Enteral Calcium or Phosphorus Supplementation in Preterm or Low Birth Weight Infants: a Systematic Review and Meta-analysis

Mohan Kumar, MD,[a] Ranadip Chowdhury, PhD,[a,b] Bireshwar Sinha, MD,[a,b] Ravi Prakash Upadhyay, MD,[a,b] Temsunaro Rongsen Chandola, PhD,[a] Sarmila Mazumder, PhD,[a] Sunita Taneja, PhD,[a] Nita Bhandari, PhD,[a] Tarun Shankar Choudhary, MD[a,c]

abstract

OBJECTIVES: To assess effects of calcium or phosphorous supplementation compared with no supplementation in human milk-fed preterm or low birth weight infants.

METHODS : Data sources include Cochrane Central Register of Controlled Trials, Medline and Embase. We included Randomized controlled trials (RCTs) and non-randomized trials (quasi-randomized).

RESULTS: Three studies (4 reports; 162 infants) were included. At latest follow-up (38 weeks), there was reduction in osteopenia (3 studies, 159 participants, relative risk 0.68, 95% confidence interval [CI] 0.46–0.99). At latest follow-up (6 weeks), there was no effect on weight (1 study, 40 participants, mean difference [MD] 138.50 g, 95% CI −82.16 to 359.16); length (1 study, 40 participants, MD 0.77 cm, 95% CI −0.93 to 2.47); and head circumference (1 study, 40 participants, MD 0.33 cm, 95% CI −0.30 to 0.96). At latest follow-up, there was no effect on alkaline phosphatase (55 weeks) (2 studies, 122 participants, MD −126.11 IU/L, 95% CI −298.5 to 46.27, $I^2 = 73.4\%$); serum calcium (6 weeks) (1 study, 40 participants, MD 0.54 mg/dL, 95% CI −0.19 to 1.27); and serum phosphorus (6 weeks) (1 study, 40 participants, MD 0.07 mg/dL, 95% CI −0.22 to 0.36). The certainty of evidence ranged from very low to low. No studies reported on mortality and neurodevelopment outcomes.

CONCLUSIONS: The evidence is insufficient to determine whether enteral supplementation with calcium or phosphorus for preterm or low birth weight infants who are fed mother's own milk or donor human milk is associated with benefit or harm.

[a]*Centre for Health Research and Development, Society for Applied Studies, New Delhi, India;* [b]*DBT/Wellcome India Alliance Clinical and Public health Fellow, Hyderabad, India; and* [c]*Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway*

Drs Kumar and Choudhary conceptualized and designed the study, designed the data collection instruments, collected data, conducted the initial analyses, prepared the initial draft, and revised the manuscript; Dr Chowdhury conceptualized and designed the study, and critically reviewed the manuscript; Drs Sinha, Upadhyay, Chandola, Mazumdar, Taneja, and Bhandari coordinated and supervised data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Tarun Shankar Choudhary, MD, Centre for Health Research and Development, Society for Applied Studies, 45, Kalu Sarai, New Delhi, 110016 India. E-mail: tarun.choudhary@sas.org.in

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Many preterm and low birth weight (LBW) infants are born with low stores of calcium and phosphorous[1,2]; and human milk may not be sufficient for adequate postnatal skeletal growth and development in these infants.[3–5] Preterm and LBW infants are at risk for hypophosphatemia, poor bone mineralization and elevated alkaline phosphatase activity, fractures, and lower than expected growth rates.[6–8]

A Cochrane systematic review of calcium or phosphorus supplementation of human milk for preterm hospitalized infants was published in 2017.[9] However, there have been no systematic reviews of calcium or phosphorous supplementation for preterm or LBW infants in either hospital or community settings since this time. The World Health Organization (WHO) currently recommends calcium and phosphorous supplements for very LBW (<1.5 kg) infants.[10]

The primary objective of this review was to assess the effect of calcium or phosphorus supplementation during infancy compared with no supplementation on mortality, morbidity, growth, and neurodevelopmental outcomes in preterm or LBW infants who are fed mother's own milk or donor human milk. The secondary objectives were to determine the optimal time of initiation, dose and duration of calcium, and phosphorus supplementation during infancy.

METHODS

Protocol

The protocol for this review was registered in PROSPERO (PROSPERO 2021 CRD42021238802).[11]

Inclusion Criteria

We included randomized controlled trials or nonrandomized trials (quasi-randomized) in which individual preterm (<37 weeks' gestational age) or LBW (birth weight <2.5 kg) infants fed mother's own milk or donor human milk were either allocated to receive enteral calcium or phosphorus supplementation and compared with a control group (placebo or no drug); allocated to different regimens of calcium or phosphorus supplementation (in terms of dosage, duration, and timing of initiation). Studies in which enteral calcium and phosphorus supplementation was provided for treatment of any disease were excluded.

Search and Extraction

A comprehensive search (Appendix 1) was conducted in the Cochrane Central Register of Controlled Trials (2016, Issue 3) in the Cochrane Library via the Cochrane Register of Studies Online,[12] Medline via PubMed,[13] and Embase[14] from inception to March 24, 2021. There were no language restrictions.

Two review authors (T.S.C., M.K.) independently screened the titles and abstracts to identify potentially relevant citations. The authors then independently assessed the eligibility of the studies in accordance with the specified inclusion criteria. Any disagreements were resolved by discussion and, if necessary, by consulting a third review author (R.C.). The reference lists of articles selected for inclusion in this review were searched to identify additional relevant articles. Screening and full text selection were managed using the Web-based software Covidence.[15] Following standard methods described in the Cochrane Handbook for Systematic Reviews of Interventions,[16] 2 review authors (T.S.C., M.K.) independently extracted data using a data abstraction form integrated with a modified version of the Cochrane Effective Practice and Organization of Care Group data collection checklist (2017).[17]

Risk of Bias

Two review authors (T.S.C., M.K.) independently assessed the risk of bias (ROB) of all included trials using the Revised Cochrane ROB tool for randomized trials (ROB 2) and ROB in nonrandomized studies of interventions.[18] In case of discrepancies among their judgments and inability to reach consensus, a third review author was consulted. We planned to use funnel plots and Egger's test to assess publication bias in outcomes with >10 studies.[19]

Statistical Analysis

The outcomes for this review were categorized into primary and secondary (Appendix 2). For each outcome, studies were pooled at the latest follow-up if >1 study were available. If single study reported an outcome, individual study effect sizes was reported. The unit of analysis was the infant.

We used relative risk (RR) and mean difference (MD) as our outcome estimate measures for categorical and continuous outcomes, respectively, and recorded them as provided in the article. We used adjusted RR or MD where studies reported and estimated unadjusted RR or MD where adjusted RR or MD was not presented. To estimate the effect of calcium or phosphorus supplementation on prespecified outcomes, we conducted a meta-analysis using "meta" command in Stata v16[20]; pooled adjusted and unadjusted RR or MD together and reported the pooled RR or MD

and corresponding 95% confidence (CI).[16]

We used a fixed-effect meta-analysis (inverse variance method) to combine data when it was reasonable to assume that studies were estimating the same underlying treatment effects. Pooled estimates of outcomes variables showing I2 >50% were presented using random effects model, restricted maximum likelihood method.[21]

We planned to perform a subgroup analyses for infants <32 weeks' gestational age (very preterm) or <1500 g birth weight (very LBW) for the primary outcomes.

The certainty of the evidence for each outcome was assessed independently by 2 review authors using the Grading of Recommendations Assessment, Development, and Evaluation approach using Grading of Recommendations Assessment, Development, and Evaluation Pro guideline development tool,[22] a Web-based tool to create a "summary of findings" table to report the certainty of the evidence (Appendix 8 and 11).

RESULTS

We found 2200 records. After removing duplicates, title, abstract, and full text screening, we included 4 reports (3 studies) that compared outcomes in calcium- or phosphorus-supplemented infants to infants who did not receive calcium or phosphorous (Appendix 3).[23–26] There were no studies that compared dose or timing of calcium or phosphorous supplementation in preterm or LBW infants. A total of 34 studies were excluded in this review (Appendix 6).

The included studies (2 RCTs and 1 quasi-randomized trial) reported on 162 preterm or LBW infants from 2 countries (Iran, United Kingdom) (Appendix 5). Two studies assessed the effect of phosphorus only (dose of 15 mg/kg per day in 1 study and 50–75 mg per day in 1 study) and 1 study assessed the effect of calcium and phosphorous combined (calcium 45 mg/kg per day, phosphorus 25 mg/kg per day). Supplementation commenced between birth and 10 days postnatal age in all 3 studies. The duration of supplementation was between 10 and 42 days in 1 study and it could not be assessed in the other 2 included studies.

The ROB assessment is summarized in Appendix 4. One study had low ROB,[23] 1 high ROB,[25] and 1 moderate ROB.[24]

Primary Outcomes

Results are summarized in Table 1 and Appendix 7. There were no mortality or neurodevelopment outcome data available for analysis.

At latest follow-up (mean [SD] 38.3 [56.9] weeks), when comparing calcium- or phosphorus-supplemented infants to unsupplemented infants, the RR for osteopenia was 0.68 (95% CI 0.46–0.99, 3 studies, 159 participants, low certainty evidence).[23–25]

At latest follow-up (6 weeks), the MD between the calcium- or phosphorus-supplemented infants compared with the unsupplemented infants in weight was 138.50 g (95% CI −82.16 to 359.16, 1 study, 40 participants, very low certainty evidence)[25]; in length was 0.77 cm (95% CI −0.93 to 2.47, 1 study, 40 participants, very low certainty evidence)[25]; and head circumference was 0.33 cm (95% CI −0.30 to 0.96, 1 study, 40 participants, very low certainty evidence).[25]

Other Outcomes

At latest follow-up, the MD between the calcium- or phosphorus-supplemented infants compared with the unsupplemented infants in alkaline phosphatase (55 weeks) was 126.11 IU/L (95% CI −298.5 to 46.27, I^2 = 73.4%, 2 studies, 122 participants, very low certainty evidence)[24,25]; serum calcium (6 weeks) was 0.54 mg/dL (95% CI −0.19 to 1.27, 1 study, 40 participants, very low certainty evidence)[25]; and in serum phosphorus (6 weeks) was 0.07 mg/dL (95% CI −0.22 to 0.36, 1 study, 40 participants, very low certainty evidence).[25]

Subgroup Analysis

For infants <32 weeks' gestational age or birth weight <1500 g, results are summarized in Appendices 9-11. There were no mortality or neurodevelopment outcome data available for analysis. At latest follow-up (mean [SD] 54.5 [70.0] weeks), when comparing calcium- or phosphorus-supplemented infants to unsupplemented infants, the RR for osteopenia was 0.29 (95% CI 0.02–3.64, I^2 = 70.8%, 2 studies, 119 participants, very low certainty evidence).[23,24] At latest follow-up, the MD between the calcium- or phosphorus-supplemented infants compared with the unsupplemented infants in serum alkaline phosphatase was −237.8 IU/L (95% CI −415.18 to −60.42, 1 study, 82 participants, very low certainty evidence).[24]

DISCUSSION

Three studies of 162 infants that compared calcium or phosphorus supplementation versus no supplementation in preterm or LBW infants were included in this review. We found low certainty evidence of reduction in osteopenia but no change in markers of growth (weight, length, and head

TABLE 1 Summary of Findings for Critical Outcomes

Calcium and/or Phosphorus Supplementation Compared With No Supplement for Preterm and/or LBW Infants					
				Anticipated Absolute Effects	
Outcomes	No. of Participants (Studies) Follow-up	(GRADE) Certainty of the Evidence	Relative Effect (95% CI)	Risk With No Supplement	Risk Difference With Calcium and/or Phosphorus Supplementation
Weight (g) follow-up: 6 wk	40 (1 RCT)	⨁◯◯◯ Very low[a]	—	The mean weight (g) was 2483 g	MD 138.5 g higher (82.16 lower–359.16 higher)
Length (cm) follow-up: 6 wk	40 (1 RCT)	⨁◯◯◯ Very low[a]	—	The mean length (cm) was 47.04 cm	MD 0.77 cm higher (0.92 lower–2.46 higher)
Head circumference (cm) follow-up: 6 wk	40 (1 RCT)	⨁◯◯◯ Very low[a]	—	The mean head circumference (cm) was 34.31 cm	MD 0.33 cm higher (0.3 lower–0.96 higher)
Serum alkaline phosphatase (IU/L) follow-up: latest mean (SD) 55 (69.3) wk; median (IQR) 55 (6–104) wk	122 (2 RCTs)	⨁◯◯◯ Very low[b]	—	The mean serum alkaline phosphatase (IU/L) was 656.13 IU/L	MD 126.11 IU/L lower (298.5 lower–46.27 higher)
Serum calcium (mg/dL) follow-up: 6 wk	40 (1 RCT)	⨁◯◯◯ Very low[a]	—	The mean serum calcium (mg/dL) was 8.39 mg/dL	MD 0.54 mg/dL higher (0.19 lower–1.27 higher)
Serum phosphorus (IU) follow-up: 6 wk	40 (1 RCT)	⨁◯◯◯ Very low[a]	—	The mean serum phosphorus (IU) was 4.36 IU	MD 0.07 IU higher (0.22 lower–0.36 higher)
Osteopenia/rickets follow-up: latest mean (SD) 38.3 (56.9) wk; median (IQR) 6 (5–104) wk	159 (3 RCTs)	⨁⨁◯◯ Low[c]	RR 0.68 (0.46–0.99)	540 per 1000	173 fewer per 1000 (292 fewer–5 fewer)

The risk in the intervention group (and its 95% CI) is on the basis of the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Grading of Recommendations Assessment, Development, and Evaluation Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, 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 certainty, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Patient or population: preterm and/or LBW infants. Setting: any high-, middle-, or low-income country; at home or in the health facility. Intervention: calcium and/or phosphorus supplementation. Comparison: no supplement. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IQR, interquartile range; RCT, randomized controlled trial. —, not applicable.

[a] Downgraded 3 levels for: very serious ROB; serious inconsistency (small number of studies); serious imprecision (wide CI).

[b] Downgraded 3 levels for: very serious ROB; serious inconsistency (high heterogeneity [$I^2 = 73.42\%$]); serious imprecision (wide CI).

[c] Downgraded 2 levels for: serious ROB; serious imprecision (suboptimal sample size).

circumference at 6 weeks follow-up). There was very low certainty evidence showing an improvement in alkaline phosphatase among infants <1.5 kg or <32 weeks' gestation at birth, but no other change in markers of bone metabolism (serum calcium or phosphorous levels). There were no studies that reported mortality, or other morbidities including bone fractures and infection, and no studies that reported developmental outcomes. We found no studies that compared dose or timing of calcium or phosphorus supplementation.

The most recent 2017 Cochrane systematic review[9] included 1 trial of 40 infants and reported similar findings that there was no evidence of a difference between calcium and phosphorus supplementation versus no supplementation for neonatal growth outcomes and a decrease in serum alkaline phosphatase concentration (MD −56.85 IU/L, 95% CI −101.27 to −12.43) at 6 weeks' postnatal age. There has been no other recent systematic reviews on calcium or phosphorous supplementation for preterm or LBW infants in either hospital or community settings.

The lack of data on calcium and phosphorus supplementation is likely because of many infants receiving human milk multicomponent fortifier that contains calcium and phosphorus, along with other micronutrients such as vitamins, minerals, energy, and protein. There have been many trials of human milk multicomponent fortification and a recent Cochrane systematic review published in 2018.[27] That systematic review reported an increased rate of weight gain (MD 1.76 g/kg per day, 95% CI 1.30–2.22), body length (MD 0.11 cm per week, 95% CI

0.08–0.15) and head circumference (MD 0.06 cm per week, 95% CI 0.03–0.08) among preterm infants.[28] Also, a reduction in markers of bone metabolism, serum alkaline phosphatase levels (weighted mean difference −142 IU/L (95% CI −204 to −80) and higher bone mineral content (weighted mean difference 12.0 mg/cm (95% CI 6.3–17.7) was reported with human milk fortification of multinutrients including calcium and phosphorus.[28] However, human milk fortification is more expensive than calcium or phosphorus supplements and also requires mixing of fortifier with breast milk or provision of donor milk with possible concerns of increased risks of contamination.

Limitations of our review included the small number of studies and participants, the high ROB, and the heterogeneity in outcomes. However, strengths were our comprehensive search strategy and systematic review methods including assessment of certainty of body of evidence using standard methods. The doses of calcium and phosphorus used in the studies were similar to those recommended by WHO[10] and other organizations, meaning our results are generalizable to low- and middle-income country settings that use WHO guidelines.

Overall, evidence is insufficient to reveal whether supplementation with calcium and phosphorus improved growth and bone health of preterm or LBW infants. Given the importance of calcium and phosphorous supplementation in preterm and LBW infants, more high-quality trials of these supplements are needed.

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ABBREVIATIONS

CI: confidence interval
LBW: low birth weight
MD: mean difference
ROB: risk of bias
RR: relative risk
WHO: World Health Organization

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