Cochrane Library

Cochrane Database of Systematic Reviews

Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants (Protocol)

Romantsik O, Calevo MG, Bruschettini M

Romantsik O, Calevo MG, Bruschettini M.
Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants.
Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012362.
DOI: 10.1002/14651858.CD012362.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants

Olga Romantsik[1], Maria Grazia Calevo[2], Matteo Bruschettini[1]

[1]Department of Paediatrics, Lund University, Skane University Hospital, Lund, Sweden. [2]Epidemiology, Biostatistics and Committees Unit, Istituto Giannina Gaslini, Genoa, Italy

Contact address: Matteo Bruschettini, Department of Paediatrics, Lund University, Skane University Hospital, Lund, Sweden. matteo.bruschettini@med.lu.se. matbrus@gmail.com.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 9, 2016.

Citation: Romantsik O, Calevo MG, Bruschettini M. Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD012362. DOI: 10.1002/14651858.CD012362.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Primary objective

To assess whether head midline position compared with any other head position is more effective in prevention or extension of germinal matrix-intraventricular hemorrhage in infants born at ≤ 32 weeks' gestational age.

Secondary objectives

To perform subgroup analyses regarding gestational age, birth weight, intubated versus not intubated, and with or without GM-IVH at trial entry (see Subgroup analysis and investigation of heterogeneity).

BACKGROUND

Description of the condition

Preterm birth remains a major risk factor for development of germinal matrix-intraventricular hemorrhage (GM-IVH), which occurs in 25% of very low birth weight (VLBW) infants (Canadian Neonatal Network 2014; Vermont Oxford Network 2013). Often, these hemorrhages occur in the first days of life (Dolfin 1983). Complications of GM-IVH, including periventricular hemorrhagic infarction (PVHI), posthemorrhagic ventricular dilatation (PHVD), and associated cerebellar hemorrhagic injury (CHI) and periventricular leukomalacia (PVL), are critical determinants of neonatal morbidity, mortality, and long-term neurodevelopmental sequelae (Sherlock 2005). Although modern perinatal medicine has led to a significant decrease in the overall incidence of GM-IVH in preterm infants (ie, from 50% in the late 1970s to current rates of 15% to 25%) (Hamrick 2004; Horbar 2002; Philip 1989), GM-IVH continues to present a significant problem in

the modern neonatal intensive care unit. The origin of GM-IVH is multifactorial, complex, and heterogeneous. Inherent fragility of the germinal matrix vasculature sets the ground for hemorrhage, and fluctuation in cerebral blood flow induces rupture of the vasculature. Furthermore, the germinal matrix lies within an arterial end zone, and it is directly connected to the deep galenic venous system (Nakamura 1990; Pape 1979), thereby exposing it to insults of arterial ischemia-reperfusion and venous congestion (Pape 1979; Takashima 1978). The immature deep galenic system is prone to venous congestion and stasis, making it of potentially major importance for the development of GM-IVH and its complications (Pape 1979; Volpe 2008). It is unknown which proportion of GM-IVH might occur because of this phenomenon. Nevertheless, many institutions adopt the practice of head midline position. Vaginal delivery, low Apgar score, severe respiratory distress syndrome, pneumothorax, hypoxia, hypercapnia, seizures, patent ductus arteriosus, infection, and other factors seem to primarily increase fluctuations in cerebral blood flow, thus representing important risk factors for the development of GM-IVH (Ballabh 2014).

Description of the intervention

It has been suggested that head position may affect cerebral hemodynamics in the preterm newborn and might be involved indirectly in development of GM-IVH. Doppler studies in term infants have shown that turning the head toward one side functionally occluded jugular venous drainage on the ipsilateral side (Cowan 1985). Moreover, an increase in intracranial pressure (Cowan 1985; Emery 1983) and in cerebral blood volume (CBV) (Pellicer 2002) after head rotation, caused by obstruction of the homolateral jugular veins, has been reported. Thus, it has been suggested that cerebral venous pressure is reduced and hydrostatic brain drainage improved if the patient is in supine midline position with the bed tilted 30° (Cowan 1985; Emery 1983). Subsequently, researchers reported an increase in cerebral blood flow (CBF) in the supine position and an increase in partial pressure of oxygen (PO_2) in the prone position in stable preterm infants (Bembich 2012). However, Ancora's study results did not show significant changes in the tissue hemoglobin index (which is proportional to changes in CBV) nor in oxygenation. Only infants with low gestational age (< 26 weeks) had a reduction in CBV with head rotation (Ancora 2010). In addition, ventilatory support has been shown to influence brain hemodynamics (Cowan 1987): Newborns on mechanical ventilation showed an increase in CBV during inspiration compared with those breathing spontaneously (Leahy 1982). However, nasal continuous positive airway pressure (nCPAP) did not seem to have an effect on CBV and CBF among preterm infants (Dani 2007; Moritz 2008).

The definition of head midline position is complex, as the position of the body may have a relevant impact. In the supine position, the infant's head is maintained in alignment with the midline. In the prone position, the head has to be turned to the side, so the head midline position is not feasible. In the lateral position, the midline position might be achieved if the head is kept aligned with midline. Maintenance of this position may require the presence of physical aids, such as nests or pillows, and active surveillance by the nurses. It has been reported that the midline position in the lateral decubitus during kangaroo care might be associated with improved early neuromotor development as assessed by the Dubowitz score (Barradas 2006). Midline position should be kept at least when the incidence of GM-IVH is greatest, that is, in the first two to three days of life. It is unknown, however, if strict observance of the midline position might confer any disadvantages, and if the head midline position with the infant supine is different from the head midline position with the infant lying on the side.

How the intervention might work

An intubated preterm infant's head may be turned toward one side (facing the ventilator, eg, a high-frequency oscillator) for prolonged periods. As impaired venous drainage and decreased cerebral tissue oxygenation are factors implicated in the pathogenesis of IVH (Noori 2014; Osborn 2003; Takashima 2009), midline head positioning during the early transitional period has been included in recent IVH prevention bundles at many institutions, albeit without strong data to support the practice (McLendon 2003; Nankervis 2010; Obladen 2008). Midline head positioning during the early transitional period might prevent the occurrence of IVH through improved venous drainage and cerebral oxygenation.

Why it is important to do this review

As noted above, GM-IVH occurs in 25% of VLBW infants (Canadian Neonatal Network 2014; Vermont Oxford Network 2013). Midline head positioning has been included in recent GM-IVH prevention bundles at many institutions, albeit without strong data to support the practice. One review recommended midline head position for preterm infants on the basis of physiological data and expert opinion; however, review authors identified no controlled trials for inclusion (Malusky 2011). Moreover, midline positioning with bed elevation of 30° has been identified as a "potentially better practice" for prevention of GM-IVH, although review authors rated the level of the evidence as low (Carteaux 2003). This systematic review will help clinicians and policy makers to provide specific recommendations about optimal head positioning, with an important impact on neonatal health and long-term outcomes for the very preterm infant.

OBJECTIVES

Primary objective

To assess whether head midline position compared with any other head position is more effective in prevention or extension of germinal matrix-intraventricular hemorrhage in infants born at ≤ 32 weeks' gestational age.

Secondary objectives

To perform subgroup analyses regarding gestational age, birth weight, intubated versus not intubated, and with or without GM-IVH at trial entry (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

We will include prospective randomized clinical controlled trials, quasi-randomized trials, and cluster-randomized controlled trials. We will exclude cross-over trials because the intervention might have a lasting effect that compromises entry to subsequent periods of the trial.

Types of participants

We will include very preterm infants (ie, ≤ 32 weeks' gestational age) of any birth weight, admitted to neonatal intensive care units. We will include studies enrolling infants with unknown GM-IVH status at enrollment; if known, we will perform subgroup analysis on the presence of GM-IVH at study entry.
We will include studies enrolling infants with existing GM-IVH and will assess the extension of hemorrhage in a subgroup of infants.

Types of interventions

Placing newborns in a head midline position compared with placing them in a prone or lateral decubitus position, or undertaking a strategy of regular position change, or having no prespecified position.
We will analyze horizontal (flat) versus head elevated positions separately for all body positions.
We will conduct the following comparisons.

- **Supine midline head position versus any other supine head position**
  - Supine midline head position with the bed at 0° versus supine head rotated 90° with the bed at 0°
  - Supine midline head position with the bed at 0° versus supine head rotated 90° with the bed tilted ≥ 30°
  - Supine midline head position with the bed tilted ≥ 30° versus supine head rotated 90° with the bed at 0°
  - Supine midline head position with the bed tilted ≥ 30° versus supine head rotated 90° with the bed tilted ≥ 30°
- **Supine midline head position versus any other prone head position**
  - Supine midline head position with the bed at 0° versus prone head rotated 90° with the bed at 0°
  - Supine midline head position with the bed at 0° versus prone head rotated 90° with the bed tilted ≥ 30°
  - Supine midline head position with the bed tilted ≥ 30° versus prone head rotated 90° with the bed at 0°
  - Supine midline head position with the bed tilted ≥ 30° versus prone head rotated 90° with the bed tilted ≥ 30°
- **Supine midline head position with the bed at 0° versus supine midline head position with the bed tilted ≥ 30°**

As the aim of this review is to assess the ability of head position to prevent GM-IVH, we will include trials in which the intervention is started within the first 48 hours of life.

Types of outcome measures

Primary outcomes

- Any germinal matrix-intraventricular hemorrhage: any IVH, grades 1 to 4 (according to Papile classification [Papile 1978])
- Severe IVH: ultrasound diagnosis grades 3 and 4 (according to Papile classification [Papile 1978])
- Neonatal death (first 28 days) or during initial hospitalization

Secondary outcomes

- Cerebellar hemorrhage on brain ultrasound in the first month of life (yes/no; Graça 2013)
- Cystic periventricular leukomalacia on brain ultrasound in the first month of life
- Brain magnetic resonance imaging (MRI) abnormalities at term equivalent age (yes/no), defined as white matter lesions (ie, cavitations; Rutherford 2010) and punctate lesions (Cornette 2002); GM-IVH (Parodi 2015); or cerebellar hemorrhage (Fumagalli 2009; Limperopoulos 2007)
- Impairment in cerebral hemodynamics in the first three days of life, assessed on cerebral near-infrared spectroscopy (NIRS)

- Retinopathy of prematurity: any and severe (≥ stage 3; ICROP 1984)
- Long-term neurodevelopmental outcomes (yes/no): cerebral palsy on physician assessment, developmental delay (ie, IQ two standard deviations (SDs) below the mean on validated assessment tools such as Bayley Mental Developmental Index) (Bayley 1993; Bayley 2006)
- Major neurodevelopmental disability: cerebral palsy, developmental delay (Bayley Mental Developmental Index (Bayley 1993; Bayley 2006) or Griffiths Mental Development Scale (Griffiths 1954) assessment > 2 SDs below the mean), intellectual impairment (IQ > 2 SDs below the mean), blindness (vision < 6/60 in both eyes), or sensorineural deafness requiring amplification (Jacobs 2013). We plan to evaluate each of these components as a separate outcome and to extract data on each long-term outcome from studies that evaluated children after 18 months' chronological age. We will separately assess data on children 18 to 24 months of age and on those three to five years of age

Search methods for identification of studies

Electronic searches

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

- Cochrane Central Register of Controlled Trials (CENTRAL), in *The Cochrane Library*
- MEDLINE (January 1996 to current date)
- Embase (January 1980 to current date)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to current date)
- 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)

We have included in Appendix 1 and Appendix 2 the full search strategies for all databases. We will apply no language restrictions and will screen the reference lists of any cited articles.

Searching other resources

We will search clinical trials registries for ongoing or recently completed trials (eg, ClinicalTrials.gov (https://clinicaltrials.gov/), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.controlled-trials.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 (OR, MB) will independently search for and identify eligible trials that meet the inclusion criteria. We will screen the titles and abstracts to identify potentially relevant citations, and will retrieve the full texts of all potentially relevant articles; we will independently assess the eligibility of studies by filling out eligibility forms designed in accordance with the specified inclusion criteria. We will review studies for relevance by assessing study design, types of participants, interventions provided, and outcome measures reported. We will resolve disagreements by discussion and, if necessary, by consultation with a third review author (MGC). We will provide in the "Characteristics of excluded studies" table details of studies excluded from the review, along with reasons for exclusion. We will contact trial authors if details of primary trials are not clear.

Data extraction and management

Two review authors (OR, MB) will independently extract data using a data extraction form developed ad hoc and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist (Cochrane EPOC Group 2013).

We will extract the following characteristics from each included study.

- Administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; details of other relevant papers cited.
- Details of the study: study design; type, duration, and completeness of follow-up (eg, > 80%); country and location of study; informed consent; ethics approval.
- Details of participants: sex, birth weight, gestational age, number of participants.
- Details of interventions: initiation and duration of head midline position; co-intervention with horizontal versus head elevated position; use of physical aids to maintain the head position.
- Details of outcomes as mentioned above under Types of outcome measures.

We will resolve disagreements by discussion. We will describe ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date.

Should any queries arise, or in cases for which additional data are required, we will contact study investigators/authors for clarification. Two review authors (MGC, MB) will use the statistical

software of The Cochrane Collaboration (Revman 2014) for data entry.

Assessment of risk of bias in included studies

Two review authors (OR, MGC) will independently assess risk of bias in all included studies using the tool of The Cochrane Collaboration designed to assess risk of bias (Higgins 2011). We will assess the following items.

- Random sequence generation: selection bias due to inadequate generation of a randomized sequence.
- Allocation concealment: selection bias due to inadequate concealment of allocations before assignment.
- Blinding of participants and personnel: performance bias due to knowledge of allocated interventions by participants and personnel during the study.
- Blinding of outcome assessment: detection bias due to knowledge of allocated interventions by outcome assessors.
- Incomplete outcome data: attrition bias due to quantity, nature, or handling of incomplete outcome data.
- Selective reporting: reporting bias due to selective outcome reporting.
- Other bias: bias due to problems not covered elsewhere in the table.

We will use a "Risk of bias" graph to illustrate risk across studies. We will resolve disagreements by consensus and, if necessary, by consultation with a third review author (MB).

Random sequence generation and allocation concealment (selection bias)

Random sequence generation

For each included study, we will categorize as follows the risk of bias regarding random sequence generation.

- Low risk: Investigators describe a random component in the sequence generation process such as referring to a random number table, using a computer random number generator, tossing a coin, shuffling cards or envelopes, throwing dice, drawing of lots, minimizing.
- High risk: Investigators describe a nonrandom component in the sequence generation process (sequence generated by odd or even date of birth, sequence generated by some rule based on date or day of admission, sequence generated by some rule based on hospital or clinic record number, allocation by judgment of the clinician, allocation by preference of the participant, allocation based on results of a laboratory test or a series of tests, allocation by availability of the intervention).
- Unclear risk: No or unclear information is provided.

Allocation concealment

For each included study, we will categorize as follows the risk of bias regarding allocation concealment.

- Low risk: Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled randomization), sequentially numbered drug containers or identical appearance, sequentially numbered sealed opaque envelopes.
- High risk: Participants and investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on open random allocation schedule (eg, a list of random numbers), unsealed or nonopaque envelopes, alternation or rotation, date of birth, case record number.
- Unclear risk: No or unclear information is provided.

Blinding of study participants and personnel (performance bias)

Care providers cannot be blinded to the intervention.

Blinding of outcome assessors (detection bias)

For each included study, we will categorize as follows the methods used to blind outcome assessors from knowledge of which intervention a participant received.

- Criteria for a judgment of 'low risk' of bias: No blinding or incomplete blinding is described, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel is ensured, and it is unlikely that the blinding could have been broken.
- Criteria for a judgment of 'high risk' of bias: No blinding of outcome assessment is described, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment is described, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
- Unclear risk: No or unclear information is provided.

Incomplete outcome data (attrition bias)

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis as follows.

- Criteria for a judgment of "low risk" of bias include:
  - no missing outcome data;
  - reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias);

- missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- for dichotomous outcome data, proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; and
- missing data imputed by appropriate methods.

- Criteria for a judgment of "high risk" of bias include:
  - reason for missing outcome data likely to be related to true outcome, with imbalance in numbers or reasons for missing data across intervention groups;
  - for dichotomous outcome data, proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate;
  - for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
  - "as-treated" analysis done with substantial departure of the intervention received from that assigned at randomization; and
  - potentially inappropriate application of simple imputation.

- Unclear risk: No or unclear information is provided.

Selective reporting (reporting bias)

For each included study, we will describe how we investigated the risk of selective outcome reporting bias and what we found. We will attempt to access all protocols of included studies through clinical trials registries (eg, ClinicalTrials.gov (https://clinicaltrials.gov/), the International Standard Randomised Controlled Trial Number (ISRCTN) registry (http://www.controlled-trials.com/)) and by direct contact with study authors.
We will assess study methods as follows.

- Low risk: The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; the study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
- High risk: Not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (eg, subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they cannot be entered into a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk: No or unclear information is provided (the study protocol is not available).

Other potential sources of bias (other bias)

For each included study, we will describe any important concerns that we had about other possible sources of bias (eg, whether a potential source of bias was related to the specific study design used).
We will assess whether each study was free of other problems that could put it at risk of bias as follows.

- Low risk: The study appears to be free of other sources of bias.
- High risk: The study has at least one important risk of bias (eg, the study had a potential source of bias related to the specific study design used, was claimed to have been fraudulent, had some other problem).
- Unclear risk: Risk of bias may be present, but information is insufficient to assess whether an important risk of bias exists or the rationale or evidence that an identified problem will introduce bias is insufficient.

Measures of treatment effect

We will follow the standard methods of the Cochrane Neonatal Review Group for data synthesis. We will extract categorical data for each intervention group and will calculate risk ratios (RRs) and absolute risk differences (RDs). We will obtain means and standard deviations for continuous data and will perform analyses using mean differences (MDs). For each measure of effect, we will calculate corresponding 95% confidence intervals (CIs). We will present the number needed to treat for an additional beneficial outcome and the number needed to treat for an additional harmful outcome (NNTB/NNTH) when RDs are found to be statistically significant ($P < 0.05$).

Unit of analysis issues

The unit of randomization will be the intended unit of analysis (individual neonate). If we find any cluster-randomized controlled trials, we will adjust analysis for the designed effect using the method stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will obtain a dropout rate for each study. We will consider a dropout rate > 20% as significant. If we find a significant dropout

rate, we will contact study author(s) to request additional data. We will perform a sensitivity analysis to evaluate the overall results with and without inclusion of studies with a significant dropout rate. If a study reports outcomes only for participants completing the trial or only for participants who followed the protocol, we will contact study author(s) to ask them to provide additional information to facilitate an intention-to-treat analysis; in instances when this is not possible, we will perform a complete case analysis.

Assessment of heterogeneity

We plan to assess clinical heterogeneity by comparing the distribution of important participant factors between trials and trial factors (randomization concealment, blinding of outcome assessment, loss to follow-up, treatment type, co-interventions). 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 to sampling error.
We will interpret the I^2 statistic as follows, as described by Higgins 2003.

- < 25%: no (none) heterogeneity.
- 25% to 49%: low heterogeneity.
- 50% to 74%: moderate heterogeneity.
- ≥ 75%: high heterogeneity.

We will consider statistical heterogeneity to be substantial when $I^2 \geq 50\%$. 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 (randomization concealment, blinding of outcome assessment, loss to follow-up, treatment types, and co-interventions). We will consider a threshold of P value < 0.1 as an indicator of whether heterogeneity (genuine variation in effect sizes) is present.

Assessment of reporting biases

We will investigate publication by using funnel plots if we include 10 or more clinical trials in the systematic review (Egger 1997; Higgins 2011).

Data synthesis

We will summarize all eligible studies in RevMan 5.3 (Revman 2014). We will use the standard methods of the Cochrane Neonatal Review Group to synthesize data using typical RR, RD, NNTB, NNTH, MD, and 95% CIs if we will include more than one trial in the meta-analysis. We will perform a meta-analysis of data from the included trials by using a fixed-effect model.

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: any intraventricular hemorrhage; severe intraventricular hemorrhage; death during initial hospitalization; cerebellar hemorrhage on brain ultrasound; retinopathy of prematurity; long-term neurodevelopmental outcome; and major neurodevelopmental disability.
Two review authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomized controlled trials as high quality but will downgrade the evidence one level for serious (and two levels for very serious) limitations on the basis of 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 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 according to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of 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

We plan to present data from the following subgroups.

- Gestational age (with two subgroups, < 26 weeks vs ≥ 26 weeks).
- Birth weight (with two subgroups, < 1000 grams vs ≥ 1000 grams).
- Intubated versus not intubated.
- With or without GM-IVH (any grade) at trial entry.

Sensitivity analysis

We will conduct sensitivity analyses to explore the effect of the methodological quality of trials, checking to ascertain whether studies with a high risk of bias will overestimate the effect of treatment.

ACKNOWLEDGEMENTS

We thank Roger Soll for his precious advice, and Colleen Ovelman and Yolanda Brosseau for their kind and efficient support.

REFERENCES

Additional references

Ancora 2010
Ancora G, Maranella E, Aceti A, Pierantoni L, Grandi S, Corvaglia L, et al. Effect of posture on brain hemodynamics in preterm newborns not mechanically ventilated. *Neonatology* 2010;**97**(3):212–7. [PUBMED: 19887848]

Ballabh 2014
Ballabh P. Pathogenesis and prevention of intraventricular hemorrhage. *Clinics in Perinatology* 2014;**41**(1):47–67. [PUBMED: 24524446]

Barradas 2006
Barradas J, Fonseca A, Guimarães CL, Lima GM. Relationship between positioning of premature infants in Kangaroo Mother Care and early neuromotor development. *Jornal de Pediatria* 2006;**82**(6):475–80.

Bayley 1993
Bayley N. *Bayley Scales of Infant Development*. 2nd Edition. San Antonio, TX: The Psychological Corporation, 1993.

Bayley 2006
Bayley N. *Bayley Scales of Infant and Toddler Development*. San Antonio, TX: Harcourt Assessment, 2006.

Bembich 2012
Bembich S, Oretti C, Travan L, Clarici A, Massaccesi S, Demarini S. Effects of prone and supine position on cerebral blood flow in preterm infants. *Journal of Pediatrics* 2012;**160**(1):162–4. [PUBMED: 22000305]

Canadian Neonatal Network 2014
The Canadian Neonatal Network™. Annual Report 2014. Written and prepared by Dr Prakesh Shah, Eugene W. Yoon, Priscilla Chan and Members of the Annual Report Review Committee. http://www.canadianneonatalnetwork.org.

Carteaux 2003
Carteaux P, Cohen H, Check J, George J, McKinley P, Lewis W, et al. Evaluation and development of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics* 2003;**11**(4 Pt 2):e489–96. [PUBMED: 12671169]

Cochrane EPOC Group 2013
Effective Practice, Organisation of Care (EPOC). Data extraction and management. EPOC Resources for Review Authors. Oslo: Norwegian Knowledge Centre for the Health Services; 2013. http://epoc.cochrane.org/epoc-specific-resources-review-authors.

Cornette 2002
Cornette LG, Tanner SF, Ramenghi LA, Miall LS, Childs AM, Arthur RJ, et al. Magnetic resonance imaging of the infant brain: anatomical characteristics and clinical significance of punctate lesions. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2002;**86**(3):F171–7. [PUBMED: 11978747]

Cowan 1985
Cowan F, Thoresen M. Changes in superior sagittal sinus blood velocities due to postural alterations and pressure on the head of the newborn infant. *Pediatrics* 1985;**75**(6): 1038-47. [PUBMED: 3889817]

Cowan 1987
Cowan F, Thoresen M. The effect of intermittent positive pressure ventilation on cerebral arterial and venous blood velocities in the newborn infant. *Acta Paediatrica Scandinavica* 1987;**76**(2):239–47. [PUBMED: 3296626]

Dani 2007
Dani C, Bertini G, Cecchi A, Corsini I, Pratesi S, Rubaltelli FF. Brain hemodynamic effects of nasal continuous airway pressure in preterm infants of less than 30 weeks' gestation. *Acta Pediatrica* 2007;**96**(10):1421–5. [PUBMED: 17714539]

Dolfin 1983
Dolfin T, Skidmore MB, Fong KW, Hoskins EM, Shennan AT. Incidence, severity, and timing of subependymal and intraventricular hemorrhages in preterm infants born in a perinatal unit as detected by serial real-time ultrasound. *Pediatrics* 1983;**71**(4):541–6.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34. [PUBMED: 9310563]

Emery 1983
Emery JR, Peabody JL. Head position affects intracranial pressure in newborn infants. *Pediatrics* 1983;**103**(6):950-3. [PUBMED: 6644434]

Fumagalli 2009
Fumagalli M, Ramenghi LA, Righini A, Groppo M, Bassi L, De Carli A, et al. Cerebellar haemorrhages and pons development in extremely low birth weight infants. *Frontiers in Bioscience* 2009;**1**:537–41. [PUBMED: 19482668]

GRADEpro [Computer program]
McMaster University. GRADEpro [www.gradepro.org]. McMaster University, 2014.

Graça 2013
Graça AM, Geraldo AF, Cardoso K, Cowan FM. Preterm cerebellum at term age: ultrasound measurements are not different from infants born at term. *Pediatric Research* 2013; **74**(6):698–704. [PUBMED: 24002327]

Griffiths 1954
Griffiths R. *The Abilities of Babies: A Study in Mental Measurement*. New York, NY: McGraw-Hill Book Co, Inc, 1954.

Hamrick 2004
Hamrick SE, Miller SP, Leonard C, Glidden DV, Goldstein R, Ramaswamy V, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. *Journal of Pediatrics* 2004;**145**(5):593–9. [PUBMED: 15520756]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [PUBMED: 12958120]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Horbar 2002
Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, et al. Members of the Vermont Oxford Network. Trends in mortality and morbidity for very low birth weight infants, 1991-1999. *Pediatrics* 2002; **110**(1 Pt 1):143–51. [PUBMED: 12093960]

ICROP 1984
International Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Pediatrics* 1984;**74**(1): 127–33. [PUBMED: 6547526]

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]

Leahy 1982
Leahy FA, Durand M, Cates D, Chernick V. Cranial blood volume changes during mechanical ventilation and spontaneous breathing in newborn infants. *Journal of Pediatrics* 1982;**101**(6):984–7. [PUBMED: 7143179]

Limperopoulos 2007
Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors?. *Pediatrics* 2007;**120**(3):584–93. [PUBMED: 17766532]

Malusky 2011
Malusky S, Donze A. Neutral head positioning in premature infants for intraventricular hemorrhage prevention: an evidence-based review. *Neonatal Network* 2011;**30**(6): 381–96. [PUBMED: 22052118]

McLendon 2003
McLendon D, Check J, Carteaux P, Michael L, Moehring J, Secrest JW, et al. Implementation of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. *Pediatrics* 2003;**111**(4 Pt 2):e497-503. [PUBMED: 12671170]

Moritz 2008
Moritz B, Fritz M, Mann C, Simma B. Nasal continuous positive airway pressure (nCPAP) does not change cardiac output in preterm infants. *American Journal of Perinatology* 2008;**25**(2):105–9. [PUBMED: 18240105]

Nakamura 1990
Nakamura Y, Okudera T, Fukuda S, Hashimoto T. Germinal matrix hemorrhage of venous origin in preterm neonates. *Human Pathology* 1990;**21**(10):1059–62. [PUBMED: 2210729]

Nankervis 2010
Nankervis CA, Martin EM, Crane ML, Samson KS, Welty SE, Nelin LD. Implementation of a multidisciplinary guideline-driven approach to the care of the extremely premature infant improved hospital outcomes. *Acta Paediatrica* 2010;**99**(2):188–93. [PUBMED: 19863632]

Noori 2014
Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. *Journal of Pediatrics* 2014;**164**(2):264–70.e1-3. [PUBMED: 24183212]

Obladen 2008
Obladen M, Metze B, Henrich W, Aktas A, Czernik C, Schulz-Baldes A. Interdisciplinary surveillance of intraventricular haemorrhage associated conditions in infants <1000 g. *Acta Paediatrica* 2008;**97**(6):731–7. [PUBMED: 18460106]

Osborn 2003
Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/ intraventricular hemorrhage in premature infants. *Pediatrics* 2003;**112**(1 Pt 1):33-9. [PUBMED: 12837865]

Pape 1979
Pape KE, Wigglesworth JS. *Haemorrhage, ischaemia and the perinatal brain*. Philadelphia: JB Lippincott, 1979.

Papile 1978
Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**(4):529–34. [PUBMED: 305471]

Parodi 2015
Parodi A, Morana G, Severino MS, Malova M, Natalizia AR, Sannia A, et al. Low-grade intraventricular hemorrhage: is ultrasound good enough?. *Journal of Maternal-Fetal and Neonatal Medicine* 2015;**28**(1):2261–4. [PUBMED: 23968243]

Pellicer 2002
Pellicer A, Gaya F, Madero R, Quero J, Cabanas F. Noninvasive continuous monitoring of the effects of the head position on brain hemodynamic in ventilated infants. *Pediatrics* 2002;**109**(3):434–40. [PUBMED: 11875138]

Philip 1989
Philip AG, Allan WC, Tito AM, Wheeler LR. Intraventricular hemorrhage in preterm infants: declining incidence in the 1980s. *Pediatrics* 1989;**84**(5):797–801. [PUBMED: 2677959]

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

Rutherford 2010
Rutherford MA, Supramaniam V, Ederies A, Chew A, Bassi L, Groppo M, et al. Magnetic resonance imaging of white matter diseases of prematurity. *Neuroradiology* 2010;**52**(6): 505–21. [PUBMED: 20422407]

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GRADE Working Group. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. www.guidelinedevelopment.org/handbook. Updated October 2013.

Sherlock 2005
Sherlock RL, Anderson PJ, Doyle LW, Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. *Early Human Development* 2005;**81**(11):909–16. [PUBMED: 16126353]

Takashima 1978
Takashima S, Tanaka K. Microangiography and vascular permeability of the subependymal matrix in the premature infant. *Canadian Journal of Neurological Sciences* 1978;**5**(1): 45–50. [PUBMED: 647497]

Takashima 2009
Takashima S, Itoh M, Oka A. A history of our understanding of cerebral vascular development and pathogenesis of perinatal brain damage over the past 30 years. *Seminars in Pediatric Neurology* 2009;**16**(4):226-36. [PUBMED: 19945657]

Vermont Oxford Network 2013
Database of Very Low Birth Weight Infants Born in 2012. Burlington, VT: Vermont Oxford Network, 2013. Nightingale Internet Reporting System (accessed April 4, 2014).

Volpe 2008
Volpe JV. *Neurology of the Newborn*. 5th Edition. Philadelphia, PA: Saunders, 2008.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

The Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Search terms

(head midline OR prone OR lateral decubitus OR posture OR lateral alternant OR ((head OR body) AND (position OR positioning)))

CONTRIBUTIONS OF AUTHORS

OR and MB reviewed the literature and wrote the protocol.

MGC commented on and reviewed the protocol.

DECLARATIONS OF INTEREST

OR, MGC, and MB have no known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Institute for Clinical Sciences, Lund University, Lund, Sweden.

to OR and MB

- Istituto Giannina Gaslini, Genoa, Italy.

to MGC

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C