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[Intervention Review]

Calcium and phosphorus supplementation of human milk for preterm infants

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ABSTRACT

Background

Preterm infants are born with low skeletal stores of calcium and phosphorus. Preterm human milk provides insufficient calcium and phosphorus to meet the estimated needs of preterm infants for adequate growth. Supplementation of human milk with calcium and phosphorus may improve growth and development of preterm infants.

Objectives

To determine whether addition of calcium and phosphorus supplements to human milk leads to improved growth and bone metabolism of preterm infants without significant adverse effects.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 3), MEDLINE via PubMed (1966 to 14 April 2016), Embase (1980 to 14 April 2016) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 14 April 2016). We also searched clinical trials databases (11 May 2016) and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised and quasi-randomised trials comparing supplementation of human milk with calcium and/or phosphorus versus no supplementation in hospitalised preterm infants were eligible for inclusion in this review.

Data collection and analysis

Two review authors (JB, JW) independently extracted data and assessed trial quality using standard methods of the Cochrane Neonatal Review Group. We reported dichotomous data as risk ratios (RRs) and continuous data as mean differences (MDs) with 95% confidence intervals (CIs). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.

Main results

This is an update of a 2001 review that identified no eligible trials. One trial including 40 infants met the inclusion criteria for this review. Using GRADE criteria, we judged the quality of the evidence as low owing to risk of bias (inadequate reporting of methods of randomisation, allocation concealment and/or blinding) and imprecision (wide confidence intervals and data from a single small trial). We found no evidence of a difference between calcium and phosphorus supplementation versus no supplementation for neonatal growth outcomes (weight, length, head circumference) at any time point reported (two, four or six weeks postnatal age). At six weeks postnatal



age, supplementation with calcium/phosphorus was associated with a decrease in serum alkaline phosphatase concentration (MD -56.85 IU/L, 95% CI -101.27 to -12.43; one randomised controlled trial (RCT); n = 40 infants). Investigators provided no data on growth at 12 to 18 months, neonatal fractures, feed intolerance, breastfeeding or any of the prespecified childhood outcomes for this review (fractures, growth, neurodevelopmental outcomes).

Authors' conclusions

We identified one small trial including only 40 infants that compared supplementation of human milk with calcium and phosphorus versus no supplementation in hospitalised preterm infants. We judged the evidence to be of low quality and found no evidence of differences between groups for clinically important outcomes including growth and fractures. Although serum alkaline phosphatase concentration was reduced in the group receiving supplementation at six weeks postnatal age, this difference is unlikely to be of clinical significance. We conclude that evidence is insufficient to determine whether benefit or harm ensues when human milk is supplemented with calcium and/or phosphorus for the hospitalised preterm infant. We see no advantage of conducting further trials of this intervention because with the advent of multi-component human milk fortifier, supplementation of human milk with calcium and/or phosphorus alone is no longer common practice. Future trials should consider assessing effects of multi-component fortifiers with different mineral compositions on clinically important outcomes during the neonatal period and in later childhood.

PLAIN LANGUAGE SUMMARY

Does supplementation of human milk with calcium and phosphorus improve growth and development in preterm infants?

What is the issue?

When babies are born too early (preterm), they have very low stores of the minerals calcium and phosphorus needed for healthy bones and growth. Human milk may not contain sufficient minerals for these babies.

Why is this important?

Calcium and phosphorus are essential for healthy bones and normal growth and development. When a baby is born preterm and does not receive enough calcium and phosphorus, bone fractures and poor growth can occur.

What evidence did we find?

We searched for evidence in April 2016 and identified one randomised controlled trial including 40 babies. Investigators reported a small decrease in the concentration of alkaline phosphatase (an enzyme involved in bone growth) among infants who had received calcium/phosphorus supplementation. We found no difference in growth between infants who had been given human milk supplemented with extra calcium and phosphorus and infants who had received no supplementation. One small trial provided the evidence, and we judged the evidence to be of low quality. Researchers reported no follow-up of these babies into childhood.

What does this mean?

Evidence is insufficient to allow a judgement as to whether extra calcium and/or phosphorus provided to preterm babies confers benefit for their bones and growth. It is no longer very common to give calcium and phosphorus supplements alone, as human milk fortifiers now available include many other components as well as minerals to support the growth and development of preterm babies. We therefore suggest that future trials conducted to examine effects of mineral supplements in preterm babies include them in multi-component human milk fortifiers and assess clinically important outcomes into childhood.