

The Effectiveness of Oral Nutritional Supplements Improves the Micronutrient Deficiency of Vietnamese Children with Stunting

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Abstract

Background: Stunted growth is a notable public health crisis in several countries that have low income, especially Vietnam. **Objective:** This study aimed to evaluate improved growth among stunted children from 24 to 48 months of age through the use of PediaSure fortified milk in Tien Hai District, Thai Binh Province, Vietnam. **Methods:** A clinical trial study was conducted with 140 children who were 24 to 48 months old and had height-for-age Z-scores (LAZ) lower than -2 SD and weight-for-height Z-scores (WHZ) lower than -1 SD. Each child was given 2 glasses of PediaSure per day continuously for 6 months. Blood samples were taken from all children at the start of the intervention and during 6 months of intervention; this was done to assess haemoglobin, albumin, zinc concentrations, C-reactive protein (CRP), and Alpha-1 glycoprotein (AGP). **Results:** Of the 140 children who participated in the initial study, only 106 children were eligible for analysis and evaluation of intervention effectiveness. After 6 months, the anaemia rate decreased from 29.2% to 10.4%. The prevalence of albumin deficiency also improved significantly from 82.1% to 20.8%. Zinc deficiency decreased from 66.0% to 29.2%. Assessing the improvement of biochemical markers by gender and age, our results showed that women had better improvement than men in Hb, albumin, and zinc. A comparing the two age groups, the results also showed that the 24-month to 36-month age groups had a better level of improvement in biochemical indices. **Conclusion:** Milk is an effective and widely accepted vehicle for the delivery of zinc, iron and other micronutrients in young children. Also, the multiple-micronutrient supplementation of milk shows strong potential to increase serum levels and decrease deficiencies of micronutrients known to impair growth, cognition, and immune responses.

Keywords: Anaemia, children, micronutrient, supplement, stunting, Vietnam.

INTRODUCTION

Stunting (length-for-age more than 2 SD below the WHO Child Growth Standards median) is an indicator of chronic undernutrition and is one of the best scales of child health inequality.^[1] It is one of the most prevalent types of malnutrition and is known to be associated with higher rates of mortality and cognitive impairment in affected children.^[1-5] Worldwide, 150.8 million children under the age of five are stunted, and in Asia, the prevalence is 23.2%.^[6] Variation in rates of stunting exists not only across continents but also within local geographies.^[7]

In Vietnam, protein-energy malnutrition and micronutrient deficiencies among children are still a major health concern.^[8] Malnutrition leads to numerous problems, such as impaired growth and cognitive development.^[9-11] Children grow rapidly, both mentally and physically, when they are of school age; at school, they generally receive less care than they did when they spent that time at home. Children in rural areas also help their parents with housework and farming. Although the prevalence of malnutrition, including stunting, has significantly declined in the past decade, recent

investigations in the rural areas of Vietnam have still shown a high prevalence of underweight and stunting.^[12,13] It was concluded that the prevention of malnutrition and micronutrient deficiencies should be given serious attention.

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Food-based interventions may have several advantages over supplement use, including the provision of additional nutrients in a familiar form that can be integrated into the usual diet and the provision of additional sources of energy and high-quality protein. Animal milk and dairy products are one of the seven food groups recommended by the World Health Organization for supplementation for young children.^[14, 15] In particular, cow's milk is a widely used product. In addition to the basic nutrients that provide energy, such as protein, lipid, and glucide, it also provides many vitamins and minerals. Milk is considered a suitable food to enhance vitamins and minerals, especially vitamins that are lost in the processing of baby food.^[16,17]

PediaSure is specially formulated to provide a complete and balanced diet for children between the ages of 1 and 10 years old, helping them to quickly catch up and continue optimal growth momentum, both physically and intellectually. PediaSure can be taken as a supplement or as a complete meal replacement. Therefore, this study aimed to investigate the effects of using PediaSure fortified milk on anaemia, albumin deficiency, and zinc deficiency among stunted children from 24 to 48 months of age in Vietnam.

METHODS

A clinical trial study was conducted in three kindergartens in the Tien Hai district, Thai Binh Province, located in the Red River Delta region of northern Vietnam.

Participants

All children in 3 kindergarten classes were invited to participate in screening studies to assess the nutritional status of the children following the criteria. After the assessment of nutritional status, children who met the selection criteria were invited to participate in the intervention study. Children were eligible when they were 24 to 48 months of age and had height-for-age Z-scores (LAZ) lower than -2 SD and weight-for-height Z-scores (WHZ) lower than -1 SD. Children were excluded if they had chronic diseases, birth defects, or severe acute illness at the time of the investigation. All parents were informed orally and in writing about the aims and procedures of the study, and written informed consent was obtained from at least one parent of each child before enrolment in the study. Children's LAZ and WHZ were calculated using the WHO Growth Standards.^[18]

Sample size

The sample size was calculated using the following formula:

$$n = Z_{\alpha,\beta}^2 \frac{2s^2}{(\mu_1 - \mu_2)^2}$$

Where, $\alpha=0.05$, $\beta=0.1$, $Z_{(\alpha,\beta)}^2 = 10.5$

Based on the results of previous studies, we calculated a minimum sample size of 100. To exclude subjects with an inflammatory index, affecting the actual outcome of the study, we opted for an additional 40% prophylaxis. The total number of subjects selected to participate in the study was 140.

Procedure

Each child was given 2 glasses of PediaSure per day continuously for 6 months. Each cup consisted of 190 ml of cooled boiled water ($\leq 37^\circ\text{C}$) mixed with 5 tablespoons brushed-across PediaSure powder (equivalent to 49 g of flour) and stirred 225 ml (1 ml is equivalent to 1 Kcal). Logistic organization of administering the mixture to the children was conducted at the schools with the support and supervision of their parents. Children were offered milk 2 times a day: 1 glass in the morning and 1 glass in the afternoon. During the days when children were not at school, they were given formula milk to drink at home. Study subjects had 3 ml of blood taken intravenously in the morning from 7–9 hours at baseline and at 6 months post-intervention to access the following:

- The rate of anaemia, albumin deficiency, and zinc deficiency in children before intervention by gender and by age group
- Changes in the average values of biochemical indicators before and after the intervention
- Changes in the rate of anaemia, albumin deficiency, and zinc deficiency in children before and after the intervention

Biochemical analysis

At the start of the intervention and after 6 months of intervention, blood samples were taken from all children. Blood samples were analyzed for haemoglobin, albumin, zinc concentrations, C-reactive protein (CRP), and Alpha 1 glycoprotein (AGP).

+ Determination of haemoglobin concentration: Determined by XS800i cell analyzer based on the following principle: whole blood is diluted with red-blood-cell breakdown solution (using sulfolysers chemicals) to release haemoglobin, then put into the system. Optical density measurement system with a wavelength of 540nm from which to calculate the amount of haemoglobin per unit of total blood volume. Children were defined as having anaemia when the Hb level in the blood was <110 g/l.

+ Quantification of albumin by colorimetric method. Albumin tests were performed on the AU680 (Beckman Coulter). Children were considered to have albumin deficiency when albumin concentration was <35 g/l.

+ CRP and AGP serum were quantified by immunoassay measurement method, performed on AU680 (Beckman Coulter). Diagnosis of acute infection was made when CRP

levels were >5 mg/l. Diagnosis of chronic infection was made when AGP levels were >100 mg/dl.

+ Determination of serum zinc concentration was assessed via atomic adsorption spectroscopy (AAS), a wavelength of 213.9 nm, and a light gap of 0.7 with a suction rate of 3 ml/min. Assessment of zinc deficiency was made when serum zinc concentrations were <10.7 $\mu\text{mol/L}$ or <70 $\mu\text{g/dl}$.

The testing techniques were performed at the Department of Hematology at Children's Hospital in Thai Binh Province. The laboratory met the ISO 17025 standard of the Preventive Medical Center of Thai Binh Province.

Data analysis

Data were entered into Epidata software then transferred to SPSS for analysis. Statistical tests were used to compare mean values and rates of iron, albumin, and zinc deficiency before and after the study. Data were presented as mean \pm standard deviations and values with percentages. Independent t-tests were used to test differences in the normal distribution of variables between groups. A P-value of <0.05 was considered statistically significant.

Ethics

The human research and ethical review committees approved the study protocol. The purpose of the study, along with the associated possible risks and benefits, was read and explained to the participating parents in their local language. Informed written consent was obtained. The procedure consisted of a study supervisor visiting the participant households and, in the presence of a third party, obtaining consent from the mother and/or father after the reading aloud of the consent form. Parents had the option of signing the consent form; however, if they are uneducated and unable to sign, the supervisor and the witness would sign to document the consent.

RESULTS

Of the 140 children with stunting nutrition who participated in the initial study, after 6 months of intervention, only 121 children were eligible for analysis and evaluation of intervention effectiveness. By comparing the effectiveness of intervention before and after, we excluded cases of inflammatory manifestations through the test indicators both before and after the intervention; this put into effect the analysis of 106 subjects.

By comparing the effectiveness of intervention before and after, we exclude cases of inflammatory manifestations through test indicators both before and after the intervention. The results showed the following: Hb concentrations increased on average by 5.9 g/l; albumin concentrations increased by an average of 8.7 g/l. The zinc concentration improved by 0.91 $\mu\text{mol/l}$ (Table 1).

Table 2 shows that the anaemia rate decreased from 29.2% to 10.4%. The prevalence of albumin deficiency also improved

significantly from 82.1% to 20.8%. Zinc deficiency also decreased from 66.0% to 29.2%.

The average Hb index after intervention in men (117.4 ± 6.8 g/l) and women (118.5 ± 8.2 g/l) was higher than before the intervention (6.3 ± 4.7 g/l and 5.6 ± 5.2 g/l, respectively); this was statistically significant with $p < 0.05$, but there was no distinction between the sexes. Comparing the rate of Hb deficiency between the sexes tends to decrease, from 34.0% to 14% in boys and from 25.0% to 7.1% in girls, with a higher efficiency index for girls than boys. The average albumin index after intervention in men (40.3 ± 3.9 g/l) and women (41.8 ± 4.2 g/l) was higher than before intervention (respectively, 32.3 ± 2.8 g/l and 32.4 ± 3.2 g/l), with $p < 0.05$. Comparing the prevalence of albumin deficiency between the sexes, both tended to decrease sharply after the intervention ($p < 0.05$), from 86.0% to 24.0% in boys and from 78.6% to 17.9% in young girls. The mean zinc index after intervention in men (11.0 ± 0.93 mg/l) and women (11.1 ± 0.91 mg/l) was higher than before intervention (respectively, 10.2 ± 1.1 mg/l and 10.1 ± 1.2 mg/l). Differences before and after intervention in both sexes were statistically significant with $p < 0.05$. The prevalence of zinc deficiency between the sexes after the intervention tended to decrease, from 64.0% to 34.0% in boys and from 67.9% to 25.0% in girls ($p < 0.05$) (Table 3).

After 6 months of intervention, the average Hb of children at 24–36 months and 37–48 months increased by an average of 5.6 ± 4.9 g/l and 6.2 ± 5.0 g/l. Statistical significance was $p < 0.05$; however, there was no difference in mean Hb between the two age groups. The rate of anaemia in children after intervention improved in both age groups as follows: from 24.5% to 9.4% in the children aged 24–36 months, with an effective index of 61.5%, and from 34.0% to 11.3% in the children aged 37–48 months, with an efficiency index of 66.7% ($p < 0.05$). Moreover, the average albumin of children at 24–36 months and 37–48 months increased by 9.2 ± 4.4 g/l and 8.3 ± 4.0 g/l. The difference, compared to before intervention, was statistically significant with $p < 0.05$, but there was no difference in average albumin between the two groups before and after the intervention. The percentage of albumin-deficient children has been improved: from 83.0% to 20.8% in the children aged 24–36-months, with an effective index of 75%, and from 81.1% to 20.8% in the children aged 37–48 months, with an efficiency index of 74.4%. Also, the mean zinc of children aged 24–36 months and 37–48 months increased by 0.87 ± 0.61 mg/l and 0.95 ± 0.67 mg/l. The increase in both age groups was statistically significant with $p < 0.05$; however, there was no difference in the mean zinc concentration between the two age groups at the time. The percentage of zinc-deficient children after intervention improved in both age groups: from 58.5% to 24.5% in the children aged 24–36-months and from 73.6% to 34.0% in the children aged 37–48 months; this was significant with $p < 0.05$ and a higher efficiency index in the group of children aged 24–36-months (Table 4).

DISCUSSION

After screening all children aged 24–48 months in 3 communes of Tien Hai district, we selected 140 eligible children with whom to intervene according to 2 criteria: HAZ-score lower than -2SD and WHZ-score lower than -1SD. The average age of the children was 34.7 months. After the intervention, 121 eligible subjects were selected for analysis. The rate of giving up after 6 months was 12 subjects, accounting for 8.6%. The reasons for ceasing participation were among the following: children who did not attend school regularly, children who moved to a different place of residence (outside the scope of the study area), and children who became sick and could not participate in end-of-term surveys. Seven subjects were not eligible to be included in the data analysis at the end of the study period, accounting for 5.0%, because the subjects did not comply with 95% or more of the milk-drinking sessions or the mothers refused to accept the blood sample. final test. The response rate was 121/140 children, accounting for 86.4%. Our results suggested that milk was an effective and widely accepted vehicle for the delivery of zinc, iron, and other micronutrients in young children. There was inconclusive evidence about the impact of iron and zinc fortification on anaemia and iron status. A meta-analysis of 21 data sets from randomized controlled iron-supplementation trials in children aged 0 to 12 years reported a significant difference in the mean change in Hb concentrations between treatment and control groups.^[19] The level of improvement of micronutrient deficiency was also clearly shown in our study. After the intervention, the anaemia rate decreased from 29.2% to 10.4%; the albumin deficiency rate has also improved significantly from 82.1% to 20.8%. Zinc deficiency decreased from 66.0% to 29.2%. The difference before and after the intervention was statistically significant with $p < 0.05$. Compared to the study of Tran Quang Trung, who intervened after 12 months, our results obtained after 6 months showed a similar reduction in the rate of anaemia and the rate of zinc deficiency. This showed that using PediaSure helped children improve micronutrient deficiencies faster than conventional supplements. Tran Quang Trung's data did not include albumin results, so we could not compare this aspect of the study.^[20] The study by Tran Thi Lan on children who received a multi-micronutrient supplement package within 26 weeks, consisting of 7 sachets with 1 sachet per week, showed that the multivitamin supplement had a markedly effective improvement on haemoglobin, retinol, zinc, and IGF-I levels, and the effectiveness index reached 65.2%; 42.2%; 76.0% with anaemia, vitamin A deficiency, and zinc deficiency.^[21]

Fortified milk showed greater improvements in anaemia prevalence, possibly related to the increased iron intake. Serum zinc concentrations were generally maintained within the normal range with small or moderate reductions in zinc intake. Brown *et al.* assessed the effect of zinc supplementation on the physical growth and serum zinc concentrations of pre-pubertal children.^[22] Zinc supplementation produced highly significant, positive responses in height and weight increments and caused a

significant increase in the children's serum zinc concentrations. The population mean serum zinc concentration appeared to be a useful indicator of the successful delivery and absorption of zinc supplements in children.^[22] In our study, milk consumption appeared to increase mean serum zinc concentrations beyond the increase observed in the baseline, indicating that a relatively moderate increase in zinc intake would already suffice in optimizing serum zinc concentrations and consequently improving zinc status and related health benefits. A meta-analysis of zinc supplementation trials confirmed that zinc has a significant but small impact on length increases in children 0–13 years of age, and there appears to be strong evidence for the contribution of zinc deficiency to growth faltering among children.^[10,23] So, the observed improvements in height gain could also be the combined result of increased intake in energy, protein, iron, and zinc.

Finally, an improvement was found in body iron stores, a decrease was found in anaemia rates, and improvement in growth points was found, combining toward a global improvement in the child's health - a functional endpoint of multiple metabolic processes. This global improvement could be due to a combination of effects of individual constituents of the intervention and/or synergistic effects among the components. Assessing the improvement of biochemical markers by gender and age, our results showed that women have better improvement than men in Hb, albumin and zinc. A comparison between the two age groups also showed that the 24-month to 36-month age groups had better levels of improvement in biochemical indices. It is of concern that, according to a previous study, about 80% of Vietnamese preschool children suffered from two or more coexisting micronutrient deficiencies.^[8] The micronutrient supplementation must be accompanied by efforts to secure energy and protein requirements, and therefore improvement of the quality of home feeding and caregiving should be considered to sustain the effect of the micronutrient supplementations. Given the design of the study, we cannot attribute effects to a specific component but only describe the collective impact of the specific micronutrient bundle tested as the experimental intervention in this study. Therefore, strategies for the prevention and control of micronutrient deficiencies, for improving public health nutrition, should be carried out with varying methods for comprehensive achievement.

CONCLUSION

Milk consumption reduced stunting and anaemia because of the increased energy and multiple micronutrient supply. Also, multiple micronutrient supplementation of milk had strong potential to increase serum levels and decrease deficiencies of micronutrients known to impair growth, cognition, and immune responses. Thus, the present study provided useful information on milk-supplement dietary intake in children, suggesting that this supplementation exerts a positive effect on iron and nutritional statuses. These complementary foods were produced in Vietnam at a lower cost compared with

available commercial Vietnamese or imported complementary foods and would be affordable for a large proportion of the population. Large-scale dissemination of such products could contribute to preventing micronutrient deficiencies in early childhood in many developing countries.

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Table 1. Micronutrient status in children at baseline and end-line in the intervention group (mean±SD)

Variables	Baseline	6 months	Change	p-value
Hb (g/l)	112.05±8.6	117.9±7.6	5.9±4.9	<0.05
Albumin (g/l)	32.3±3.0	41.1±4.1	8.7±4.2	<0.05
Zinc (μmol/l)	10.1±1.1	11.0±0.96	0.91±0.64	<0.05

Table 2. The proportion of study subjects with deficiency levels at baseline and after 6 months

Variables	Baseline		6 months		p-value
	N	%	N	%	
Anemia (Hb <110g/l)	31	29.2	11	10.4	<0.05
Albumin deficiency (< 35 g/l)	87	82.1	22	20.8	<0.05
Zinc deficiency (Zn<10.7μmol/l)	70	66.0	31	29.2	<0.05

Table 3. Change in micronutrient status and prevalence of deficiency levels by gender at baseline and after 6 months

Variables	Boys (n=50)	Girls (n=56)	p-value
Hb (g/l, mean±SD)			
Baseline	111.1±8.2	112.9±8.9	>0.05
6 months	117.4±6.8	118.5±8.2	>0.05
Change	6.3±4.7	5.6±5.2	>0.05
p-value	<0.05	<0.05	
Anemia [n (%)]			
Baseline	17 (34.0)	14 (25.0)	>0.05
6 months	7 (14.0)	4 (7.1)	>0.05
p-value	<0.05	<0.05	
Albumin (g/l, mean±SD)			
Baseline	32.3±2.8	32.4±3.2	>0.05
6 months	40.3±3.9	41.8±4.2	>0.05
Change	8.0±4.0	9.4±4.3	>0.05
p-value	<0.05	<0.05	
Albumin deficiency [n (%)]			
Baseline	43 (86.0)	44 (78.6)	>0.05
6 months	12 (24.0)	10 (17.9)	>0.05
p-value	<0.05	<0.05	
Zinc (mg/l, mean±SD)			
Baseline	10.2±1.1	10.1±1.2	>0.05
6 months	11.0±0.93	11.1±0.91	>0.05
Change	0.82±0.65	0.99±0.62	>0.05
p-value	<0.05	<0.05	
Zinc deficiency [n (%)]			

Baseline	32 (64.0)	38 (67.9)	>0.05
6 months	17 (34.0)	14 (25.0)	>0.05
p-value	<0.05	<0.05	

Table 4. Change in micronutrient status and prevalence of deficiency levels by age at baseline and after 6 months

Variables	Children aged 24-36 month (n=53)	Children aged 37-48 month (n=53)	p-value
Hb (g/l, mean±SD)			
Baseline	112.9±7.5	111.1±9.6	>0.05
6 months	118.6±7.3	117.3±7.8	>0.05
Change	5.6±4.9	6.2±5.0	>0.05
p-value	<0.05	<0.05	
Anemia [n (%)]			
Baseline	13 (24.5)	18 (34.0)	>0.05
6 months	5 (9.4)	6 (11.3)	>0.05
p-value	<0.05	<0.05	
Albumin (g/l, mean±SD)			
Baseline	32.2±3.3	32.6±2.8	>0.05
6 months	41.3±4.4	40.9±3.9	>0.05
Change	9.2±4.4	8.3±4.0	>0.05
p-value	<0.05	<0.05	
Albumin deficiency [n (%)]			
Baseline	44 (83.0)	43 (81.1)	>0.05
6 months	11 (20.8)	11 (20.8)	>0.05
p-value	<0.05	<0.05	
Zinc (mg/l, mean±SD)			
Baseline	10.4±1.1	9.9±1.2	<0.05
6 months	11.3±0.9	10.9±0.9	<0.05
Change	0.87±0.61	0.95±0.67	>0.05
p-value	<0.05	<0.05	
Zinc deficiency [n (%)]			
Baseline	31 (58.5)	39 (73.6)	>0.05
6 months	13 (24.5)	18 (34.0)	>0.05
p-value	<0.05	<0.05	