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Sunlight for the prevention and treatment of hyperbilirubinemia in term and late preterm neonates (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Sunlight for the prevention and treatment of hyperbilirubinemia in term and late preterm neonates

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ABSTRACT

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

To evaluate the efficacy of sunlight administered alone or with filtering or amplifying devices for the prevention and treatment of clinical jaundice or laboratory-diagnosed hyperbilirubinemia in term and late preterm neonates.

BACKGROUND

Phototherapy for the treatment of hyperbilirubinemia or jaundice was first reported in the *Lancet* in 1958 after the use of the first artificial light sources in Rochford Hospital in Essex, England. Rochford Hospital conducted this experimental treatment after an observation was made by one of their nurses; Nurse Ward took the babies out to the courtyard regularly for sunlight and fresh air, and noticed that the babies' jaundice faded from the areas of their skin that were exposed to sunlight (Stokowski 2011). Although phototherapy is now given with specialized devices that deliver a certain wavelength of light, sunlight remains a potential source of treatment for hyperbilirubinemia.

Description of the condition

Hyperbilirubinemia is defined as an elevated level of bilirubin in the serum. Pathologic unconjugated hyperbilirubinemia includes jaundice appearing within the first 24 hours of life or a rate of rise of serum bilirubin level exceeding 0.2 mg/dL/hour (AAP 2004). The Bhutani nomogram guides clinicians with absolute values indicating need for phototherapy or exchange transfusion, based on the baby's age and specific risk factors, but these are only established for babies of gestational age 35 weeks and older. Hyperbilirubinemia for these infants is defined as a serum bilirubin level greater than the 95th percentile for age on the Bhutani nomogram. There are no absolute values defining hyperbilirubinemia in preterm neonates, though consensus statements with suggested values do exist (Cashore 2000; Maisels 2012; Morris 2008). Regardless, hyperbilirubinemia is to be avoided as severe elevations can lead to bilirubin-induced neurologic dysfunction (BIND), comprised of acute bilirubin encephalopathy and kernicterus. This occurs most often in cases of severe hyperbilirubinemia, where unconjugated bilirubin levels exceed 20 mg/dL. In several studies, bilirubin levels greater than 20 mg/dL occur in 0.007% to 2% of neonates (Ebbesen 2012; Kuzniewicz 2014; Manning 2007; McGillivray 2016). However, these studies were all conducted in upper-mid-

dle- or high-income countries (UHIC). One background study of the burden of hyperbilirubinemia at one large urban hospital in Nigeria found that 17% of babies had acute bilirubin encephalopathy and 31.5% received exchange transfusions, far higher numbers than are reported in the literature in UHIC (Emokpae 2016). Etiologies for hyperbilirubinemia in this study included ABO incompatibility, rhesus incompatibility, sepsis, asphyxia, and exposure to hemolytic agents. These findings indicate that hyperbilirubinemia and its sequelae still place a substantial burden on low- or middle-income countries (LMIC).

Neonatal hyperbilirubinemia occurs due to a variety of factors. Bilirubin is a product of heme catabolism, and 80% to 90% of hyperbilirubinemia occurs due to the breakdown of hemoglobin (Wong 2017). Neonate are uniquely predisposed to physiologic hyperbilirubinemia since they have an increased number of red cells and these have a shorter life span than in adults. Additionally, neonates have increased enterohepatic circulation as they often have decreased gastrointestinal tract motility in the first few days of life, and so bilirubin is often reabsorbed. The liver enzyme responsible for conjugating bilirubin, uridine diphosphate glucuronosyltransferase (UDPGT), in neonates has only 1% of the activity of the same enzyme in adults. This is all compounded by a physiologic volume restriction due to the low volumes of breast milk that are available to neonates in the first three to five days of life, leaving them uniquely predisposed to hyperbilirubinemia (Kawade 1981; Maisels 2012; Stokowski 2011).

There are several pathologic mechanisms that can be responsible for hyperbilirubinemia in neonates as well, and these often underlie the severe cases of hyperbilirubinemia necessitating exchange transfusions or leading to BIND. These include red blood cell hemolysis due to blood-type incompatibility, structural instability, autoimmune hemolysis, and erythrocyte enzymatic defects, among others. Bowel obstruction or ileus, hypothyroidism, or rare conditions like Crigler-Najjar can also lead to decreased bilirubin clearance.

Many LMIC lie in sub-Saharan Africa or Southeastern Asia, where higher population rates of illnesses such as glucose-6-phosphate dehydrogenase (G6PD) deficiency put their population at increased risk of neonatal hyperbilirubinemia. In addition, there are many barriers to treating hyperbilirubinemia in resource-limited settings, including lack of medical care surrounding birth and the neonatal period, lack of maternal understanding of jaundice and the associated risks, local herbal or traditional practices that may be harmful, lack of availability of tests for bilirubin levels, shortage or lack of functioning phototherapy machines, and lack of trained clinicians who understand how to use phototherapy correctly (Olusanya 2015). Infants in these countries are also at higher risk for infection, are more likely to be exclusively breastfed (and so volume contracted), and their mothers are less likely to have undergone Rh screening or received Rho(D) Immune Globulin (RhoGAM) to prevent Rh isoimmunization.

It should be stated that in many LMIC, lower cutoff points for the treatment of hyperbilirubinemia than those discussed in the above definitions are prudent, given the higher incidence of severe hyperbilirubinemia as well as the limitations to timely screening, diagnosis, and treatment already described.

Description of the intervention

Since the 1950s, the allopathic medical community has formally recognized phototherapy as an effective therapy for hyperbilirubinemia. However, it was not widely adapted until the landmark study by Lucey and colleagues in *Pediatrics* in 1968, in which a randomized controlled trial (RCT) of 111 infants showed that exposure to phototherapy safely prevented hyperbilirubinemia in neonates (Lucey 1968). Since that time, phototherapy has been widely adopted in UHIC. Phototherapy reduces hyperbilirubinemia by converting bilirubin to water-soluble isomers, bypassing liver metabolism (Stokowski 2011). Phototherapy devices should ideally emit light between 460 nm and 490 nm, in the blue-green spectrum, as this is most readily absorbed and most effective (Bhutani 2011). Phototherapy devices should not emit any ultraviolet (UV) light or infrared (IR) radiation. Phototherapy is provided via blue light-emitting diodes (LEDs), halogen white lamps, fluorescent blue lamps, or fiberoptic light pads at a prescribed dose, or irradiance. The dose commonly ranges from 6 μW/cm^2/nm to 30 μW/cm^2/nm depending on the desired amount of phototherapy, and can be adjusted by changing the number of lights on the infant, the distance the light is from the infant's skin, and the surface area of skin exposed (Bhutani 2011). However, while phototherapy is a safe and relatively inexpensive treatment, it is not always readily available in resource-limited settings, where, for example, consistent access to an electrical source may not be available, or economic constraints may not allow for the purchase of an adequate number of phototherapy devices. It common for infants in LMICs to be forced to go without phototherapy, even when their clinical status would merit treatment. But as previously discussed, phototherapy utilizes light emitted in a spectrum that is naturally emitted by the sun (hence Nurse Ward's discovery in Essex, England). It is then worth determining if sunlight itself - a resource that is readily available and free worldwide - can safely be used for the treatment of hyperbilirubinemia in neonates, and if so, how. Safety is a concern as unfiltered sunlight includes harmful IR and UV light, which has been associated with sunburn, hyperthermia, and a long-term risk of various malignancies of the skin. This may involve technology that amplifies or filters the sunlight to make it safer. One such device is a filtered-sunlight phototherapy canopy (FSPT) that has imbedded commercial window tinting films that remove most UV and a portion of IR light (Slusher 2014). Potential risks of such devices include possible increased risk of hyperthermia and potential for diminished efficacy of sunlight as a treatment. We are not aware of every device that has been invented or trialed that may be utilized for the administration of sunlight as a treatment for hyperbilirubinemia, but would like to

include and assess any that are reported in the literature in this analysis.

How the intervention might work

Sunlight obviously can treat hyperbilirubinemia, as this is how the treatment of phototherapy was discovered, and the sun emits blue-green light in the spectrum needed to most effectively convert bilirubin to its water-soluble isomers for excretion. Phototherapy is also often used for the prevention of phototherapy in high-risk but asymptomatic babies. Sunlight can likewise be used to prevent hyperbilirubinemia or jaundice before they present in infants considered at risk. However, there is concern for potential safety issues when using sunlight for the treatment or prevention of hyperbilirubinemia, as sunlight also emits UV light and IR radiation, and there is the potential for the infants to have hyperthermia or sunburn, and to be put at risk for the development of neoplasia of the skin. Also, sunlight cannot be applied at prescribed dosages, as the amount and intensity of sunlight available on any given day cannot be controlled. Nevertheless, if sunlight can be utilized in a safe and controlled manner to provide phototherapy, it could be extremely helpful in mitigating morbidity and mortality from hyperbilirubinemia in LMICs.

Why it is important to do this review

- To evaluate the potential to save lives and reduce acute and chronic morbidity from hyperbilirubinemia and its sequelae.
- To determine cost benefit.
- To investigate potential benefit to maternal-child interaction (less separation/interruption to maternal child bonding).
- To deliver the United Nations Sustainable Development Goal to end preventable deaths of newborns and children under five years of age, with all countries aiming to reduce neonatal mortality below 12 per 1000 live births by 2030.
- A search of PubMed revealed no systematic reviews of sunlight in the prevention or treatment of hyperbilirubinemia.

OBJECTIVES

To evaluate the efficacy of sunlight administered alone or with filtering or amplifying devices for the prevention and treatment of clinical jaundice or laboratory-diagnosed hyperbilirubinemia in term and late preterm neonates.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs, quasi-randomized trials, and cluster RCTs. We will exclude crossover RCTs.

Types of participants

Term (37+0 weeks' gestation or greater) and late preterm infants (35+0 to 36+6 weeks' gestation) enrolled by one week' postnatal age.

We will include studies of either the clinical finding of jaundice or the diagnosis of hyperbilirubinemia to be inclusive of studies performed at extremely resource-limited settings where hyperbilirubinemia cannot be measured.

We will perform separate comparisons in four distinct populations.

- Low-risk term and late preterm infants (based on risk criteria as defined by Bhutani 1999).
- Infants identified as 'at risk' for hyperbilirubinemia: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, and albumin less than 3 g/dL (Bhutani 1999).
- Infants with clinical jaundice (at the discretion of the caregiver).
- Infants with confirmed hyperbilirubinemia as defined by the Bhutani nomogram and determined by serum bilirubin measurement (Bhutani 1999).

Types of interventions

Sunlight with or without filtering devices or amplification devices compared to no treatment, other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), or other sunlight devices.

We will conduct the following comparisons and subgroup analyses.

Comparison 1: low-risk term and late preterm infants (based on risk criteria defined by Bhutani 1999).

- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 2: in infants identified as 'at risk' for hyperbilirubinemia: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, and albumin less than 3 g/dL (Bhutani 1999).

- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 3: in infants with clinical jaundice (at the discretion of the caregiver).
- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 4: in infants with confirmed hyperbilirubinemia as defined by the Bhutani nomogram and determined by serum bilirubin measurement.
- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Types of outcome measures

Primary outcomes

- Use of conventional phototherapy, if sunlight (with or without filters or amplification) was first used for prevention or early treatment.
- Treatment failure requiring exchange transfusion (as defined by receiving an exchange transfusion; or bilirubin level greater than 15 mg/dL in the first 24 hours of life, greater than 17 mg/dL in the first 48 hours of life, or greater than 20 mg/dL after 72 hours of life) (Bhutani 1999).
- Acute bilirubin encephalopathy, defined as retrocollis and opisthotonus in association with irritability, drowsiness, poor or no feeding, alternating tone, high-pitched or shrill cry, lethargy, coma, fever, or seizures (AAP 2004; Johnson 2002).
- Chronic bilirubin encephalopathy or kernicterus, defined as athetoid cerebral palsy, auditory dysfunction, dental-enamel dysplasia, paralysis of upward gaze, and, occasionally, intellectual and other disabilities (AAP 2004).
- Death.

Secondary outcomes

- Duration of treatment from initiation to end (hours).
- Peak bilirubin levels during hospitalization (mg/dL) (and if known, what hour or day of life this bilirubin was measured).
- Rate of change of serum bilirubin (mg/dL/hour) from initiation of sunlight or phototherapy to cessation of either treatment.
- Days in hospital.
- Rate of rehospitalization within seven days of discharge for treatment for hyperbilirubinemia.
- Athetoid cerebral palsy.
- Auditory dysfunction (defined as failed OAE or ABR hearing screen, or caregiver report that the child is deaf or has difficulty with hearing).
- Total cost (USD).
- Sunburn (as defined in individual studies).
- Hyperthermia (defined as temperature greater than 38 °C) while receiving sunlight or conventional phototherapy.
- Maternal satisfaction (as defined in individual studies).
- Nursing staff satisfaction (as defined in individual studies).
- Need for fluid supplementation (defined as either intravenous fluids, nasogastric fluids, or supplemental formula or breast milk in addition to breastfeeding).
- Cessation of breast milk feeding.

Search methods for identification of studies

See: Cochrane Neonatal standard search strategy.
We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and report the date this was done.

Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via Ovid (1946 to present); PubMed (for the previous year); Embase via Ovid (1974 to present); and CINAHL via EBSCOhost (1981 to present) using the following search terms: Phototherapy AND (Hyperbilirubinemia, Neonatal[MeSH] OR jaundice, neonatal[MeSH] OR Hyperbilirubinemia OR hyperbilirubinaemia OR jaundice OR icter*) AND (Heliotherapy[MeSH] OR sunlight OR sun*[tiab] OR solar OR heliotherapy OR window), plus database-specific limiters for

RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will apply no language restrictions. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform, and the ISRCTN Registry).

Searching other resources

We will review the reference lists of all identified articles for relevant articles not identified in the primary search.

Data collection and analysis

We will use the standard methods of Cochrane Neonatal Group.

Selection of studies

We will identify and exclude duplicates and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Data extraction and management

Two review authors (DH and DE) will screen the title and abstract of all studies identified by the search strategy and two review authors will independently assess the full articles for all potentially relevant trials. We will exclude studies that do not meet all the inclusion criteria, and we will state the reason for exclusion. We will discuss any disagreements until consensus. We will use a standard data collection form that is adapted for the purpose of collected all identified outcome measures.

Assessment of risk of bias in included studies

Two review authors (DH and DE) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2017):

- 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 any disagreements by discussion or by 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 analyze the treatment effects in the individual trials using Review Manager 2014 and report risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CI). We will determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomized trials and the neonatal unit (or subunit) for cluster-randomized trials.

An infant will be considered only once in an analysis. We will exclude infants with multiple enrollments as we will not be able to address the unit of analysis issues that arise.

For cluster-randomized trials, we will undertake analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

Dealing with missing data

Where data are missing, and cannot be derived as described, we will approach the analysis of missing data as follows.

- We will contact the original study investigators to request the missing data where more than 20% of data are missing (Guyatt 2017).
- Where possible, we will impute missing standard deviations (SDs) using the coefficient of variation (CV) or calculate them from other available statistics including standard errors, CIs, t values and P values.
- If the data are assumed to be missing at random, we will analyze the data without imputing any missing values.
- If this cannot be assumed, then we will impute the missing outcomes with replacement values, assuming all to have a poor outcome. We will conduct sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

We will assess clinical heterogeneity by visual inspection of forest plots and statistical heterogeneity using the I^2 statistic. We will calculate the I^2 statistic for each RR analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. We will define heterogeneity as: I^2 statistic less than 25%: none; I^2 statistic 25% to 49%: low; I^2 statistic: 50% to 74% moderate; I^2 statistic 75% or greater: high. If we detect

'high' levels of heterogeneity (I^2 statistic of 75% or greater), we will explore the possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

We will assess publication bias by visual inspection of funnel plot asymmetry in meta-analyses with at least 10 studies. If we find significant asymmetry in the funnel plot, we will report this in the corresponding results.

Data synthesis

Quality of the evidence

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

- Use of conventional phototherapy, if sunlight (with or without filters or amplification) was first used for prevention or early treatment

- Treatment failure requiring exchange transfusion (as defined by receiving an exchange transfusion; or bilirubin level greater than 15 mg/dL in the first 24 hours of life, greater than 17 mg/dL in the first 48 hours of life, or greater than 20 mg/dL after 72 hours of life) (Bhutani 1999).

- Acute bilirubin encephalopathy, defined as retrocollis and opisthotonus in association with irritability, drowsiness, poor or no feeding, alternating tone, high-pitched or shrill cry, lethargy, coma, fever, or seizures. (AAP 2004; Johnson 2002).
- Chronic bilirubin encephalopathy or kernicterus, defined as athetoid cerebral palsy, auditory dysfunction, dental-enamel dysplasia, paralysis of upward gaze, and, occasionally, intellectual and other disabilities (AAP 2004).
- Death.

Two authors (DH and DE) will independently assess the quality of the evidence for each of the primary 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 GDT Guideline Development Tool 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.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- 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.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Where there are enough studies, we will undertake the following subgroup analyses.
Comparison 1: low-risk term and late preterm infants (based on risk criteria defined by Bhutani 1999).

- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 2: in infants identified as 'at risk' for hyperbilirubinemia: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, and albumin less than 3 g/dL (Bhutani 1999).

- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 3: in infants with clinical jaundice (at the discretion of the caregiver).

- Sunlight (with or without filters or amplification) versus no treatment.
- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Comparison 4: in infants with confirmed hyperbilirubinemia as defined by the Bhutani nomogram and determined by serum bilirubin measurement.

- Sunlight (with or without filters or amplification) versus no treatment.

- Sunlight (with or without filters or amplification) versus other sources of phototherapy (fluorescent blue lights, blue LED lights, halogen white lamp, fiberoptic blanket), and include irradiance if known.
- Sunlight filtering or amplifying device of one type versus sunlight filtering or amplifying device of another type (as defined by individual studies).

Sensitivity analysis

We will undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomization and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up. We will define heterogeneity as: I^2 statistic less than 25%: none; I^2 statistic 25% to 49%: low; I^2 statistic 50% to 74%: moderate; I^2 statistic 75% or greater: high.

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The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Standard search methodology

The RCT filters have been created using Cochrane's highly sensitive search strategies for identifying randomised trials (Higgins 2017). The neonatal filters were created and tested by the Cochrane Neonatal Information Specialist.

MEDLINE via Ovid:

1. exp infant, newborn/
2. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
3. 1 or 2
4. randomised controlled trial.pt.
5. controlled clinical trial.pt.
6. randomized.ab.
7. placebo.ab.
8. drug therapy.fs.
9. randomly.ab.

10. trial.ab.
11. groups.ab.
12. or/4-11
13. exp animals/ not humans.sh.
14. 12 not 13
15. 3 and 14

PubMed:

((infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infant[TIAB] OR infants[TIAB] OR infantile[TIAB] OR infancy[TIAB] OR neonat*[TIAB]) AND (randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]))

Embase via Ovid:

1. exp prematurity/
2. exp infant/
3. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
4. 1 or 2 or 3
5. (human not animal).mp.
6. (randomised controlled trial or controlled clinical trial or randomised or placebo or clinical trials as topic or randomly or trial or clinical trial).mp.
7. 4 and 5 and 6

CINAHL:

(infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomised controlled trial OR controlled clinical trial OR randomised OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library:

(infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU)

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodologic quality of the trials. For each trial, we will seek information regarding the method of randomization, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the 'Characteristics of included studies' table. 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 categorize the method used to generate the allocation sequence as:

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

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorize the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- 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 categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk, high risk, or unclear risk for participants; and
- 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 categorize the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorize the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- 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 randomized 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 reinclude missing data in the analyses. We will categorize the methods as:

- low risk (less than 20% missing data);
- high risk (20% missing data or greater); or
- 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. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- 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);
- 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 were 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); or
- 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:

- low risk;
- high risk; or
- unclear risk.

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

CONTRIBUTIONS OF AUTHORS

DH: participated in the design and drafting of the protocol.

DE: participated in the design and drafting of the protocol.

RFS: participated in the design and drafting of the protocol.

DECLARATIONS OF INTEREST

DH: none.

DE is an Associate Editor of Cochrane Neonatal but did not participate in the editorial review of the protocol.

RFS is the Co-ordinating Editor of Cochrane Neonatal but did not participate in the editorial review of the protocol.

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