Effects of Nutrient Fortified Complementary Food Supplements on Anemia of Infants and Young Children in Poor Rural of Gansu[1]

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Objective To assess the effectiveness of complementary food supplements with protein and multi-micronutrients on hemoglobin and anemia in infants and young children. **Methods** In 5 poor counties of Gansu, 984 children aged 6-12 months were enrolled and divided into two groups. In addition to the usual home-made complementary food, all the children were fed one sachet of either Formula I or Formula II supplements each day. Protein and micronutrients were provided in Formula I, while the same energy intake was secured in Formula II as in Formula I. A massive dose of vitamin A was supplemented to all the children every 6 months. Hemoglobin test was done at the same time. **Results** Prevalence of anemia was about 35% in both Formula I and Formula II group at baseline, and there were no differences in hemoglobin concentration between the two groups. During the 6-month and 12-month supplementation, hemoglobin of children in Formula I group was higher than that in Formula II group ($P<0.05$), and hemoglobin increase in Formula I group was significantly higher than that in Formula II group ($P<0.001$). After 6- and 12-month supplementation, the prevalence of anemia in Formula I group dropped to 19.1% and 8.2% respectively, and it was 28.0% and 12.4% in Formula 2 group. The prevalence of anemia in Formula I group was significantly lower than that in Formula II group ($P<0.05$). After adjusting age and hemoglobin level at baseline, the hemoglobin increase at age of 24 months in formula 1 group was higher (10.7 g/L *vs* 7.9 g/L, $P<0.0001$). **Conclusion** Micronutrient fortified complementary food supplements, with large-dose vitamin A, is effective for children aged 6-12 months in terms of iron deficiency prevention.

Key words: Food fortification; Complementary food supplements; Infants and young children; Hemoglobin; Iron deficiency anemia

INTRODUCTION

In most developing countries iron deficiency anemia (IDA) is one of common nutritional deficiency diseases in children, especially in infants and young children under 2 years of age. While iron requirement of infants can not be met by breastfeeding after age of 6 months, iron fortification of complementary food is an essential way to ensure an optimal growth of the infant[1]. It is estimated that about 75%-100% of the iron and zinc needed for their growth should be provided by complementary food. However, in most developing countries, complementary food consists primarily of cereals, which are low in vitamins and minerals, resulting in deficiency of iron and zinc among children aged under 24 months[2]. Multiple nutrient deficiency, for example, protein, iron, zinc, calcium, and vitamin A inadequacy in young children is common, and the prevalence of anemia during infancy after weaning and early childhood is higher than at any other time in the life cycle of the Chinese population.

Nutrition education programs are encouraged to improve complementary feeding by food diversity and proper use of local food, but the high requirement of young children is far beyond the total intake of micronutrients in the small amount of food consumed. So, new approaches such as home-level fortification have been broadly recommended to provide additional micronutrients to regular home made complementary food, and Sprinkles, Foodlet, and Spread *etc*. are applied to address nutrition improvement in children under 24 months in developing countries[3].

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In the rural counties of western China, complementary feeding practice is poor in terms of its timing and food diversity[4], and anemia prevalence in children aged 6-24 months in Gansu province was 35% in 2001. Development of effective and feasible approaches to eliminate anemia is extremely needed. This paper presents an effectiveness study of a fortified complementary food supplement for anemia prevention.

SUBJECTS AND METHODS

Study Population

In 2001, 1 500 children were sampled from the children aged 4-12 months in 5 poor counties (Dingxi, Qingshui, Jingtai, Tianzhu, and Jingning) in Gansu of China. In each county, at least 2 townships were selected, where villages were randomly sampled. In the sampled villages all the children aged 4-12 months were taken until the amount of children reached 200; these children were recruited as Formula I group, while another 100 children aged 4-12 months were selected as Formula II group in the nearby township with similar natural and economic conditions. In this paper only the effect of complementary food supplements on children aged 6-12 months were discussed.

Methods

A baseline survey on physical growth and complementary feeding status of children was conducted, and then all children were fed one sachet of either Formula I or Formula II supplements. Formula I was soybean powder-based and contained iron (6 mg, in NaFeEDTA), zinc (4 mg, in Zn sulfate), calcium (385 mg, in Ca carbonate), Vitamin D (7 μg, in vitamin D_3 oil 1 million IU/g), vitamin B_2 (0.2 mg, vitamin B_2 10% in Maltodextrin). Formula II was rice powder-based with added vegetable oil to reach the same calorie level as that of Formula I, i.e., 44 kcal/10 g. The supplements were either directly to or separately from the usual home-made complementary food of the child. In addition, a massive dose of vitamin A was given to children in both groups (every 6 months, 1 dose of 100 000 vitamin A for children aged under 12 months and 200 000 IU for children over 12 months) .

Evaluation Index

Blood hemoglobin Blood hemoglobin was measured by the cyanmethemoglobin method every 6 months. According to the altitude of this study area, the cutoff point of anemia for children was adjusted to 115 g/L[5].

Effect size Effect size reflects the correlation between processes and outcomes of the research[6]. Specifically, the value of effect size was obtained by dividing the difference between the average changed values of the Formula I group and the Formula II group by the standard deviation of average change values of both groups. In general, effect sizes of 0.2 are considered small, effect sizes of 0.5 are considered moderately large, and those of 0.8 are considered large.

Statistical analysis All data were entered into EPIDATA 3.02. The data was cleaned and analyzed using SAS 9.1.3. The statistics methods included *t*-test, χ^2 test and variance analysis. *P* value that less than 0.05 was considered statistically significant.

Ethical approval Ethical approval for this study was obtained from the Ethics Committee of the Chinese Center for Disease Control and Prevention. Informed consent was obtained from parents or guardians of children who were involved in the project.

RESULTS

Characteristics of the Sample

The baseline survey was conducted in Tianzhu, Jingning, Dingxi, Qingshui, and Jingtai of Gansu province from October through November of 2001. Hemoglobin tests were done for 984 children. The average concentration was 118.0±11.6 g/L, the prevalence of anemia was 35.6%, and no difference was observed between the two groups. There was no difference in age and gender distributions in the two groups.

Hemoglobin tests were conducted after 6-month and 12-month supplementation in all children. Among them, 721 children got full data of baseline and two follow-ups, and 263 children missed once or twice hemoglobin follow-ups, but there was no significant difference in baseline hemoglobin level and anemia prevalence between the two sample groups (P>0.05). During the whole follow-up process, 671 children were tested for hemoglobin concentration in both the baseline survey and the final survey. The hemoglobin concentration and prevalence of anemia of all children tested in both surveys had no significant difference with those of other 313 children at baseline (P>0.05). The above result indicated that the hemoglobin concentration of children fed for 12 months and aged 24 months could represent the overall changes.

Changes in Hemoglobin Concentration and Prevalence of Anemia during 12-Month Supplementation

At baseline, hemoglobin concentration in Formula II group was slightly higher than that in Formula I group, but the difference was not statistically significant (*P*>0.05). Hemoglobin concentration of children in Formula I group was significantly higher than that of children in Formula II group after 6- and 12-month supplementation (*P*<0.05). In both groups hemoglobin concentration was increased along with age increase (*P*<0.001) (Table 1).

TABLE 1

Hemoglobin Concentrations of Children in Both Groups (g/L)

	Formula I ($\bar{x} \pm s$)	Formula II ($\bar{x} \pm s$)
Baseline	118.1±11.7	118.5±11.6
6-Month Follow-up	123.3±10.7	121.0±11.2*
12-Month Follow-up	127.8±9.7	126.0±10.0**

Note. *Formula I *versus* Formula II, *P*=0.01. **Formula I *versus* Formula II, *P*=0.019.

The increases of hemoglobin concentration in Formula I group at 6-month and 12-month follow-ups were significantly higher than in Formula II group (*P*<0.05); however, the hemoglobin concentration changes in the two groups were not statistically significant between 6-month and 12-month follow-ups. The effect size of hemoglobin concentration change in formula I over formula II was at a middle level, 0.27 and 0.21, respectively (Table 2).

TABLE 2

Differences in Hemoglobin Concentration Increases during Follow-ups (g/L)

	Formula I	Formula II	Effect Size
6-month Follow-ups	+5.2	+2.6*	0.27
12-month Follow-ups	+9.7	+7.5**	0.21

Note. *Formula I *versus* Formula II, *P*=0.0003. **Formula I *versus* Formula II, *P*=0.005.

Figure 1 shows the hemoglobin concentration distributions of children in both groups at baseline and at 12-month follow-up survey. The two curves on the left represent hemoglobin concentration distributions in both groups at baseline, which were almost identical. After 12-month supplementation, the curves moved horizontally to the right, and hemoglobin concentrations increased significantly. Notably, the scope of movement in Formula I group was larger, indicating that changes of hemoglobin concentration in Formula I group were higher than those in Formula II group.

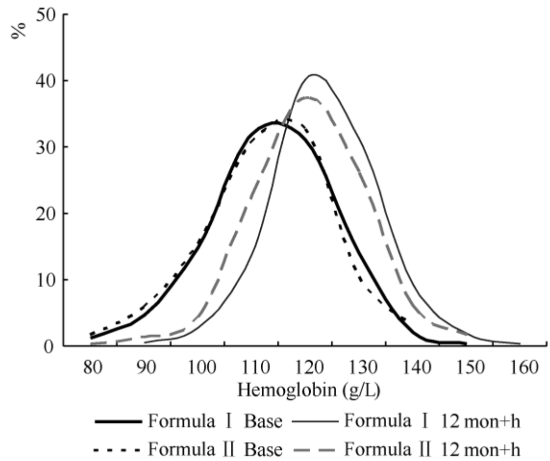

FIG. 1. Hemoglobin concentration distribution at baseline and 12-month Follow-up survey.

Prevalence of anemia in Formula I group and Formula II group were 34.8% and 34.9% respectively at baseline, showing no significant difference. At 6-month and 12-month follow-ups, the prevalence of anemia dropped significantly to 19.1% and 8.2% respectively in Formula I group, and dropped to 28.0% and 12.4% respectively in Formula II group. The prevalence of anemia in Formula I group was significantly lower than that in formula II group at the 6-month follow-up survey (*P* <0.05) (Table 3).

TABLE 3

Prevalence of Anemia of Children in Both Groups (%)

	Formula I	Formula II
Baseline	34.8	34.9
6-month Follow-ups	19.1	28.0*
12-month Follow-ups	8.2	12.4**

Note. *Formula I *versus* Formula II, *P*=0.008. **Formula I *versus* Formula II, *P*=0.074.

Impacts on Anemic Infants

At baseline, there were 175 and 76 anemic children in the two respective groups without any significant difference in hemoglobin concentrations. At 6-month follow-up, hemoglobin concentration in Formula I group was significantly higher than that in Formula II group (*P*<0.0001). At 12-month follow-up, hemoglobin concentration in Formula I group was still higher than that in Formula II group (*P*<0.01) (Table 4).

TABLE 4

Changes in Hemoglobin Concentrations of Anemic Children (g/L)

	Formula I ($\bar{x} \pm s$)	Formula II ($\bar{x} \pm s$)
Sample Size	175	76
Baseline	105.5±7.0	105.8±7.1
6-Month Follow-up	117.3±12.4	111.7±8.4*
12-Month Follow-up	123.3±10.3	119.4±9.3**

Note. *Formula I *versus* Formula II, *P*<0.0001. **Formula I *versus* Formula II, *P*=0.005.

Comparing the differences of hemoglobin concentrations between two consecutive follow-up surveys, children in Formula I group had significant increase of hemoglobin concentration than those in Formula II group (*P*<0.0001) (Table 5). In turn, the effect size of hemoglobin concentration changes in Formula 1 group over Formula 2 group was at a medium level of 0.54 in 6-month follow-up and 0.41 in 12-month follow-up. The anemia prevalence during 6-month follow-up dropped significantly, to 46.9% and 65.8% in Formula I group and Formula II group respectively, and during 12 month follow-up further dropped to 20.0% and 29.0% accordingly. The differences between the two groups were statistically significant (*P*<0.001).

TABLE 5

Hemoglobin Concentration Increases of Anemic Children during Follow-up Survey (g/L)

	Formula I	Formula II	Effect Size
6-month Follow-up	+11.8	+5.8*	0.54
12-month Follow-up	+17.8	+13.5**	0.41

Note. *Formula I *versus* Formula II, *P*<0.0001. **Formula I *versus* Formula II, *P*=0.0026.

Impacts on Non-anemic Children

At baseline, there were 328 and 142 non-anemic children in the two respective groups and the hemoglobin concentration difference during baseline survey was not statistically significant, and the hemoglobin concentration of the children was maintained at a relatively stable range with no significant increase after 12 months supplementation (Table 6).

TABLE 6

Hemoglobin Concentration Changes of Non-anemic Children in Two Groups (g/L)

	Formula I ($\bar{x} \pm s$)	Formula II ($\bar{x} \pm s$)
Sample size	328	142
Baseline	124.8±7.4	125.2±7.0
6-month Follow-up	126.5±8.0	126.0±9.1
12-month Follow-up	130.3±8.4	129.5±8.5

During the supplementation period, 4.3% and 1.8% of these non-anemic children in Formula I group turned to anemic children at 6-month follow-up and 12-month follow-up, and in Formula II group it was 7.8% and 3.5% respectively, and the differences were statistically insignificant (*P*>0.05).

Hemoglobin Concentration in All Children Reaching 24 Months

When the children were reaching 24 months of age, the hemoglobin concentration in Formula I group was higher than that in Formula II group (*P*=0.0001). Adjusting the age and hemoglobin level at baseline, hemoglobin concentration increase in Formula I group (10.7 g/L) was higher than that in Formula II group (7.9 g/L) and the difference was statistically significant (*P*<0.0001) (Table 7).

TABLE 7

Changes in Hemoglobin Concentrations and Prevalence of Anemia in Two Groups

	Formula I	Formula II
Baseline		
Hemoglobin (g/L) ($\bar{x} \pm s$)	118.3±11.4	118.0±11.3
Prevalence of Anemia %	32.9	37.4
Final Follow-up		
Hemoglobin (g/L) ($\bar{x} \pm s$)	129.0±8.8	126.1±9.1*
Prevalence of Anemia %	5.3	8.9
Hemoglobin Change (g/L)	+10.7	+7.9**

Note. *Formula I *versus* Formula II, *P*=0.0008. **Formula I *versus* Formula II, *P*=0.0005.

DISCUSSION

The program was for the first time carrying out a large-scale nutrition intervention using a nutrient-fortified food supplement to improve complementary feeding among children under 24 months in rural China. This study aimed to prevent micronutrient deficiency, especially anemia without changing the usual home-made complementary feeding. To keep the cost of the food supplements low, only iron, zinc, calcium, vitamin D, and vitamin B_2 were fortified, which are the nutrients most commonly inadequate in Chinese diet. The addition of 4 g protein and fat from soybeans was also beneficial for children's growth. Other home fortification of complementary foods, Foodlet and Sprinkles, also provide multiple micronutrients necessary for infants in line with local food characteristics. Spread, lipid-based supplements, provides some energy, essential fatty acids and protein, whereas Sprinkles and Foodlet do not[3]. Complementary food supplements (Formula I) also contained high-quality protein, calories, iron, zinc, and other micronutrients. All of them have common advantages: it does not require major changes in dietary practices, allows the child to obtain a full dose of micronutrients when mixed with a small quantity of food, and is better accepted.

During this study, the prevalence of anemia in Formula I group dropped by 47% (from 34.9% to 18.5%) at the 6-month follow-up. At the 12-month follow-up, the prevalence of anemia was less than 10%. Eighty percent of the anemic children at baseline in Formula I group was cured of anemia after 12-month supplementation. During the process of supplementation, the hemoglobin concentration of the children was increasing significantly, which indicate that Formula I had satisfactory effects on anemia prevention and treatment. This was the joint effort of iron, other micronutrients and massive dose of vitamin A supplementation. For children in Formula II group, the prevalence of anemia declined slightly at 6-month follow-up, which might be due to their growing-up. The prevalence of anemia dropped significantly at 12-month follow-up only after the supplementation of the large dose of vitamin A.

As for prevalence of anemia, 5%-12% is considered low-grade public health problem and 12%-19% a medium-grade one[7]. At 12-month follow-up, the prevalence of anemia was 12.3% in Formula II group and 7.5% in Formula I group, which fell into the low-grade category. Usually, the prevalence of iron deficiency is 2-2.5 times that of anemia in developing countries[8]. The deleterious effects of iron deficiency on cognitive development in infants are well documented. Studies of long-term effects of iron deficiency anemia in Costa Rica showed that anemic infants had lower test scores at age 5, as compared with the anemic infants at their early infancy; when participants were followed up into adulthood, these differences not only persisted but were increasing, with particular negative effects on those in low socioeconomic status[9]. In our study, at 12-month follow-up, there was a 4 percentage difference between the two groups, with Formula II group having 50% more anemic children than the Formula I group, which indicated that even though the anemia rates and hemoglobin concentrations of children improved in both groups, the effect of Formula I was stronger and more prompt.

Our results regarding the efficacy of these supplements for preventing anemia and iron deficiency are consistent with those of other studies of multiple micronutrient supplementations. Sprinkles was the first supplementation designed for the prevention and treatment of children's iron deficiency anemia; there were effective improvements in hemoglobin in 2 months[10]. Further investigations on medium anemic children indicated that Sprinkles could effectively prevent anemia[11]. In addition, Sprinkles including iron and zinc could be used in anemia treatment[12]. The recent study in rural Haiti also showed that 2 months of Sprinkles supplementation were effective in reducing anemia among children aged 9 to 24 months with high anemia prevalence[13].

Foodlet had significant positive effects on hemoglobin and iron status in cohorts of Indonesian, Peruvian, South African, and Vietnamese infants[14]. In Malawi, undernourished infants aged 6-17 months consuming modified Spread had a significantly higher hemoglobin concentration than those who received no supplement[15]. Lopriore *et al.* reported that a highly nutrient-dense fat-based Spread fortified with vitamins and minerals produced a 2-fold increase in hemoglobin concentration compared with a control group, although the children in that study were older[16]. All 3 options for home fortification of complementary foods were effective for reducing the prevalence of iron deficiency in Ghana. Between 6 and 12 months, the percentage of anemic infants decreased significantly in all 3 intervention groups, from 23%-30% at 6 months and to 10%-18% at 12 months[17]. Ecuador's National Food Nutrition Program provided a micronutrient fortified complementary food beginning at 6 months. Anemia prevalence dropped from 76% in both groups at baseline to 27% in supplemented children, but only to 44% in control children. Children in the intervention group had significantly higher hemoglobin values and were significantly less likely to be anemic than children in the control group[18].

However, children above 6 months usually suffer from more than one micronutrient deficiency in rural areas; iron supplementation alone might not be enough to reduce the anemia rate, which explained why the prevalence of anemia of pre-school children did not change after 6 months of iron supplementation in Mexico. The children were suffering from other micronutrients deficiency too[19], and so multiple micronutrients should be provided as Formula I in this study.

The iron in Formula I group is 6 mg Fe as NaFeEDTA, which is easy to be absorbed[20]. During the supplementation period, the hemoglobin concentration of anemic children increased rapidly from the baseline level. For non-anemic children, no significant change was observed in hemoglobin concentration at 6-month and 12-month follow-up without adverse effects occurred, and this indicates that the supplementation of iron at 6 mg per day as NaFeEDTA is safe and feasible. Home fortification of complementary foods with low amounts of highly bioavailable iron is an effective approach.

Children in the Formula II group did not get iron supplemented, but prevalence of anemia dropped from 34.9% at baseline to 12.4% during 12-month follow-up. There are two possible explanations. Firstly, all children were given large doses of vitamin A supplements at 6, 12, and 18 months of intervention. In developing countries, vitamin A deficiency usually exists along with iron deficiency, and a large portion of children with iron deficiency anemia suffer from sub-clinical vitamin A deficiency[21]. Vitamin A plays an important role in improving iron absorption and utilization in the iron supplementation process[22], thus improving the hemoglobin concentration of children[23-24]. Secondly, it might be partly due to the natural increase of hemoglobin concentration along with age increase. According to data from the nutrition surveillance in China, the prevalence of anemia of children was declining from the peak at age of 12 months down to age of 5 years. The average prevalence of anemia was 29% among children of 18-24 months in rural China[25]. By 12-month follow-up, the anemia rate of children in Formula II group dropped to 12.4%, indicating that the large dose of vitamin A could contribute, to a certain extent, to the decrease of anemia rate in the Formula II group.

In conclusion, as a home level fortification food supplement, Formula I has a strong effect on increasing hemoglobin concentration and reducing the anemia prevalence in the children under 2 years of age. Supplementation of large doses of vitamin A might promote iron absorption; however, compared with the supplementation of iron and other micronutrients, its effect is slow and limited. It is feasible to reduce or eliminate anemia by adding food supplement with fortified multi-micronutrients into the regular complementary food of infants and young children. Further challenges being faced are to scale up food supplementation intervention by exploring effective model to achieve an availability, accessibility, and affordability of such product in poor rural areas in China.

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