Enteral Zinc Supplementation in Preterm or Low Birth Weight Infants: A Systematic Review and Meta-analysis

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abstract

BACKGROUND AND OBJECTIVES: Evidence on the effect of zinc supplementation on health outcomes in preterm or low birth weight (LBW) infants is unclear. We estimated the effect of enteral zinc versus no zinc supplementation in human milk fed preterm or LBW infants on mortality, growth, morbidities, and neurodevelopment.

METHODS: Data sources include PubMed, Cochrane Central and Embase databases through March 24, 2021. Study selection was randomized or quazi-experimental trials. Two reviewers independently screened, extracted data, and assessed quality. We reported pooled relative risks (RR) for categorical outcomes, and mean differences (MD) for continuous outcomes.

RESULTS: Fourteen trials with 9940 preterm or LBW infants were included. Moderate to low certainty evidence showed that enteral zinc supplementation had little or no effect on mortality (risk ratio 0.73, 95% confidence interval [CI] 0.46 to 1.16), but increased weight (MD 378.57, 95% CI 275.26 to 481.88), length (MD 2.92, 95% CI 1.53 to 4.31), head growth (MD 0.56, 95% CI 0.23 to 0.90), and decreased diarrhea (RR 0.81; 95% CI 0.68 to 0.97). There was no effect on acute respiratory infections, bacterial sepsis, and psychomotor development scores. The effect of zinc supplementation on mental development scores is inconclusive. There was no evidence of serious adverse events. Eight trials had some concerns or high risk of bias, small-sized studies, and high heterogeneity between trials led to moderate to very low certainty of evidence.

CONCLUSIONS: Zinc supplementation in preterm or LBW infants have benefits on growth and diarrhea prevention. Further research is needed to generate better quality evidence.

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Zinc is an essential micronutrient required for multiple physiologic functions. Zinc deficiency is associated with childhood morbidities and impaired developmental outcomes.[1,2] Preterm (<37 weeks gestation) or low birth weight (LBW, <2500 g) infants have low body stores of zinc because of reduced time for placental transfer, low intake, and excessive endogenous losses.[3,4] It is plausible that zinc supplementation during early childhood might benefit preterm or LBW infants by reducing the risk of morbidities, like diarrhea and sepsis, and improving growth and development.[5]

In 2011, a systematic review examined the effect of zinc supplementation in breastfed LBW infants from low- and middle-income countries and reported no effect on diarrhea, respiratory infection, hospitalization, or growth and reported insufficient evidence on mortality.[6] However, there have been new trials since that time. A recent Cochrane review (2021) assessed the effect of enteral zinc supplementation in preterm breastfed or formula-fed infants on mortality, growth, morbidities, and neurodevelopment.[7] However, there was no analysis on "human milk fed" preterm or LBW infants.

Thus, our primary objective was to assess the effect of zinc compared with no zinc supplementation on mortality, morbidity, growth, and development in LBW and/or preterm infants who are fed mother's own milk or donor human milk. The secondary objective was to determine the effect of different dose and timing of zinc supplementation.

METHODS

This review was registered in PROSPERO (CRD42021238971). Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P) guidance was followed.[8]

Search and Data Extraction

An electronic search was conducted on PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Register of Studies Online, and Embase through March 24, 2021. There were no date or language restrictions (Appendix 1). We also searched the reference lists of the selected articles to identify additional relevant articles.

We used the Covidence systematic review software,[9] Veritas Health Innovation, Melbourne, Australia, for the review. Two review authors independently screened the titles and abstracts to identify relevant citations. The review authors retrieved the full texts of the relevant articles and independently assessed the eligibility of the studies using predefined inclusion criteria and performed data extraction. For data extraction, a modified version of the Cochrane Effective Practice and Organization of Care Group[10] data collection checklist (Cochrane EPOC Group 2017) was used, which included study identifiers and context, study design and limitations, intervention specifics, and outcome effects. We also collected data on explanatory variables, including if the babies were very low birth weight (VLBW) <1.5 kg or if the gestational age was <32 weeks. Any disagreements or discrepancies between reviewers was resolved by discussion and by consulting a third review author. Study authors were contacted where the full text was not available or to obtain any additional information.

Inclusion Criteria and Outcomes

We included randomized control trials (RCT)s and quasi-randomized trials in which individual preterm or LBW infants fed with mother's milk or donor human milk were either allocated to receive zinc or no zinc supplementation. We assessed enteral zinc supplementation alone, or in combination with other micronutrients, if the control group also received the same micronutrients. We excluded studies where infants were formula-fed or had other specific comorbidities, such as human immunodeficiency virus.

The key outcomes studied were mortality, morbidity, hospitalization, sepsis, acute respiratory infection, diarrhea, necrotizing enterocolitis, growth (weight, length, and head circumference) at latest follow up, neurodevelopment (mental and psychomotor development). All outcomes were measured at latest follow up.

Statistical Analysis

The analysis was done using Stata 16 software (Texas)[11] following the Cochrane Handbook for Systematic Reviews of Interventions recommendations.[8] We reported pooled relative risks (RR) for categorical outcomes, and mean differences (MD) for continuous outcomes along with respective 95% confidence intervals (CIs) using the "meta" command in Stata.

If the relative risk was not provided, we calculated it using the available data in the article. Adjusted results were preferred over unadjusted results whenever available. Fixed-effects meta-analysis (inverse variance method) was used to pool data to estimate effects. In situations of high heterogeneity (ie, I^2 value greater than 50%),[12] a random effects model using the Restricted Maximum Likelihood Method (REML) was used. Egger's test was used to assess publication bias for outcomes with more than 10 studies.

Subgroup analyses decided a priori were based on gestational age (<32

weeks; very preterm), birth weight (<1500 g; VLBW); dose of zinc (<3, 3–5, >5 mg per day); age at enrolment; income level of the country (high or upper middle and lower middle or low income) and fortification of breastmilk.

Assessment of the risk of bias for included studies was done using revised Cochrane "Risk of bias" tool for randomized trials and risk of bias in nonrandomized studies of interventions tool for nonrandomized studies.[8] Certainty of evidence for the pooled estimates for the outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[13]

RESULTS

Our search on March 24, 2021 resulted in 1922 records. After title and abstract screening, we examined 315 full text articles. 14 trials were included that compared enteral zinc to no zinc supplementation in preterm or LBW infants[3,14–26] (Appendix 2). The included studies reported on 9940 preterm or LBW infants from 11 countries of which 3.1% (2 trials, 304 infants) were VLBW or very preterm.[21,23] Of the included studies, 1 was a cluster randomized trial,[24] 1 was a quasi-randomized trial,[16] and the remaining 12 were individually randomized controlled trials. Six trials[3,20–24] had low risk of bias, and others had some concerns or high risk of bias (Appendix 3). Three trials were conducted in high-income countries,[16,23,26] three in upper middle-income countries,[14,15,18] and eight in low or lower-middle income countries.[3,17,19–22,24,25] The median (IQR) dose of zinc used in the studies was 5 (5 to 7) mg. The time of start of intervention ranged from birth to 5.2 weeks and the median (interquartile range [IQR]) duration of supplementation was 140.7 days (98 to 182.7 days) (Appendix 4). There were no studies that compared dosing or timing.

Primary Outcomes

Findings are summarized in Table 1 and Appendix 5. Six trials with a total of 8801 LBW or preterm infants reported infant deaths with a median follow-up duration of 26 (14 to 152) weeks.[18,19,22–24] The pooled RR of zinc supplementation on mortality was 0.73 (95% CI 0.46 to 1.16, I^2 = 59%, low certainty). In a sensitivity analysis, excluding studies that enrolled term LBW infants, the pooled RR of zinc supplementation for mortality was 0.68 (95% CI 0.43 to 1.09, I^2 = 52%, 4 trials,[19,23,24] 1609 participants).

At latest follow up (median 26, IQR 20 to 26 weeks), the RR for hospitalization in infants supplemented with zinc versus no zinc was 0.70 (95% CI 0.24 to 2.00, I^2 = 82%, 2 trials,[18,19] 277 infants, very low certainty). The mean difference in the duration of hospitalization, in infants who received zinc supplementation versus no zinc supplementation was 3.49 days (95% CI −7.11 to 14.08; I^2 = 49%, 2 trials, 398 infants).

At latest follow up (20 to 52 weeks), we found a mean difference of 378.6 g in weight (95% CI 275.26 to 481.88, I^2 = 45%, 8 trials,[3,14,16,17,19,21,23,25] 798 participants, moderate certainty) 2.9 centimeters in length (95% CI 1.53 to 4.31, I^2 = 77%, 6 trials,[3,16,17,19,21,25] 529 participants, low certainty), and 0.56 centimetres in head growth (95% CI 0.23 to 0.90, I^2 = 41%, 5 trials,[14,17,19,21,25] 466 infants, low certainty).

At latest follow up (median 26, IQR 20 to 52 weeks) we found a RR of 0.81 for diarrhea (95% CI 0.68 to 0.97, I^2 = 28%, 6 trials,[3,17–19,22] 1947 infants, moderate certainty). At latest follow up (median 13, IQR 6 to 20 weeks), the RR for acute respiratory infections was 0.32 (95% CI 0.09 to 1.17, I^2 = 0%, 2 trials,[17,19] 172 infants, very low certainty) and for sepsis was 1.12 (95% CI 0.62 to 2.02, I^2 = 18%, 2 trials,[19,23] 265 participants, low certainty). We found a single trial[23] (n = 193) that reported the effect of zinc supplementation on necrotizing enterocolitis (RR 0.08, 95% CI 0.00 to 1.33), bronchopulmonary dysplasia (RR 0.66, 95% CI 0.31 to 1.40), retinopathy of prematurity (RR 0.14, 95% CI 0.01 to 2.70), and fever (RR 1.66, 95% CI 1.09 to 2.53, 1 trial,[20] 82 infants).

At latest follow up (52 weeks) we found a mean difference between the infants with zinc and no zinc supplementation[15,26] of −4.18 in Bayley Scale of Infant Development version 1 (BSID I) mental development scores (95% CI −6.51 to −1.85, I^2 = 9%, 2 trials, 301 infants, low certainty); and of 5.75 in BSID psychomotor development scores (95% CI −4.83 to 16.33, I^2 = 95%, very low certainty). In 72 infants Mathur et al[19] used the Amiel-Tison scale for measuring neurodevelopment and reported a RR of 0.09 for "hyperexcitability" (95% CI 0.01 to 0.7) and a RR of 0.22 for "brisk bicipital reflex" (RR 0.22, 95% CI 0.07 to 0.7), but alertness and attention was similar across groups (RR 0.47, 95% CI 0.05 to 4.99).

No studies reported serious adverse events. Two trials[17,22] reported vomiting as an adverse event but showed no substantial difference between the zinc and no zinc groups.

Subgroups

Two trials provided <3 mg per day, 10 trials provided 3 to 5 mg per day, and 4 trials provided >5 mg per day of elemental zinc to the infants. There was no clear evidence of difference in effect for the mortality by dose of zinc supplementation (<3 mg, 3 to 5 mg

TABLE 1 Summary of Findings: Effect of Zinc on Critical Outcomes in LBW or Preterm Infants:

Outcomes	No of Participants (studies) Follow Up	Certainty of the Evidence(GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Zinc Supplementation	Risk Difference With Enteral Zinc Supplementation
Mortality latest follow up (62.2 [62.8] weeks; 26 [14–152.1] weeks)	8801 (6 RCTs)	⨁⨁◯◯ Low[a]	RR 0.73 (0.46 to 1.16)	28 per 1000	8 fewer per 1000 (15 fewer to 5 more)
Hospitalization latest follow up (24 [3.5] weeks; 26 [20–26] weeks)	277 (2 RCTs)	⨁◯◯◯ Very low[b]	RR 0.70 (0.24 to 2.00)	317 per 1000	95 fewer per 1000 (241 fewer to 317 more)
Wt latest follow up (25 [17.4] weeks; 22 [13.5–39] weeks)	798 (8 RCTs)	⨁⨁⨁◯ Moderate[c]	—	Mean wt 5162.9 gm	MD 378.57 g higher (275.26 higher to 481.88 higher)
Length latest follow up (46.8 [45.0] weeks; 36.1 [20–52.1] weeks)	529 (6 RCTs)	⨁⨁◯◯ Low[d]	—	Mean length 60.4 cm	MD 2.92 cm higher (1.53 higher to 4.31 higher)
Head growth latest follow up (23.0 [17.6] weeks; 20 [13–24] weeks)	466 (5 RCTs)	⨁⨁◯◯ Low[e]	—	Mean head circumference 37.8 cm	MD 0.56 cm higher 0.23 higher to 0.90 higher)
Diarrhea latest follow up (30.4 [18.3] weeks; 26 [20.1–52.1] weeks)	(6 RCTs)	⨁⨁⨁◯ Moderate[f]	RR 0.81 (0.68 to 0.97)	135 per 1000	26 fewer per 1000 (43 fewer to 4 fewer)
Acute respiratory infection latest follow up (13 [9.9] weeks; 13 [6–20] weeks)	172 (2 RCTs)	⨁◯◯◯ Very low[g]	RR 0.32 (0.09 to 1.17)	106 per 1000	72 fewer per 1000 (96 fewer to 18 more)
Sepsis latest follow up (17 [4.2] weeks; 17 [14–20] weeks)	265 (2 RCTs)	⨁⨁◯◯ Low[h]	RR 1.12 (0.62 to 2.02)	130 per 1000	16 more per 1000 (49 fewer to 132 more)
Mental development scores latest follow up (52 wk; 52 wk)	301 (2 RCTs)	⨁⨁◯◯ Low[i]	—	Mean score 110.4	MD 4.18 SD lower (6.51 lower to 1.85 lower)
Psychomotor development latest follow up (52 wk; 52 wk)	301 (2 RCTs)	⨁◯◯◯ Very low[j]	—	Mean score 98.3	MD 5.75 SD higher (4.83 lower to 16.33 higher)

Patient or population was low birth weight or preterm infants. The setting was a community and healthcare setting in Bangladesh, Brazil, Chile, Egypt, India, Iran, Italy, Nepal, South Korea, Spain and Tanzania. The intervention used was enteral zinc supplementation. The comparison group used no zinc supplementation. The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Outcomes shown as (mean [SD]; median [interquartile range]). GRADE 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 and 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, and 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, and the true effect is likely to be substantially different from the estimate of effect. CI, confidence interval; RR, risk ratio; MD, mean difference; —, not applicable.

[a] Downgraded 2 levels for serious inconsistency (I square value 58.9%, $P = .18$, nonoverlapping of confidence intervals on visual inspection of the forest plot), serious imprecision (wide confidence interval).

[b] Downgraded 3 levels for very serious risk of bias (all included studies have high risk of bias); serious inconsistency (I square value is 82.3%, $P = .50$, inconsistency suspected on visual inspection of the forest plot); serious imprecision (wide confidence interval).

[c] Downgraded 1 level for serious risk of bias (the high-quality studies contributed to 43% of the weightage in the meta-analyses).

[d] Downgraded 2 levels for serious risk of bias (the high-quality studies contributed to 32.9% of the weightage in the meta-analyses) and serious inconsistency (I square value is 77.2%, $P = .00$, inconsistency suspected on visual inspection of the forest plot). Publication bias was suspected only for the outcome of length. However, we have not downgraded for this given there were less than 10 studies included the analysis.

[e] Downgraded 2 levels for very serious risk of bias (all the included studies are of low quality).

[f] Downgraded 1 level for serious risk of bias (the high-quality studies contributed to 43.0% of the weightage in the meta-analyses).

[g] Downgraded 3 levels for very serious risk of bias (both the included studies are of low quality), serious indirectness (only 2 studies with small sample size reported this outcome), and serious imprecision (wide confidence interval).

[h] Downgraded 2 levels for serious indirectness (only 2 studies with small sample size reported this outcome) and serious imprecision (wide confidence interval).

[i] Downgraded 2 levels for very serious risk of bias (all the included studies are of low quality) and serious inconsistency (I square value is 57.7%, $P = .03$ inconsistency suspected on visual inspection of the forest plot).

[j] Downgraded 3 levels for very serious risk of bias (all the included studies are of low quality), serious inconsistency (I square value 97.7%, $P = .30$, inconsistency suspected on visual inspection of the forest plot.), and serious imprecision (wide confidence intervals).

and >5 mg). There were no data for morbidity outcomes including diarrhea. Compared with no zinc, the MD for weight in infants supplemented with 3 to 5 mg per day of zinc was 316.47 g (95% CI 161.75 to 471.19, 5 trials), whereas that was 550.98 g (95% CI 246.39 to 855.56, 3 trials) for zinc >5mg per day. Compared with no zinc, the MD for length in infants supplemented with zinc 3 to 5 mg per day was 2.18 cm (95% CI, 0.71 to 3.65,

4 trials), and that for zinc >5 mg per day was 3.90 (95% CI 1.46 to 6.34, 2 trials). Compared with no zinc, the relative risk of diarrhea in zinc supplemented infants with <3 mg per day was 1.0 (95% CI 0.72 to 1.39, 1 trial), and that with 3-5 mg per day was 0.75 (95% CI 0.62 to 0.92, 5 trials) (Appendix 5).

In very preterm and VLBW infants, a single available trial with 193 participants reported a 71% decrease in the risk of death with zinc supplementation (RR 0.29, 95% CI 0.11 to 0.76).[23] There was substantial effect of zinc supplementation on weight, length and head growth, and no effect on sepsis in very preterm or VLBW infants (Appendix 5 and 6). Subgroup analyses by country income, age of enrolment, fortification of human milk, wherever available, are described in Appendix 5.

DISCUSSION

Our systematic review included 14 trials of 9940 preterm or LBW infants from 11 countries. We found low to moderate certainty evidence that enteral zinc supplementation increased weight, length, and head circumference and decreased diarrhea at the end of latest follow up. We found very low to low certainty evidence that zinc may have little or no effect on mortality, acute respiratory infection, sepsis, and hospitalization. We also found very low to low certainty evidence from 2 trials that zinc supplementation may decrease mental development scores and may have no effect on psychomotor development scores. There were no reports of reported serious adverse events.

A systematic review in 2011 of 3 trials and 2220 participants on zinc supplementation in LBW breastfed infants did not find evidence of an effect of zinc on all-cause mortality, infectious morbidities, and growth.[6] However, there have been 7 more relevant studies since 2011. A recently published Cochrane systematic review in 2021 assessed the effect of zinc supplementation in breastfed or formula-fed preterm infants and included 5 trials.[7] The review reported similarities with our review on improved weight gain (standardized mean difference in z scores [SMD] 0.46, 95% CI 0.28 to 0.64, 5 RCT, 481 participants, moderate certainty), linear growth (SMD 0.75, 95% CI 0.36 to 1.14, 3 RCTs, 289 participants, low certainty), but reported little to no effect on head growth (SMD 0.21 95% CI −0.02 to 0.44). The review did not report on diarrhea but reported little or no effect on sepsis (RR 1.11, 95% CI 0.60 to 2.04). The review also reported a decrease in mortality (RR 0.55, 95% CI 0.31 to 0.97, 3 RCT, 345 participants, low certainty), but found no studies reporting neurodevelopment or long-term growth outcomes. The differences in the estimates between our review and this Cochrane review are primarily because of the difference in the study populations and inclusion criteria. We included all available studies on zinc supplementation in preterm or LBW infants who were fed with mother's milk or donor milk and excluded studies where infants were exclusively fed on formula. The Cochrane 2021 review included infants irrespective of breastfed or formula-fed, but only included preterm infants and excluded studies with term LBW infants. Infant formula contains high levels of zinc and other micronutrients, and it is likely that effects of zinc supplementation are different in human milk fed only infants than formula fed infants.

We reported a decrease in BSID mental development scores and no effect on psychomotor development scores from 2 trials.[15,26] In 1 of these included trials (Ashworth A et al 1998[15]), there was an error in the manufacturing of zinc solution that led to 1 cohort of infants being provided 1 mg instead of 5 mg. Later, a second cohort of infants was recruited in the study that received 5 mg of zinc. Because of this error, there might be a baseline imbalance in infants allocated to treatment and control groups that may influence the neurodevelopment outcome measure in this trial. Given the high risk of bias in the included studies, the effect of zinc on neurodevelopment scores seems inconclusive and should be interpreted with caution. In another trial, zinc supplementation showed improved neurodevelopmental outcomes assessed using Amiel-Tison scale.[19] The 2021 Cochrane review,[7] did not include these trials as the population did not meet their specified inclusion criteria of preterm infants, although they were LBW infants. Moreover, the reliability of BSID score (gold standard for childhood developmental assessment) is debatable when measured before 24 months of age.[27–29] We graded this evidence as low to very low certainty because of small sample size, inconsistency, and risk of bias in the included studies. More studies as well as longer-term follow up of zinc supplemented infants is necessary to clarify this observation and generate better quality evidence.

Other systematic reviews have shown that zinc supplementation improved linear growth in under 5 children,[30] weight-for-age and weight-for-length Z scores in infants[31] but had no effect on mental or motor development in infants.[32] Zinc supplementation is also seen to have preventive effects on diarrheal and respiratory illness.[33,34] Biologically, the effects on infections and growth are plausible given the role of zinc in basic metabolic and cellular functions, synthesis of proteins and enzymes, carbohydrate metabolism, cell division, immunity,

and skeletal growth.[35–37] However, mechanisms for the effect on zinc on neurodevelopmental outcomes are sketchy.

The key limitations were high heterogeneity between studies and high risk of bias in 55% of the included studies. Although, we conducted subgroup analysis defined a priori, much of the heterogeneity remain unexplained. Data were limited for outcomes of acute respiratory infection, sepsis, necrotising enterocolitis, and neurodevelopment, and for the subgroup of VLBW or very preterm infants, as many of these were assessed in 1 or 2 studies. No studies compared dosing or timing of initiation. The strengths of our study include extensive literature search in multiple databases and inclusion of relevant studies with a total of 9940 preterm or LBW infants. To minimize data availability bias, we contacted study authors to get relevant data related to our study population. The statistical power for some of the critical outcomes was high. The included trials were undertaken in a variety of healthcare settings including high-, middle- and low-income settings, with the period of follow-up ranging from 42 weeks post-conceptual age to 35 months of age. These factors are to be considered in relation to generalizability of the findings for each outcome. Although, our review findings are applicable to human milk fed LBW or preterm infants, globally including LMICs, caution is warranted as the certainty of evidence ranges from moderate to very low.

It is standard practice in many neonatal units to give VLBW infants a multicomponent fortifier with human milk, which provides an additional 0.5 to 1.8 mg/kg per day of zinc until the infant reaches a weight of 1800 to 2000 g.[38] Few units provide zinc as an individual supplement. Our review provides moderate to very low certainty evidence suggesting that enteral zinc compared with no zinc supplementation in human milk fed preterm or LBW infants can prevent diarrhea, improve weight, length, and head growth, but may have little or no benefits in reducing deaths. Our findings on mental development require further research. Further studies on dosing and timing of zinc supplementation are needed. Large-scale, high-quality trials among infants with different gestational age groups and birth weight categories including very preterm and VLBW infants will be helpful to generate better quality evidence.

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ABBREVIATIONS

BSID: Bayley Scale of Infant Development
CI: confidence interval
GRADE: Grading of Recommendations Assessment, Development and Evaluation
LBW: Low birth weight
MD: mean difference
RCT: randomized controlled trial
RR: relative risk
SMD: standardized mean difference
VLBW: very low birth weight
WHO: World Health Organization

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