-term or "near term" or term or perinatal or prematur* or pre-term or preterm or "pre term" or "low birth weight" or "low birth-weight" or LBW or VLBW (Word variations have been searched)
12. MeSH descriptor: [Infant] explode all trees
13. (2 or 3 or 4) and (5 or 6 or 7) and (8 or 9) and (10 or 11 or 12)
14. (1) and (5 or 6 or 7) and (8 or 9)
15. 13 or 14

PubMed

1. (birth OR newborn* OR neonat* OR infan* OR gestation* OR near-term OR term OR perinatal OR prematur* OR pre-term OR preterm OR "pre term" OR "low birth weight" OR "low birth-weight" OR LBW OR VLBW OR ((35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42) AND weeks)) AND (Asphyxia* OR Hypoxia OR Hypoxic OR Hypoxemia OR Hypoxaemia OR Ischemia OR Ischaemia OR Ischemic OR Ischaemic) AND (Hypothermia OR Cooling) AND (Xenon OR Xe) AND (NOTNLM OR publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR indatareview[sb] OR pubstatusaheadofprint)

Appendix 2.
' Risk of bias' tool

We will evaluate the following issues and enter the findings into the ' Risk of bias' table.

1. Sequence generation (checking for possible selection bias)

Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as follows.

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

2. Allocation concealment (checking for possible selection bias)

Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as follows.

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

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

Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or class of outcomes. We will categorise the methods according to the following:

1. Low risk, high risk, or unclear risk for participants;
2. low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias)

Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. We will assess blinding separately for different outcomes or class of outcomes. We will categorise the methods as follows:

1. Low risk for outcome assessors;
2. high risk for outcome assessors;
3. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, 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 supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as one of the following:

1. Low risk (< 20% missing data);
2. high risk ($\geq$ 20% missing data);
3. unclear risk.

6. Selective reporting bias

Are reports of the study free of suggestion of selective outcome reporting?

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

1. Low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
2. high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
3. unclear risk.

7. Other sources of bias

Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as follows:

1. Low risk;
2. high risk;
3. unclear risk.

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

- CR: reviewed the literature, and designed and wrote the protocol.
- JC and PD edited the protocol draft and contributed to overall design, background, search strategy, definitions of interventions and outcomes, and protocol revision.

DECLARATIONS OF INTEREST

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JC: None

PD: None

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