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Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD012409.
DOI: 10.1002/14651858.CD012409.pub2.

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[Overview of Reviews]

Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 6, 2018.

Citation: Shepherd E, Salam RA, Middleton P, Han S, Makrides M, McIntyre S, Badawi N, Crowther CA. Neonatal interventions for preventing cerebral palsy: an overview of Cochrane Systematic Reviews. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD012409. DOI: 10.1002/14651858.CD012409.pub2.

ABSTRACT

Background

Cerebral palsy is an umbrella term that encompasses disorders of movement and posture attributed to non-progressive disturbances occurring in the developing foetal or infant brain. As there are diverse risk factors and aetiologies, no one strategy will prevent cerebral palsy. Therefore, there is a need to systematically consider all potentially relevant interventions for prevention.

Objectives

Primary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions for preventing cerebral palsy (reducing cerebral palsy risk).

Secondary

To summarise the evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions that may increase cerebral palsy risk.

Methods

We searched the *Cochrane Database of Systematic Reviews* (27 November 2016) for reviews of neonatal interventions reporting on cerebral palsy. Two review authors assessed reviews for inclusion, extracted data, and assessed review quality (using AMSTAR and ROBIS) and quality of the evidence (using the GRADE approach). Reviews were organised by topic; findings were summarised in text and were tabulated. Interventions were categorised as effective (high-quality evidence of effectiveness); possibly effective (moderate-quality evidence of effectiveness); ineffective (high-quality evidence of harm); probably ineffective (moderate-quality evidence of harm or lack of effectiveness); and no conclusions possible (low- to very low-quality evidence).

Main results

Forty-three Cochrane Reviews were included. A further 102 reviews pre-specified the outcome cerebral palsy, but none of the included randomised controlled trials (RCTs) reported this outcome. Included reviews were generally of high quality and had low risk of bias, as determined by AMSTAR and ROBIS. These reviews involved 454 RCTs; data for cerebral palsy were available from 96 (21%) RCTs involving 15,885 children. Review authors considered interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy (3); interventions for neonates born preterm and/or at low or very low birthweight (33); and interventions for other specific groups of 'at risk' neonates (7). Quality of evidence (GRADE) ranged from very low to high.

Interventions for neonates with perinatal asphyxia or with evidence of neonatal encephalopathy

Effective interventions: high-quality evidence of effectiveness

Researchers found a reduction in cerebral palsy following therapeutic hypothermia versus standard care for newborns with hypoxic ischaemic encephalopathy (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.54 to 0.82; seven trials; 881 children).

No conclusions possible: very low-quality evidence

One review observed no clear differences in cerebral palsy following therapeutic hypothermia versus standard care.

Interventions for neonates born preterm and/or at low or very low birthweight

Possibly effective interventions: moderate-quality evidence of effectiveness

Researchers found a reduction in cerebral palsy with prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants (RR 0.54, 95% CI 0.32 to 0.92; one trial; 644 children).

Probably ineffective interventions: moderate-quality evidence of harm

Researchers reported an increase in cerebral palsy (RR 1.45, 95% CI 1.06 to 1.98; 12 trials; 1452 children) and cerebral palsy in assessed survivors (RR 1.50, 95% CI 1.13 to 2.00; 12 trials; 959 children) following early (at less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants.

Probably ineffective interventions: moderate-quality evidence of lack of effectiveness

Trial results showed no clear differences in cerebral palsy following ethamsylate versus placebo for prevention of morbidity and mortality in preterm or very low birthweight infants (RR 1.13, 95% CI 0.64 to 2.00; three trials, 532 children); volume expansion versus no treatment (RR 0.76, 95% CI 0.48 to 1.20; one trial; 604 children); gelatin versus fresh frozen plasma (RR 0.94, 95% CI 0.52 to 1.69; one trial, 399 children) for prevention of morbidity and mortality in very preterm infants; prophylactic indomethacin versus placebo for preventing mortality and morbidity in preterm infants (RR 1.04, 95% CI 0.77 to 1.40; four trials; 1372 children); synthetic surfactant versus placebo for respiratory distress syndrome in preterm infants (RR 0.76, 95% CI 0.55 to 1.05; five trials; 1557 children); or prophylactic phototherapy versus standard care (starting phototherapy when serum bilirubin reached a pre-specified level) for preventing jaundice in preterm or low birthweight infants (RR 0.96, 95% CI 0.50 to 1.85; two trials; 756 children).

No conclusions possible: low- to very low-quality evidence

No clear differences in cerebral palsy were observed with interventions assessed in 21 reviews.

Interventions for other specific groups of 'at risk' neonates

No conclusions possible: low- to very low-quality evidence

Review authors observed no clear differences in cerebral palsy with interventions assessed in five reviews.

Authors' conclusions

This overview summarises evidence from Cochrane Systematic Reviews regarding effects of neonatal interventions on cerebral palsy, and can be used by researchers, funding bodies, policy makers, clinicians, and consumers to aid decision-making and evidence translation. To formally assess other benefits and/or harms of included interventions, including impact on risk factors for cerebral palsy, review of the included Reviews is recommended.

Therapeutic hypothermia versus standard care for newborns with hypoxic ischaemic encephalopathy can prevent cerebral palsy, and prophylactic methylxanthines (caffeine) versus placebo for endotracheal extubation in preterm infants may reduce cerebral palsy risk. Early (at less than eight days of age) postnatal corticosteroids versus placebo or no treatment for preventing chronic lung disease in preterm infants may increase cerebral palsy risk.

Cerebral palsy is rarely identified at birth, has diverse risk factors and aetiologies, and is diagnosed in approximately one in 500 children. To date, only a small proportion of Cochrane Systematic Reviews assessing neonatal interventions have been able to report on this outcome. There is an urgent need for long-term follow-up of RCTs of such interventions addressing risk factors for cerebral palsy (through strategies such as data linkage with registries) and for consideration of the use of relatively new interim assessments (including the General Movements Assessment). Such RCTs must be rigorous in their design and must aim for consistency in cerebral palsy outcome measurement and reporting to facilitate pooling of data and thus to maximise research efforts focused on prevention.

PLAIN LANGUAGE SUMMARY

Interventions for babies from birth to one month of life for preventing cerebral palsy: an overview of Cochrane Systematic Reviews

What is the issue?

'Cerebral palsy' is a term that includes a group of conditions affecting people's ability to move; it is the most common physical disability in childhood. Cerebral palsy is usually due to events before, during, or after childbirth that lead to injury to babies' developing brains. No single cause of cerebral palsy is known. For many children, the cause of cerebral palsy is unclear, but many risk factors are known. The biggest risk factor is preterm birth (birth before 37 weeks of pregnancy). Other risk factors during the neonatal period (birth to one month of life) include prolonged loss of oxygen during birth; brain injury; strokes or seizures; disorders of the heart, blood vessels, airways, and lungs; prolonged mechanical assistance for breathing; some infections; jaundice (yellow discolouration of the skin and eyes due to excess bilirubin in the blood); and some syndromes or abnormalities of chromosomes (structures that hold genes).

Why is this important?

As there are different risk factors for and causes of cerebral palsy, it is likely that different interventions may be needed to prevent cerebral palsy by reducing risk factors. This overview summarises evidence about preventing cerebral palsy that has been presented in Cochrane Systematic Reviews of interventions during the neonatal period.

What evidence did we find?

We searched for evidence on 27 November 2016, and identified 43 Cochrane Reviews assessing interventions during the neonatal period that reported some information on cerebral palsy. These Reviews were all of moderate to high quality, but the quality of the evidence about cerebral palsy ranged from very low to high. Three Reviews assessed interventions for newborn babies who may have had a lack of oxygen at or around the time of birth; 33 Reviews assessed interventions for babies born preterm or at low birthweight; and seven Reviews assessed interventions for other groups of newborn babies at risk of injury to their brains (such as newborn babies with low blood sugar at birth).

We found that one intervention was effective for cerebral palsy prevention. Newborn babies who may have had a lack of oxygen at or around the time of birth who had induced hypothermia (cooling of their body or just their brain) were less likely to develop cerebral palsy than babies who did not receive hypothermia (seven trials; 881 children; high-quality evidence). We found that one intervention was possibly effective for cerebral palsy prevention. Preterm newborns who received methylxanthines (caffeine) when weaning from machine-assisted breathing (extubation from mechanical ventilation) was planned were less likely to develop cerebral palsy than babies who received a placebo (one trial; 644 children; moderate-quality evidence). We found one intervention that was probably ineffective and may cause harm: Preterm newborns who received early (at less than eight days of age) corticosteroids to prevent chronic lung disease were more likely to develop cerebral palsy than babies who received a placebo (12 trials; 959 children; moderate-quality evidence). We found that five other interventions were probably ineffective (did not prevent or increased the chance of cerebral palsy) (moderate-quality evidence). Review authors did not find enough evidence to say whether the other interventions prevented, increased, or had no impact on cerebral palsy (low- or very low-quality evidence).

What does this mean?

This overview identified one intervention that was effective in preventing cerebral palsy (induced hypothermia for newborn babies who may have had a lack of oxygen), one that was possibly effective for preventing cerebral palsy (caffeine for preterm babies weaning from machine-assisted breathing), one that appeared to cause harm (corticosteroids at less than eight days of age for preterm babies to prevent chronic lung disease), and five that did not appear to make a difference. For the other interventions assessed, there was not enough evidence to allow conclusions. It is important that additional good quality trials assessing interventions that might impact cerebral palsy risk factors conduct long-term follow-up to measure the impact of these interventions. We identified over 100 other Cochrane Reviews that may in the future provide information on interventions during the neonatal period for preventing cerebral palsy if they include long-term follow-up.