Original Article

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Efficacy of High-Dose vs. Standard-Dose Enteral Zinc Supplementation on Growth and Zinc Status in Very Preterm Infants: A Randomized Controlled Trial

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Abstract:

Objective: Preterm infants are at a heightened risk of zinc deficiency. Supplemental zinc may reduce mortality rates and enhance immunomodulatory functions. However, enteral zinc administration may negatively influence copper and iron absorption in the gastrointestinal tract. Therefore, we investigated the efficacy of high and standard doses of enteral zinc supplementation in this population.

Material and Methods: We included very preterm neonates (gestational age <32 weeks; birth weight <1,800 g) and randomly administered high- (10 mg/day) or standard-dose (1 mg/day) zinc supplements. Intergroup differences in growth parameters and serum zinc levels were compared with baseline within-participant changes.

Results: Forty participants were enrolled (n=20 per group), with mean gestational age and birth weight of 29.0 weeks and 1,173.8 g, respectively. No significant disparities in baseline characteristics or intervention variables, including the duration of supplementation (47 vs. 35 days) and average daily caloric intake (132.75 vs. 133.33 kcal/kg/day), were observed. The mean increments in weight, weight-for-age Z-score, and serum zinc levels were 14.92 vs. 15.57 g/kg/day, -0.04 vs. 0.10, and -0.7 vs. 4.2 μg/dL for the high- and standard-dose groups, respectively. No significant differences in growth velocity, Z-scores, serum copper and ferritin levels, or clinical outcomes were observed between the groups.

Conclusion: There were no significant differences in the mean changes in growth parameters and serum zinc levels from baseline to post-intervention between neonates receiving high-dose and those receiving standard-dose zinc supplements.

Keywords: growth, mortality, neonatal intensive care unit, newborn, premature infant, zinc

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Introduction

Zinc is a co-factor involved in growth, cell differentiation, major pathways of metabolism, and immune function[1]. Zinc is therefore important for normal growth, tissue maintenance, and wound healing[2]. In two meta-analyses involving term neonates, zinc supplementation was found to promote growth in infants <6 months of age[3] and prevent diarrhea in children aged 6 months to 12 years[4]. Meta-analyses involving preterm (<37 weeks of gestation) or low birth weight (BW <2,500 g) infants showed that zinc supplementation increased growth[1,5] and reduced all-cause mortality[1] and diarrhea[5].

With increasing survival and greater numbers of very low birth weight (VLBW; <1,500 g) or very preterm (<32 weeks of gestation) infants[6], their nutritional needs become more important. Since fetal zinc accretion occurs in the third trimester[7], very preterm neonates are exceptionally vulnerable to zinc deficiency due to a combination of limited prenatal stores, physiological immaturity, and high metabolic demands[8]. Therefore, preterm and small for gestational age (SGA)[9-11] infants are at risk of symptomatic zinc deficiency. Symptoms of zinc deficiency include failure to thrive despite sufficient caloric intake, dermatitis, and increased susceptibility to infection[12]. The prevalence of subclinical zinc deficiency in preterm infants was 25–50%[12,13].

The recent recommendation from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition, published in 2023, recommends enteral zinc intake of 2–3 mg/kg/day in preterm infants with a birth weight of <1,800 g[14] (the former ESPGHAN's recommendation in 2010 was 1.1–2.0 mg/kg/day)[15]. Zinc concentration in preterm human-[16] and formula milk[17] is 3.37 (2.26–4.47) mg/L and 1.5–6 mg/L, respectively. However, net absorption was significantly improved with human milk compared to formulas in a previous study (60% vs. 20%)[17]. Preterm infants consuming 180 mL/kg/day of fortified human milk receive approximately 0.5–1 mg/kg/day of zinc[17] and 1–2 mg/kg/day of zinc supplementation, meeting the new recommendation.

In two recent meta-analyses[1,5], there were two randomized controlled trials (RCTs) focused on VLBW infants. The outcomes (growth and mortality) of zinc sulfate (10 mg/day) supplementation were especially beneficial in the studies by Terrin[18] and Kumar[19]. The mortality rate in the zinc group was lower than that in the placebo group (5/97 vs. 17/96; relative risk 2.37; 95% confidence interval 1.08–5.18; (p-value=0.006)[18]. Moreover, body weight was higher in the zinc group than in the placebo group (body weight at discharge, 2208±501 g vs. 1889±639 g; p-value=0.001[18]; body weight at 52 weeks of postconceptional age, 4120±635 g vs. 3404±802 g; p-value=0.0003)[19]. Daily weight gain was comparable between the zinc (18.2±5.6 g/kg/day) and control 17.0±8.7 g/kg/day; (p-value=0.48) groups[18].

Zinc toxicity is not a clinical problem and is considered relatively safe; however, enteral zinc administration has the potential to negatively influence copper and iron absorption in the gastrointestinal (GI) tract[2,12,20,21]. In Terrin's study, vomiting was not significantly different between the zinc and control groups (p-value=0.40)[18].

We investigated the efficacy of high (10 mg/day) and standard (1 mg/day) doses of enteral zinc supplementation to promote growth in very preterm infants until discharge or 44 weeks' postmenstrual age (PMA), whichever came first.

Material and Methods

Study design and patient domains

This double-blind, single-center, parallel, pragmatic, randomized, placebo-controlled trial was conducted between January 2024 and December 2025 in a university-based tertiary referral neonatal intensive care unit in Southern Thailand and included very preterm neonates. The study design was approved by the Ethics Committee of our center. Written informed consent was obtained from the parents of the infants enrolled in the study. Stratification was

performed based on birth weight (BW: 401–999, 1000–1499, or 1500–1800 g) and SGA (yes or no). Participants were randomly allocated (1:1) to one of the two treatments (high- or standard-dose zinc supplementation) using an allocation sequence generated via a computer with a permuted block and kept as consecutive numbers by a statistician. Allocation concealment was ensured using identical, opaque, sealed envelopes. The two doses of zinc preparations were provided in identical bottles, without indication of group identity or content, by a registered neonatal pharmacist (assigned participants to interventions and was the only unblinded investigator) in the study center. Dedicated nurses, registered nurses, and attending neonatologists were blinded to the allocations.

Very preterm neonates (gestational age [GA]: $24^{0/7}$–$32^{6/7}$ weeks and BW: 401–1,800 g) were admitted to the neonatal unit; body weight at enrollment was >800 g. Stable neonates with complete enteral feeding (150 mL/kg/day) for at least a few days were assessed for eligibility. We excluded: (1) an outborn neonate who was admitted to the study center after seven days of life; (2) neonates with congenital infections; (3) neonates with malformations, syndromes, or genetic defects; (4) neonates with evidence of culture proven sepsis, necrotizing enterocolitis (NEC), or those declared dead before enrollment; (5) neonates who underwent GI surgery or had high GI fluid output (usually ileostomy losses); (6) neonates who were unstable during weighing and on intercostal drainage tube or drainage; (7) neonates who needed diuretics for more than seven days; (8) neonates with severe birth asphyxia (5-minute Apgar score <4); or (9) neonates whose parents decided not to participate in the study. If a neonate developed recurrent definite NEC (stage II >1 episode) or advanced NEC (stage III), stopped enteral feeding for more than 14 days, was suspected of serious zinc side effects (rash, hives, itching, red, swollen, blistered, peeling skin with or without fever, wheezing, swelling [mouth, face, lips, or tongue], or diarrhea), or the parents decided not to continue participating in the study, the neonate was withdrawn from the study. This study was approved by the Human Research Ethics Committee of our institution (approval no. REC. 66–451–1–1) and registered at ClinicalTrials.gov (NCT06219525).

Routine nutritional care

After birth, VLBW infants receive starter solutions (comprising glucose, protein, and calcium) as soon as venous access is available. The parenteral nutrition (PN) is started within 24–48 h of life following the ESPGHAN guidelines of 2018 (including zinc supplementation 400–500 µg/kg/day in preterm infants)[22] and maintained through a central vascular access to ensure adequate nutrients, fluids, and electrolytes until full enteral feeding is reached. Neonates receiving PN receive zinc 400 µg/kg/day intravenously until PN is stopped.

Enteral feeding was started within a few days of life at 10–20 mL/kg/day (BW <1000 g) or 20–30 mL/kg/day (BW <1800 g), divided into 8–12 feeds using maternal milk (first priority), pasteurized donor milk (for which informed consent was obtained), or preterm formula (24 kcal/oz). In the absence of signs of feeding intolerance in the previous 24 h, the daily increment in enteral volume was 10–20 mL/kg/day (BW <1000 g) or 20–30 mL/kg/day (BW <1800 g). Enteral feeding was discontinued in the case of suspected NEC. If the neonate stopped enteral feeding, zinc supplementation was withheld until full enteral feeding and a stable clinical condition were achieved.

Human milk fortification using concentrated preterm formula (one spoon added to 10 mL of sterile water; to increase calories to 4–10 kcal/oz in human milk, depending on weight gain) was added when enteral feeding was achieved at 120 mL/kg/day. In routine care, human milk fed to VLBW infants is fortified to 22–25 kcal/oz using a concentrated preterm formula when enteral feeding is 150

mL/kg/day. Therefore, very preterm infants with faltered growth still had poor weight gain (13 g/kg/day) after fortification of milk to 22–25 kcal/oz, which was considered hypercaloric milk (26–30 kcal/oz) by the attending staff. If this infant still had poor weight gain, we considered increasing the enteral volume to 180 mL/kg/day. No probiotics, prebiotics, or lactoferrins were administered.

Infants who weighed less than 1,800–2,000 g received an MTV drop (Munti-Vim drops; B.L. Hua & Co., Ltd., Bangkok) of 1 mL/day, which was prescribed irrespective of body weight, after full enteral feeding until 6–12 months. A daily iron (Ferrous fumarate drops; Olic Thailand; with each 0.6 mL containing 15 mg of elemental iron; milk was avoided for 1 hour before and after taking iron supplement) intake of 2–3 mg/kg/day starting at 2 weeks of age or full enteral feeding is reached; it is recommended for VLBW infants until 6–12 months[14].

Intervention

After obtaining informed consent, neonates were randomized into two groups: Group A (10 mg/day high-dose zinc sulfate; 450 mOsm/kg H_2O) and Group B (1 mg/day standard-dose; 45 mOsm/kg H_2O). Both preparations, provided by the Songklanagarind Hospital Pharmacy, were identical in appearance, taste, and packaging. To ensure blinding, an unblinded pharmacist labeled each 60-mL opaque container simply as "zinc solution" with patient identifiers, concealing the dosage from both investigators and the statistician.

Following randomization, blinded nurses administered 1 mL of the assigned solution via a tuberculin syringe once daily, one hour post-feeding. To prevent interference, zinc was not given with iron-containing meals or within one hour of milk intake. If vomiting occurred within 15 minutes, the dose was repeated and recorded. Supplementation continued until discharge or 44 PMA.

Outcome and definitions

The outcomes were growth parameters and blood zinc levels before and after zinc intervention (within-participant changes). SGA was defined as a newborn whose BW was below the 10th percentile of GA. The average daily calories were calculated as the sum of the total calories consumed during zinc supplementation divided by the duration of zinc supplementation.

Growth velocities and delta Z-scores were calculated from the start of the intervention until its conclusion (defined as at least two weeks of treatment completed by 44 weeks' PMA or discharge, whichever occurred first). Daily infant weight was measured by nurses to the nearest 1 g using a calibrated electronic scale. The weight gain rate (g/kg/day) was calculated using the two-point average method: $Rate=([W_2-W_1]\times1000)/([W_2+W_1]/2\times[D_2-D_1])$, where W is weight in grams, D is day, 1 is the beginning of the time interval, and 2 is the end[23]. Length and head circumference (HC) were assessed weekly to the nearest 0.1 cm. Velocities (cm/week) were calculated as the difference between measurements taken before and after the intervention. Weight-for-age, length-for-age, and HC-for-age Z-scores were determined using Fenton reference growth charts, appropriate for PMA[24].

Blood levels of zinc and copper (Colorimetric technique, Mindray BS 360-E™, Shenzhen Mindray Bio-Medical Electronics, Shenzhen, China) and ferritin (Chemiluminescence immunoassay method, Alinity i™, Abbott Laboratories Co. Ltd., Illinois, USA.) were measured within a few days before and after the Zn supplementation. Although there are few reports on serum zinc levels in infants, zinc deficiency in preterm infants is defined by the ESPGHAN as a serum zinc concentration of <74 μg/dL[16]. We applied a serum copper reference value of 9–46 μg/dL for 1–5 days old and 30–40 μg/dL for preterm infants[25].

Mortality was defined as in-hospital mortality after the intervention. NEC was defined according to the modified

Bell's classification as definite (stage II_{A-B}) or advanced (stage III_{A-B})[26]. Bronchopulmonary dysplasia was defined according to the former[27] and new[28] National Institute of Health consensus definitions. Ventilator-associated pneumonia and central line-associated bloodstream infections followed recent National Healthcare Safety Network guidelines for infants aged <1 year[29,30]. Late-onset sepsis was defined as culture-proven sepsis occurring after 72 hours of life. This required clinical signs of sepsis combined with at least one positive blood culture for Gram-negative bacteria or fungi (Candida spp.), or at least two positive cultures for commensal organisms. Surgical retinopathy of prematurity was defined as ROP requiring treatment with either laser photocoagulation or intravitreal anti-vascular endothelial growth factor therapy. Eye examinations were performed only in neonates with indications for screening[31]. The length of hospital stay was defined as the duration of hospital stay during admission until discharge. Daily hospital cost was derived by dividing the total hospital cost by the duration of hospitalization (1 USD=32 Thai Baht).

Sample size calculation

In a previous RCT involving very preterm infants (GA 24–32 weeks in Italy, 10 mg/day vs. 1 mg/day)[18], body weight at discharge was higher in the zinc group than in the placebo group (2,208±501 g compared with 1,889±639 g). Using a significance level of <5%, with 80% power, a sample of 102 neonates was required (51 neonates per arm). The sample size was increased to approximately 20% for participant withdrawal. Therefore, the target sample size was 120 (60 neonates/arm). Very preterm infants (GA 24–32 weeks and BW 401–1,800 g) without malformations or syndromes were admitted to the study center at a rate of 90–100 neonates annually. We anticipated a 50%–70% participation rate among parents, due to the fragility of the neonates. Accordingly, we planned to achieve recruitment within 2 years. The present study represents a preliminary analysis of the data.

Statistical analysis

The R program (version 4.5.1[32]), encompassing the EpiCalc package (version 4.1.0.1[33]), was used to analyze the data. Categorical variables are presented and compared using percentages and the χ^2 test or Fisher's exact test. Parametric and non-parametric continuous variables are presented as mean±standard deviation (S.D.) and median (interquartile range, [IQR]) and were compared using t-test or rank sum test (for normally or non-normally distributed continuous variables, respectively). Differences in the growth parameters and blood levels were compared with within-participant changes. All p-values were two-tailed, and values <0.05 were considered significant.

Results

Overall, 79 neonates were assessed for eligibility, and 39 were excluded (Figure 1). Forty participants were enrolled in this study. The mean GA and BW were 29.0±2.2 weeks and 1,173.8±327.9 g, respectively. The baseline characteristics and interventions of the neonates who received high and standard doses of zinc supplementation did not differ significantly between the groups (Table 1). The number of neonates who received exclusive breast milk (including maternal milk or pasteurized donor milk) in the high-dose and standard-dose groups was 13 and 18, respectively.

Before and after zinc intervention, growth parameters, blood levels, and clinical outcomes were not significantly different between neonates who received high and standard doses of zinc supplementation (Tables 2–4). Individual Zn levels of neonates who received high-dose or standard-dose Zn supplementation at baseline and post-intervention are shown in Figure 2. No deaths, NEC, or vomiting were observed in either group.

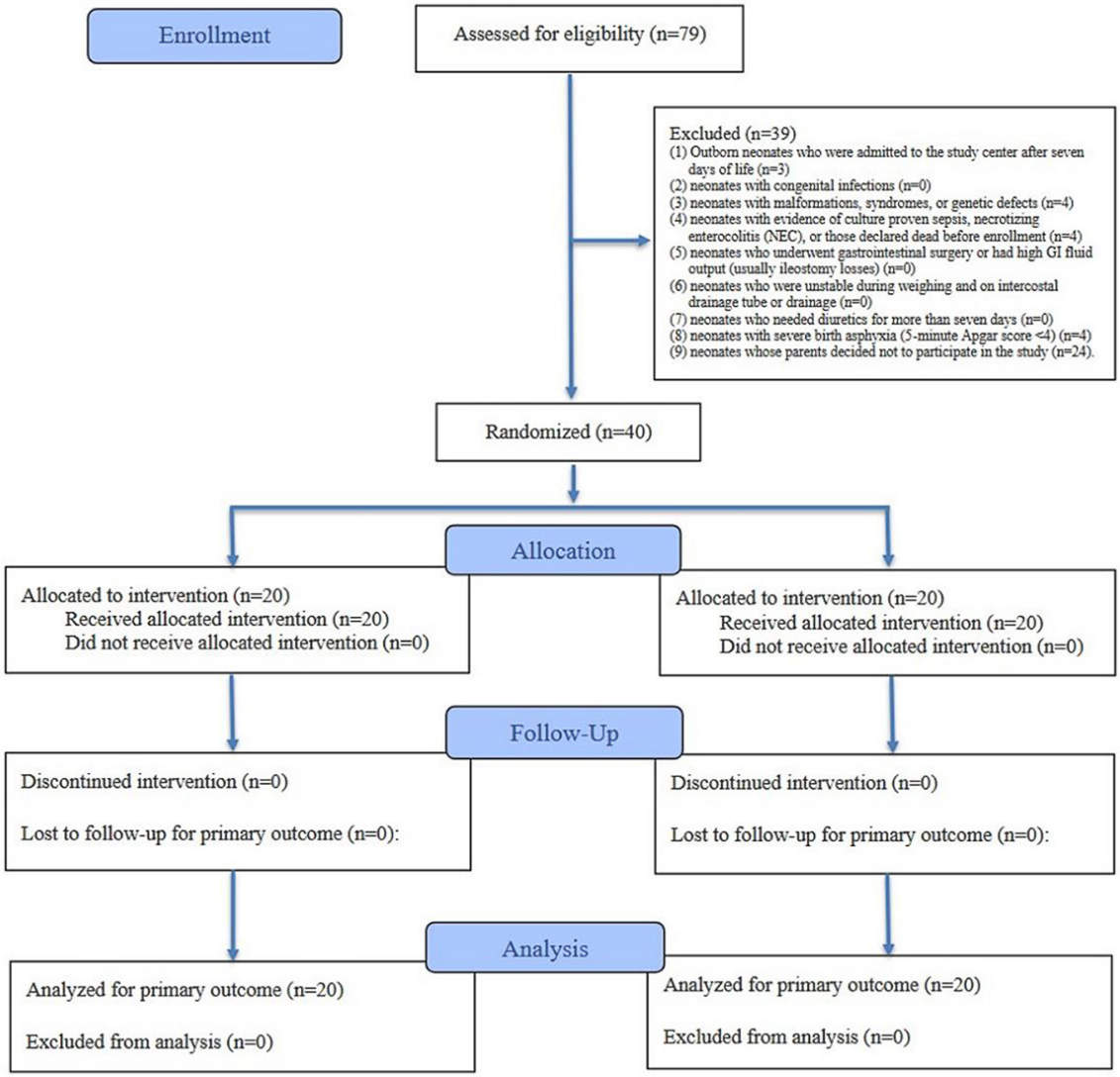

Figure 1 CONSORT flow diagram

Discussion

There were no statistically significant differences in the delta changes of growth parameters (weight gain and weight-for-age Z-score were specifically evaluated) or serum zinc, copper, and ferritin levels between neonates receiving high- versus standard-dose zinc supplementation. Compared to previous RCTs, the baseline characteristics and year of study differed from those in this study (Table 5).

In an Indian study[19], most participants were full-term VLBW (74%) and SGA (71%). The growth velocity at 40 weeks PMA, similar to that post-intervention (38–39 weeks PMA), did not differ between the groups. In an Italian study[18], the weight at discharge in the 10 mg/day zinc group was significantly higher than that in the 1 mg/day zinc group. However, there was no difference in daily weight gain between the groups (18.2 vs. 17.0 g/kg/day),

Table 1 Baseline characteristics and intervention of neonates who received high- or standard-dose zinc supplementation

Baseline characteristics	High-dose (n=20)	Standard-dose (n=20)	p-value
Gestational age, weeks*	28.9±2.6	29.2±1.9	0.63
Birth weight, g*	1162.1±360.7	1185.4±300.6	0.83
Length at birth, cm*	36.5±3.6	36.8±2.9	0.77
Head circumference at birth, cm*	26.2±2.6	27.1±2.3	0.23
Male sex, n (%)	12 (60.0)	8 (40.0)	0.34
Small for gestational age, n (%)	4 (20.0)	4 (20.0)	>0.99
Cesarean delivery, n (%)	16 (80.0)	17 (85.0)	>0.99
5-min Apgar score†	8 (7, 9)	8 (8, 9)	0.79
Duration of parenteral nutrition, days†	10 (7, 14)	13 (11, 17)	0.08
Intervention			
Date of start zinc supplementation, days†	15 (13, 19)	19 (15, 22)	0.19
Duration for zinc supplementation, days*	47±26	35±17	0.08
Average daily calories, kcal/kg/day*	132.8±10.6	133.3±13.0	0.88
Postmenstrual age of stop zinc, weeks*	38.8±3	37.6±1.8	0.14

*=Data are presented as mean±standard deviation, †=The data are shown as the median (interquartile range)

Table 2 Growth parameters of neonates who received high- or standard-dose zinc supplementation at the start and end of intervention

Growth Parameters	High-dose (n=20)	Standard-dose (n=20)	p-value
Weight*			
Start, g	1343.2±309.4	1438.5±275.8	0.31
Stop, g	2752.3±613.9	2535.8±536.3	0.24
Difference, g/days	30.3±5.1	30.8±5.0	0.72
Difference, g/kg/day	14.9±2.4	15.6±1.6	0.32
Weight-for-age Z-score†			
Start	-1.06 (-1.76, -0.77)	-0.71 (-1.69, -0.55)	0.22
Stop	-0.84 (-1.44, -0.69)	-0.71 (-1.73, -0.04)	0.63
Difference	-0.04 (-0.07, 0.34)	0.10 (-0.08, 0.35)	0.99
Length			
Start, cm*	37.9±3.4	38.7±2.5	0.39
Stop, cm*	46.0±2.4	45.3±2.4	0.35
Difference, cm/week†	1.2 (1.1, 1.4)	1.3 (1.2, 1.5)	0.28
Length-for-age Z-score			
Start*	-1.44±0.87	-1.23±1.17	0.52
Stop†	-1.22 (-2.00, -0.90)	-1.08 (-1.56, -0.41)	0.29
Difference†	-0.03 (-0.17, 0.36)	0.14 (-0.12, 0.37)	0.67
Head circumference*			
Start, cm	26.9±2.5	27.8±1.6	0.21
Stop, cm	32.9±1.8	32.3±2.0	0.33
Difference, cm/week	0.9±0.3	0.9±0.3	0.57
Head circumference-for-age Z-score			
Start*	-1.44±0.99	-1.14±1.11	0.37
Stop†	-0.67 (-1.01, -0.35)	-0.54 (-1.21, 0.06)	0.60
Difference*	0.74±0.75	0.44±0.89	0.26

*=Data are presented as mean±standard deviation, †=The data are shown as the median (interquartile range)

Table 3 Blood level of neonates who received high- or standard-dose of zinc supplementation at the start and end of intervention

Blood Level	High-dose (n=20)	Standard-dose (n=20)	p-value
Zinc, μg/dL			
Start*	116.2±28.2	82.2±34.3	0.002
Stop*	115.5±25.5	86.4±20.8	<0.001
Difference*	-0.7±36.9	4.2±45.3	0.71
Start <74, n (%)	1 (5)	9 (45)	0.01
After <74, n (%)	1 (5)	5 (25)	0.18
Copper, μg/dL			
Start*	33.3±14.0	39.4±18.1	0.24
Stop*	45.3±20.8	41.4±15.0	0.51
Difference*	12.0±26.6	2.0±22.6	0.21
Start <30, n (%)	8 (40)	7 (35)	>0.99
After <30, n (%)	3 (15)	6 (30)	0.45
Ferritin, μg/L†			
Start	300.4 (211.1, 472.4)	318.0 (182.2, 512.5)	0.72
Stop	164.0 (120.7, 235.0)	178.0 (116.7, 259.0)	0.83
Difference	-115.1 (-258.2, -52.6)	-98.8 (-313.7, -45.4)	0.95

*Data are presented as mean±standard deviation, †The data are shown as the median (interquartile range)

Table 4 Clinical outcomes of neonates who received high- or standard-dose zinc supplementation at discharge

Outcomes	High-dose (n=20)	Standard-dose (n=20)	p-value
Bronchopulmonary dysplasia (former), n (%)			0.68
No	7 (35)	10 (50)	
Mild	6 (30)	6 (30)	
Moderate	5 (25)	3 (15)	
Severe	2 (10)	1 (5)	
Bronchopulmonary dysplasia (new), n (%)			0.61
No	12 (60)	13 (76.5)	
I	4 (20)	2 (11.8)	
II	2 (10)	2 (11.8)	
III	2 (10)	0 (0)	
Ventilator-associated pneumonia, n (%)	1 (5)	0 (0)	>0.99
Central line-associated bloodstream infection, n (%)	1 (5)	0 (0)	>0.99
Late-onset sepsis, n (%)	1 (5)	0 (0)	>0.99
Surgical retinopathy of prematurity, n (%)	1 (5)	0 (0)	>0.99
Periventricular leukomalacia, n (%)	1 (5)	1 (5)	>0.99
Length of hospital stay, d, mean±S.D.	66.3±33.1	54.5±23.2	0.20
Daily hospital cost, USD, median (interquartile range)	170.0 (150.6, 175.6)	166.7 (153.7, 195.5)	0.47

S.D.=standard deviation, USD=the United States dollar

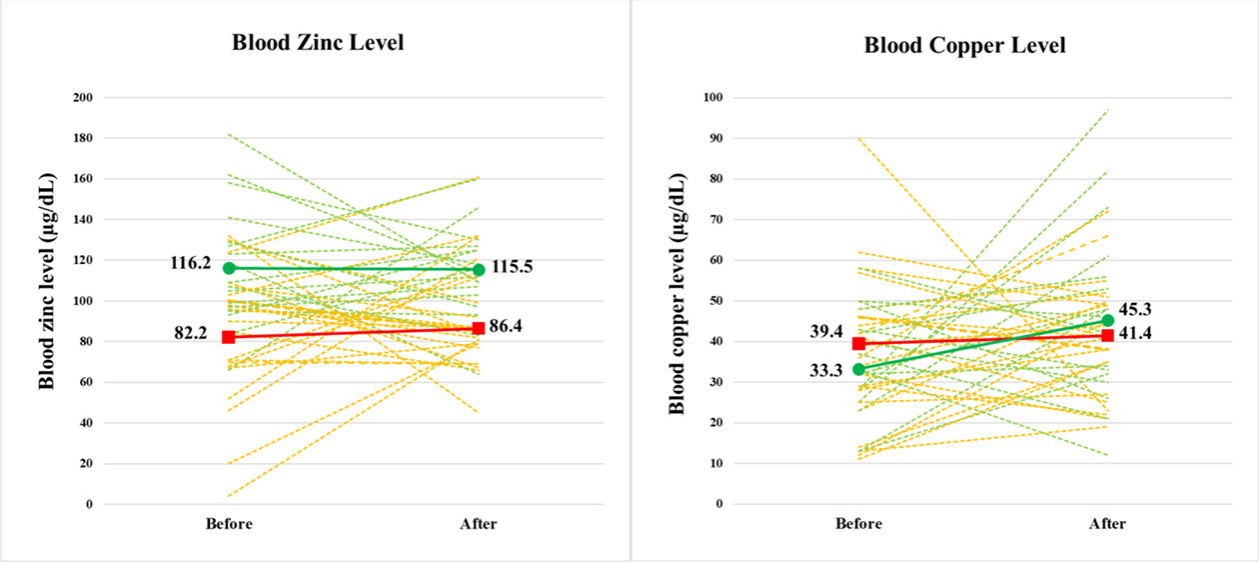

Figure 2 Individual (dashed line) and average (solid line) zinc and copper levels before and after the high-dose (green line) and standard-dose (red line) zinc supplementation

similar to the results of this study (14.92 vs. 15.57 g/kg/day). In an Indonesian study[34], weight gain (g/day) in zinc supplementation was higher than in the placebo group 9.1 vs. 7.0 g/day, (p-value=0.02). Contrarily, weight gain (g/day) in this study did not differ in the high- and standard-dose zinc supplementation groups (30.3 vs. 30.8 g/day). In routine practice, hypercaloric milk (26–30 kcal/oz) has a target weight of 17–20 g/kg/day or 20–30 g/day. However, previous RCTs did not mention the type of milk, fortification, average daily calorie intake[18,19,34], and zinc status[18,19,35] that affected growth velocity. Here, no deaths or NEC were observed. We hypothesize that most participants in this study were exclusively breastfed and were in the new era of neonatal care (compared with those in 2009–2012[18], 2019–2020[34], and 2014–2015[35]).

In a prospective observational Japanese study comparing high-dose (>3 mg/kg/day) and low-dose (<3 mg/kg/day) zinc supplementation, growth parameters (weight, length, HC, and Z-score), and zinc levels at 40 weeks PMA or NICU discharge did not differ between groups from April 2009 to June 2023[36] and from November 2020 to August 2021[37]. The zinc level in this study was higher than that in a Japanese study at baseline (116.2 and 82.2 µg/dL in 10 mg/day and 1 mg/day) and on days 7–20 (73.5 and 81.0 µg/dL in the high and low dose groups), and post-intervention (115.5 and 86.4 µg/dL in 10 mg/day and 1 mg/day) and on days 49–62 (70 and 68 µg/dL in the high and low dose groups).

In this study, the zinc levels at baseline and post-intervention in the high-dose group were significantly higher than those in the standard-dose group. However, the birth weight in the high-dose group was lower than that in the standard-dose group, and the percentage of SGA infants was the same in both groups. Whereas the difference of copper level in the high-dose group was higher than in the standard-dose zinc supplementation group (12 vs. 2 µg/dL), we found no similar data in the previous RCTs.

Table 5 The previous randomized controlled trial of zinc supplementation in very low birth weight infants

Country, Year, n[Reference]	Population (GA and BW)	Intervention and control	Outcome	Note
India, 2012, n=91[19]	34 weeks, 1,300 g	10 vs. 0 mg/day for 60 d	No difference in growth parameters at 40 weeks PMA, but weight, length, and HC showed differences in the zinc group at 52 weeks PMA.	Preterm infant, 26%. SGA, 71%. Death, 22 neonates (24%). No zinc level reported.
Italy, 2013, n=193[18]	28 weeks, 1,073 g	10 vs. 1 mg/day until discharge or 42 weeks PCA	In the high-dose zinc group, weight at discharge was higher, and mortality and NEC rates were lower than those in the lower zinc group.	2009–2012, No difference in daily weight gain (18.2 vs. 17.0 g/kg/day) and vomiting. No zinc level reported.
Indonesia, 2023, n=76[34]	31 weeks, 1,394 g	10 vs. 0 mg/day until discharge or 40 weeks PMA	In the zinc group, weight gain (g/day) and zinc level after supplementation were higher than in the placebo group (9.1 vs. 7.0 g/day and 75.3 vs. 57.1 μg/dL).	2019–2020, SGA 15.6%, Death 5 neonates (3%). No difference in NEC and side effects
Turkey, 2024, n=195[35]	29 weeks, 1,182 g	12 vs. 3 mg/day until discharge	In the high-dose zinc group, the rate of NEC, culture-proven late-onset sepsis, and feeding intolerance was lower than that in the low-dose group.	2014–2015, SGA 14.4%, Death 5 neonates (2.6%). No zinc level reported
This study	29 weeks, 1,173.8 g	10 vs. 1 mg/day until discharge or 44 weeks PMA	No differences in growth parameters and blood zinc, copper, and ferritin levels	2024–2025, SGA 20%. No case of death and NEC.

BW=birth weight, GA=gestational age, HC=head circumference, NEC=necrotizing enterocolitis, SGA=small for gestational age, PCA=postconceptional age, PMA=postmenstrual age

A key strength of this study is the comprehensive monitoring of intervention variables and clinical outcomes, which included precise documentation of the initiation and duration of zinc supplementation, average daily caloric intake, use of fortified human milk, and PMA at discharge. Furthermore, we conducted a rigorous assessment of growth trajectories using absolute values and Z-scores along with biochemical markers, including serum zinc, copper, and ferritin levels. Nevertheless, certain limitations of this study warrant consideration. Although the primary objective was to conduct a larger-scale, hypothesis-generating RCT, the final cohort was constrained to 40 neonates. Consequently, the absence of statistically significant differences between the groups may be attributed to this limited sample size, which likely resulted in insufficient statistical power to detect subtle clinical effects.

Conclusion

In clinical practice, when delivered via hypercaloric milk, no significant disparities have been observed in growth velocity or zinc status between high-dose (10 mg/day) and standard-dose (1 mg/day) regimens. Due to the limited sample size, the broader clinical implications of high-dose supplementation remain unclear. Nevertheless, these findings highlight the need for individualized zinc monitoring and tailored supplementation strategies to mitigate the risk of zinc deficiency in preterm infants. Large-scale randomized controlled trials are warranted to clarify the optimal dose and long-term benefits.

Clinical trial registration

This trial was registered in the ClinicalTrials.gov database (https://clinicaltrials.gov/ct2/show/NCT06219525). First posted registration: January 23, 2024.

Conflict of interest

There are no potential conflicts of interest to declare.

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